Biomedical Innovation Systems in India: Issues and Challenges in Translational Research in Select Diseases

Thesis submitted to Jawaharlal Nehru University for award of the Degree of

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DECLARATION

I declare that the thesis entitled **"Biomedical Innovation Systems in India: Issues and Challenges in Translational Research in Select Diseases"** submitted by me for the award of the degree of **Doctor of Philosophy** of Jawaharlal Nehru University is my own work. The thesis has not been submitted for any other degree of this university or any other university.

Swarup Kishan Jena 22/7/19
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CERTIFICATE

We recommend that this thesis be placed before the examiners for evaluation.

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ADA:	American Diabetes Associations
ADME:	Absorption, Distribution, Metabolism, and Excretion
AYUSH:	Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy
BDTD:	Biomedical Device and Technology Development Programme
BIG:	Biotechnology Ignition Grant
BIPP:	Biotechnology Industry Partnership Programme
BIRAC:	Biotechnology Industry Research Assistance Council
BIS:	Biomedical Innovation Systems
CCRAS:	Central Council for Research in Ayurvedic Sciences,
CCRS:	Central Council for Research in Siddha
CCRUM :	Central Council for Research in Unani Medicine
CDSCO:	Central Drugs Standard Control Organisation
CHC :	Community Health Centre
CKD :	Chronic Kidney Disease
CLIR :	Cross Lingual Information Retrieval (WIPO)
COPD:	Chronic Obstructive Pulmonary Disease
CPCSEA:	Committee for the Purpose of Supervision and Control of Experiments on Animals
CRO :	Contract Research Organization
CRTDH:	Common Research and Technology Development Hub
CSIR:	Council of Scientific & Industrial Research
CTRI:	Clinical Trial Registry-India
CTs:	Clinical Trials
CVD:	Cardiovascular disease
D-CLIP:	Diabetes Community Lifestyle Improvement Program
DFU:	Diabetic Foot Ulcers
DGHS :	Directorate General of Health Services
DHR:	Department of Health Research
DIPP:	Department of Industrial Policy & Promotion
DPCO:	Drug Price Control Order
DPP-4:	Dipeptidyl-peptidase-4 (DPP-4) inhibitors

DSIR:	Department for Scientific & Industrial Research
DST:	Department of Science and Technology
GLP:	Good Laboratory Practices
GLP-1:	Glucagon-like peptide-1 (GLP-1) agonist
HRHR:	High Risk - High Reward Research
ICTRP:	International Clinical Trials Registry Platform
IDF:	International Diabetes Federation
IDSP:	Integrated Disease Management Programme
IMPRINT:	Impacting Research Innovation and Technology
INDIAB:	INdia DIABetes study
IRHPA:	Intensification of Research in High Priority Area
LIS:	Local Innovation System
MHRD:	Ministry of Human Resource Development
NBA:	National Biodiversity Authority
NBE:	New Biological Entities
NCCP:	National Cancer Control Program
NCE:	New Chemical Entities
NHP:	National Health Policy
NHSRC:	National Health Systems Resource Centre
NIAW:	National Institute of Animal Welfare
NIH:	National Institutes of Health , USA
NIS:	National Innovation System
NLEP:	National Leprosy Eradication Program
NPCBVI:	National Programme for Control of Blindness & Visual Impairment
NPCDCS:	National Programme on Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke
NPHCE :	National Programme for Health Care of the Elderly
NPPA:	National Pharmaceutical Pricing Authority
NRDC:	National Research Development Corporation
NRHM:	National Rural Health Mission
NVBDCP:	National Vector Borne Disease Control Programme
OAD:	Oral Anti Diabetic Drugs

OECD:	Organisation for Economic Co-operation and Development
PACE:	Promoting Academic Research Conversion to Enterprise
PCT:	Patent Co-operation Treaty
PD:	Pharmcodynamics
PHC:	Primary Health Centre
PK:	Pharmacokinetics
PPAR:	Peroxisome proliferator-activated receptor
PPP:	Public- Private Partnership
PRCs:	Project Review Committees
PRISM:	Promoting Innovations in Individuals, Startups and MSMEs
PRP:	Patients Registry Programme
rDNA:	Recombinant Deoxyribonucleic Acid
RIS:	Regional Innovation System
RMD:	Rural Medical Dispensary
RNA:	Ribonucleic acid
RNTCP:	Revised National TB Control Program
SAHAJ:	Scientific Infrastructure Access for Harnessing Academia University Research Joint Collaboration
SFD:	French Society for the study of Diabetes
SGLT2:	Sodium glucose co-transporter 2 (SGLT2) inhibitors
SIBRI:	Small Business Innovation Research Initiative
SIS:	Sectoral Innovation System
SPARSH:	Social Innovation programme for Products: Affordable & Relevant to Societal Health
SRISTI:	Shared Research Infrastructure for Science, Technology and Innovation
TIS:	Technological Innovation System
TKDL:	Traditional Knowledge Digital Library
UHC:	Urban Health Centre
WHO- EM:	List of Essential Medicine, WHO
WIPO:	World Intellectual Property Organization
YDR:	Young Diabetes Registry

CHAPTER ONE
INTRODUCTION

1.1 Background

The dichotomy of health care in India

The contemporary world could be characterised well by the global health burden that appears to shift gear increasingly. On the one hand, diseases like plague, polio, cholera, tuberculosis are declining due to effective management by government & international agencies, timely intervention, massive scale immunization, improved sanitation and lifestyle of individuals; on the other hand chronic diseases like cancer, diabetes, cardiovascular diseases (heart diseases) are on the exponential increase (ICMR, India: Health of the Nation's States 2017;NHP,2017). The increasing incidences of these diseases pose widespread social and economic impacts, wreaking havoc on all levels of society right from the households to health care systems and national and global economies.

In its attempt to attain the Millennium Development Goals, India led a focused fight to improve and advance its health care system. Some of the significant achievements include a reduction in maternal and child mortality. The much-admired successes of this period are the complete eradication of polio and the significant reduction of cases in Leprosy. There is stagnation or decline in various infective and vector-borne diseases like Kala-azar, Lymphatic filariasis, cholera etc. (MDG, 2015; WHO world health statistics 2017) the AIDS control program also registered good progress with a decline from a 0.41 % prevalence rate in 2001 to 0.27% in 2011.

India today has a state of the art armoury of interventions, technologies, knowledge and information required for providing better health care to the people. The gaps in health outcomes refuse to decline. The National Health Policy of 1983 and the National Health Policy of 2002 did their job well, in guiding the way for the health sector in the Five- Year Plans and for different schemes (for centrally sponsored, state-sponsored & PPP) to address the context-specific health challenges (mainly communicable diseases, water-borne diseases) at that time. Now after more than a decade since the last health policy released, the context has changed precisely because the Health preferences and priorities are changing (NHP, 2017). These chronic diseases are held responsible for more than Sixty per cent of all global deaths (WHO, 2017).

The differential approach in health policy

Currently, the national health programmes in India offers universal coverage account for not more than ten per cent of all mortalities and about fifteen per cent of all morbidities (NHP, 2017). Most of well- structured established national programmers' are in only selected few communicable diseases like National TB control program, National Vector Borne Diseases control programme, AIDS control program etc. while over seventy-five per cent of communicable diseases are not part of any existing national health programmes in India. The contribution of communicable diseases in the entire disease burden is only twenty-four per cent. Non-communicable diseases now make the biggest chunk of the country's disease burden accounting for fifty-three per cent of death in the country (WHO Global status of NCD, 2014).

The communicable and non-communicable disease dichotomy is problematic from a public health management perspective, as the strategies for disease management, the resources, institutions and approaches are entirely different. In this era of health transition, the challenges become more evident when disease possessing not only co-morbidity but also multi-morbidity (Oni, 2015). A person with diabetes or hypertension (non-communicable disease) can possess multiple complications such as TB, HIV (communicable disease), heart and cardiovascular diseases at the same time. Jena (2018) observe the causes of diabetes, public health issues related to it and national level disease burden as well as technical capacity to deal with the increasing cases of diabetes. The authors argue that a multi-level policy approach is needed to tackle the regulatory challenges in Diabetology. The inherent problem lies at the disease level leads to a pertinent question: *Does 'one size fits all' approach is suitable to address the public health problems? Or more context-specific disease management policy intervention requires.*

There is also a health policy shift from treatment approach to a preventive approach recently. Such an approach makes a clear distinction between hospitals based current care modalities in treatment approach, with prevention-oriented more personalised health services. The re-orientation of health services from the eradication of the disease to its prior management and control are due to a shift in disease pattern from acute to chronic disease problems. (Batchelor, 2015) However, there is no clear boundary between treatment and prevention approach, as both necessary for alleviating the health problem and reducing the impact.

The both preventive and treatment approach that addresses larger health problems, requires intervention at different level in the form of new drug development, diagnostics, devices, medical procedures at one hand, also utilization of existing resources in an effective way through innovative clinical practices and policy and programmes at national, regional, local and community level at other end. *How scientific research (basic as well as translational), pharmaceutical innovations, health and research institutions in India ponders on the current health crisis? Do scientific or clinical research, and their agendas drive around public health priorities, or that follows a different path or trajectory of notions? Does clinical innovation is only driven by health priorities (prevalence or incidence rate) or any factors beyond health parameters influences innovations, such as market, profit, policies(industry, health, government), infrastructure, finance?*

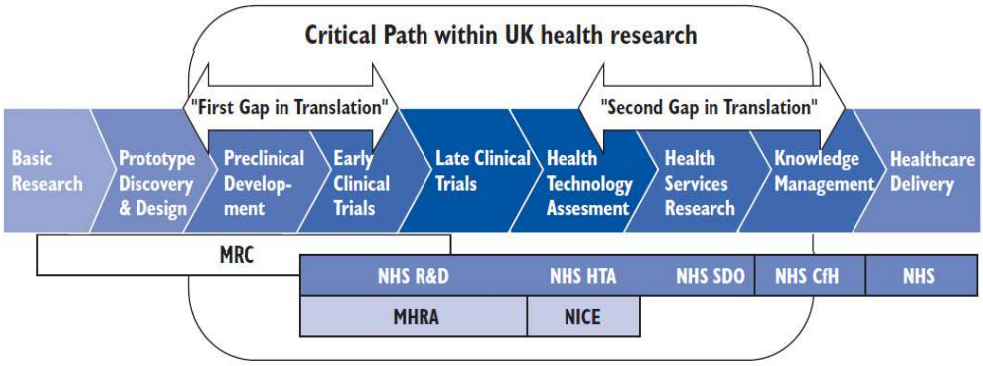
Canvassing the whole mechanism requires a co-ordinated approach from basic and applied researchers, scientists, public research organisations, clinical researcher and clinical practitioners at local community level. The current study focuses on a specific disease, to understand the dynamics through biomedical innovation system approach.

1.2 Biomedical research, innovation and translational Process

Biomedical Research is a multi-disciplinary knowledge field where the objective is to understand the physical, chemical, functional mechanism of a disease and find solutions to cure the disease (National Library of Medicine, 2019). The research field consists of three major division basic, applied and clinical research with different objectives and set-ups to serve a common goal (to cure diseases). Basic research is the laboratory research that gathers fundamental knowledge; applied research harness knowledge from basic research to develop the product, artefact or process (drug, device or surgical process) and clinical research execute the products or process in the clinical setup for treatment purpose. The *translational*

process is the interface between basic and clinical research, the process known as 'bench-to-bed' from laboratory research to clinical setup (Woolf, 2008). The translation process is the connecting link between the three core knowledge fields of biomedical research. The most challenging part of the process is the transfer of knowledge from one core field to another. In the current regimes, translational research is current policy focus, a mechanism to evaluate scientific progress of a system. **Figure 1** gives a schematic representation of the translational process and challenges.

Figure 1: Translational Process: Path from basic research to deliverable product



(Source: Cooksey report research pathway – Douet et al. 2010)

Biomedical innovation is the integration of modern biotechnological processes in traditional pharmaceutical innovation that integrates for the development of products (Ramani, 2002). The modern biotechnological process includes laboratory-based stem cell research, nanotechnology, system biology, generic engineering, recombinant DNA technologies and other platform-based technologies have driven innovation in medicine and biology (OECD, 2016). The biomedical innovation is a complex, multiphase, multidirectional innovation process that integrated laboratory research, translational and clinical research to develop a product. Biomedical innovation is not one, but much diverse innovation such as drug development, devices and diagnostic innovations, medical-surgical procedures; those have a *unique path of translation* and trajectory of development.

1.3 System approach to Innovation:

Due to this inter-disciplinary, complex nature of knowledge production and diffusion in biomedical Innovation and translational processes, a system approach is necessary for identification and to understand the complex dynamics among innovation actors, institutions and organisations.

A systems approach to innovation has bagged a high-flying position in academic literature. An innovation system conceptualises in different analytical levels such as the National Innovation System (NIS), Sectoral System of Innovation (SSI) and Technological Innovation System (TIS). All system approach has similar structural components consist of actors, organisations and institutions, but different in approach. Over the period the system boundaries became analytical problems, hence system approach shift towards context-specific innovation (Carlsson 2002, Mina,2007), where system boundaries draw around two elements ***Context*** *and* ***Purpose*** of the research.

Biomedical innovation process involves high-tech scientific knowledge field such as biotechnology, molecular biology, nanotechnology, diagnostic and system biology. The USA and other developed countries (mostly Germany and UK) are global leaders in the biomedical innovation, where India and china are a technological follower or catch-up countries. In the technological innovation process, *the nature of knowledge is always Global.* Technological innovation system focuses on *knowledge base* rather *system boundaries. The functions of innovation are more important than the structure in TIS.* The current study took the Technological Innovation System approach to understand biomedical innovation process around the knowledge field of Diabetology in India. The rationale behind choosing the TIS and Knowledge field are mention in detail in the following chapters.

1.4 Statement of the Research problem

There is limited empirical literature available in the domain of biomedical innovation in India. The innovation scholars took sectoral approaches to understand the sector-specific issues and capabilities in the pharmaceutical and biotechnology sectors in India. India has not been able to cope up with the innovation capabilities in the modern emerging biomedical innovations field like regenerative medicines, stem cell research, RNA interference despite prowess in pharmaceutical and process engineering (Chaturvedi, 2007). In BIS, the capabilities of systems vary as the innovation process involves several disciplines that follow the different trajectory of the development process for healthcare, biotechnologies, in-vitro diagnosis, pharmaceutical innovation (Lander and Thorsteinsdotttir, 2011). There are other sector-specific innovation studies in the emerging areas of biomedical research such as nanotechnology, generic engineering, stem cells technology (Abrol, Prajapati, & Singh, 2011; Kumar & Desai, 2014; Tiwari & Desai, 2011) addressing, mapping and identifying capabilities problem in the specific area of knowledge field.

The sectoral approach is a more homogenous mixture of actor and an organisation in biomedical sectors that is not best suited to capture the larger picture of the complex nature of interactions in the whole biomedical innovation process. The translational process lies in the intersection of different stages and sectors. The sectoral approach is unable to give the impetus to the translational research problem that mostly lies in the intersectoral space.

There are few studies which identify the inter-sectoral transitional problem from basic research to translational research. Visalakshi, 2009 identifies problems associated with the commercialisation process in the biotechnology sector and reasons for failures in the commercialisation of biomedical innovation in India. Similarly, Acharya (2013) identified challenges related to biotechnology incubation centres (startup) in India. However, the approaches are limited to specific activities.

The sector-specific approach overlooks the internal dynamics within the biotech or pharma sector, where certain diseases enjoy preferential treatment over others due to many external factors going well beyond the prevalence rate, incidences, affected population etc. Some innovation scholar studies the dynamics of Type I, II, III disease. Chaturvedi, (2004) suggested that the paucity of Innovation in neglected diseases in India can address with a push-pull mechanism to tackle twin problems of lack of innovation and lack of access in India.

The scientific and innovation studies in biomedical research emphasised in the innovation in pharmaceutical industries, science- and a translational base such as research organisation, university and industries actors (firms and CROs). However, innovation studies have not given enough attention to the role of hospital and clinical practice in the innovation process. In biomedical innovation, clinical knowledge is core to the innovation process, but we were unable to find any innovation studies in India that address the complex dynamics of medical innovation the knowledge formation, development and diffusion.

In the biomedical innovation process feedback mechanism, a continuous interaction among different disciplines and profession requires for the developing innovation capabilities. Clinical practices help in reducing the uncertainty of medical innovations through the legitimisation of product or process (Gelijns 1998); it also contributes to new knowledge related to the user- problem. Post innovation improvement is a well-built and sturdy indicator of the process of gathering of medical knowledge, its course of motion over the period in search of better solutions to a clinical problem. (Metcalfe, 2005). Organisational learning and practising communities are two important components for the growth of new knowledge in the biomedical innovation process (Brown and Duguid, 1991) There is an absence of linkages between hospital/ clinician with science or translational based biomedical community in India (Lele, 2005).

In the preceding context, the study will focus on comprehending the dynamics of the innovation process and the trajectory of the development process from the basic research stage, applied research, clinical trial and clinical practices. While focusing on a specific disease as a knowledge field, the study will consider both drug and device innovations process in a particular knowledge field.

1.5 Objective:

The main objective of the thesis is to understand the biomedical innovation process through translational research (bench to bed) in India. The study emphasised on how basic research translates from one stage to another stage to form a useful product. Further, the translational process is difficult to execute; hence, the thesis also emphasis on identifying the challenges in translational process and evidence of successful translational research in India.

The biomedical innovation is a complex, multi-phase process hence the study takes a systematic approach to identify the structure of biomedical innovation in India and analyse functions from Technological Innovation System perspective using a knowledge field (Diabetology) as a unit of analysis. The rationale behind taking a disease as a knowledge field is to understand innovation and translation process for drug development, diagnostic and device innovations that address the particular societal problem (to cure diabetes)

We raise the detailed research questions at the end of chapter two after review the theoretical and empirical literature and present an overview of biomedical innovation and translational research process.

1.5 Outline of the thesis

Chapter 1- Introduction: The first chapter describes the central issues of the thesis gives an introductory idea of the biomedical innovation system and translational research in India. The chapter also gives a glimpse of the system approach to innovation and the rationale behind the use of TIS as a framework in this study. This chapter outlines the statement of the research problem and research objective of this study.

Chapter 2 Theoretical Perspective and Review of Literatures: This chapter provides an extensive review of the theoretical perspective on the systems of innovation. The review the empirical literature focuses on the biomedical innovation process & translational research. This chapter further explores the context-specific challenges to biomedical innovation in India. The research questions for this study are drawn from the theoretical and empirical literature review.

Chapter 3 Analytical Framework and Methodology: This chapter provides an analytical framework for analysing both the structure and the functions of innovation. The second section describes the methodology and different methods that have been used at various stages to identify and analyse the structure and function of the biomedical innovation system in India.

Chapter 4 Diabetology as Knowledge field: Global perspective: This chapter is a prologue to the analysis chapter on biomedical innovation system in India. The knowledge formation in the technological system is often global. The chapter conceptualises Diabetology as a knowledge field and describes the origin, evolution of technological knowledge and different technological factors in this field

Chapter 5 Biomedical Innovation System in India- I *(TIS Structure and Functions in Diabetology)*: This chapter provides the structure and function of innovation in the knowledge field of Diabetology in India using TIS framework.

Chapter 6 Biomedical Innovation System in India- II *(Clinical trials, clinical practices, policies & programmes)*: Clinical Trial is the fulcrum to any biomedical research holds a critical position in between the laboratory research and final product that can be useful for the humanity. This chapter also focuses on evidence-based research, clinical trials and evidence-based public policy formulation, the role of funding agencies, policy institutes.

Chapter 7 Issues & Challenges in Translational research: This chapter identifies issues and challenges at basic research, applied research, clinical research and translational research, problems in the market, clinical practices and public policy level. This chapter is also identifying challenges related to key innovation indicators such as research financing, research infrastructures, human resources, policy, guidance problems. This chapter identifies successful translational products and artefacts that developed in the Indian biomedical innovation eco-system, also the product at various stages of development.

Chapter 8 Conclusion: This chapter discusses the concluding remarks, limitation and future scope of this study.

CHAPTER TWO

THEORETICAL PERSPECTIVE AND REVIEW OF LITERATURES

2.1 Introduction

This chapter provides an extensive review of the theoretical perspective on the systems of innovation and the context-specific issues and challenges related to the development of biomedical innovation system in India. The theoretical literature gives an impetus to the system of innovation framework, analytical problems associated with different innovation systems and how context-specific innovation helps in resolving the issues of system boundaries. In building a context-specific innovation system, where a disease is a unit of analysis, how technological innovation system is relevant and appropriate for this purposed study.

Biomedical Research is conducted to increase fundamental knowledge and understanding of the physical, chemical and functional mechanisms of human life processes and diseases.'(National Library of Medicine, 2019) The endpoint of biomedical research is to generate new knowledge in understanding and solving the human problem (disease). A context-specific innovation system constructs for problem-solving, where a system builds around a specific problem sequence. Here, in biomedical innovation, the sequence of the problem is a disease. The core knowledge field of biomedical research evolved around the understanding of the physiological and functional mechanism of a disease.

The review of empirical literature focuses on the biomedical research, biomedical innovation process, translational research, relevance of translational research in biomedical innovation, the role of basic sciences, translational research, clinical trials, and clinical practices in biomedical innovation. This chapter further explores the context-specific challenges to biomedical innovation system in India.

The research questions for this study are drawn from the theoretical and empirical literatures are mentioned at the end of this chapter.

2.2 System approach to Innovation:

Biomedical research is a complex multidisciplinary process of innovation. There are three major knowledge bases in the system, apparently known as science base, translational base and clinical bases. The innovation eco-system for all three bases has different objectives and involves a complex network of actor and institutions to serve a different purpose. Translational research is an instrument connecting these knowledge bases *(bench to bed).*

Due to this interdisciplinary nature of knowledge production and diffusion, *System approaches*[1] is inevitable for identification of innovation actor, institutions and organisation. The innovation system are not confirmed to the R&D system in laboratories, but ranges of other economic, social, political factors influence the system. The identification of barriers, the process that hinders or enhance or influence biomedical research at different stages of innovation process also an important objective of this study, hence a System approach will be most suitable for this study. System of innovation is larger than R&D system; it includes a system of technological diffusion and how institutions and similar factors influence both.

A systems approach to innovation has taken a prominent position in the academic literature over the year. Policymakers across the globe influence by the innovation system approach and use innovation indicator to access and evaluate policies and programmes. Over the time innovation system has been conceptualised in different analytical level, most prominent among them are National systems of innovation (Freeman, 1987; Nelson, 1992), Regional innovation system (Asheim and Isaksen, 1997; Cooke et al., 1997), Sectoral systems of Innovation (Malerba, 2002), Technological innovation systems (Carlsson and Stankiewicz, 1991; Bergek et al., 2008,) and socio-technical innovation (Bijker, 1995; Geels, 2004). There are some structural elements in system approaches such as Actors, organisation and institutions are common to all different forms of the innovation system.[2]

[1] A set of complexes of different elements and components when come together in an order where each component is affected by the felicitation or challenges of each another, is called a 'system'. Here the whole complex works collectively, with some practical and clearly stated functions. The system concept by its very name suggests that it is a structure of various actors that collectively perform a critical role in shaping and sizing innovation performance. (Nelson& Rosenberg, 1993;5-6)

[2] Organisations' and 'Institutions' form the core of the innovation system framework. Among them the organizations are those formal structures which are created with full awareness to serve some explicit purposes. They are known as Player/Actors, while 'Institutions' are sets of commonalities such as norms, habits, established practices, rules or laws that provide the framework under which the interactions and exchanges between individuals, groups and organizations occur. 'Institutions 'are the rules of the game. *(System of innovation: Terminologies) in Edquist C. (2006)*

Earlier innovation framework such as NIS, RIS and LIS are on physical or geographical division. In the late 1980s, a new perspective on innovation framework National Innovation System (NIS) emerged in STI literature with the seminal contribution of scholars like Freeman (1987), Lundvall (1992), Nelson (1992). NIS is a set of distinct institutions which jointly and individually contribute to the development and diffusion of new technologies, provides the framework within which governments implement policies to influence the innovation process (Metcalfe, 1995). It is a system of interconnected institutions to create, store and transfer the knowledge, skills and artefacts which define new technologies. In Lundvall's word in the national innovation system, the elements and relationships interact in the production, diffusion process contributes to the new or existing knowledge field or economic use rooted inside the borders of a nation-state. (Lundvall, 1992). The element of nationality is fundamental to this system that influences technological policy. Based on the same notion of spatial or geographical division *Regional Innovation System* and *Local Innovation System* are developed.

On contrast to spatial based classification, Malerba's (1997) SIS system approach is based on sectoral classification[3]. The system composed of a set of agents carrying out market and non-market interactions for the creation, development and diffusion of new sectoral products. These agents are individuals and organisations at various levels of aggregation, with specific learning processes, competencies, structure, beliefs and goals. Their interaction is shaped by institutions in the sectors and interconnected through the processes of communication, exchange, cooperation, competition and command. The sectoral system approach is built upon three main components such as *knowledge and technology, actors and networks & institutions* (Malerba 2002). The sectoral approach may have similarity in structure regarding actors or institutions, but the rate of innovation and the process of organisation activities greatly differs across the sector. Similar to the notion of Sectoral approach, Technological Innovation System has set of major element that includes *technologies, actors, networks and institutions*, which actively contribute to the development of a particular technological field or areas of knowledge production or a particular technology (e.g. a specific technical knowledge field or a product and its applications) (Bergek 2008). The

An actor is a participant in an action or process. e.g.: employers are key actors within industrial relations, executive decision-makers, politicians and bureaucrat, are the key actors in policy formation. Doctors, clinician, patients, paramedics, researchers are key actors in health sector.

[3] A sector is defined as an area of activities where the innovation actions are unified and determined by related product categories for a given or promising demand; which happen to have and share the same basic knowledge.

innovation eco-system of a particular technological policy is not aligned from the national focus of other policies, laws and regulations which condition the innovative environment. Hence each innovation system has commonalities in the form of structure such as actors, institutions their interactions; however, different in terms of their approaches. *More details information about technological innovation framework is given later in this chapter.*

Irrespective of different approaches, the innovation framework has some commonalities and sets around some basic principles' i*nnovation and learning* at the centre of system approach. The systems approach is *holistic and interdisciplinary* consider economic factors along with institutional, organisational, social and political factors in the system that influence innovation study.

Historical perspective is important to study innovation. The time lag between a technical invention and its transformation into an important economic innovation and its widespread diffusion is long and time- consuming process. Systems of innovation as a whole cumulatively develop over time and accumulate of knowledge and skill. These elements capture the co-evolution of knowledge, innovations, organisations and institutions. Although NIS, RIS has no mention of historical perspective, TIS takes historical conation via evolutionary theory. History matters in the process of innovation due to path dependency. The historical process is not just for the innovation process but also the organisations and institutions. The reason for evolutionary approaches in TS is its *'ability to bring within the single conceptual framework the institutional and organisational as well as the cognitive/cultural aspects of social and economic change'* (Carlsson, 1995). All innovation scholars agree that technological changes are an evolutionary process. Systems of innovation approach compatible with evolutionary theories of innovation and share a close affinity between them. Systems of innovation as a whole cumulatively develop over time and accumulate of knowledge and skill. These elements capture the co-evolution of knowledge, innovations, organisations and institutions.

The most striking characteristics of the system of innovation are giving prime importance to the 'role of Institution'. The network of institutions (freeman), the institutional setup (Lundvall), importance of institutions and mechanism of supporting technical innovation, (Nelson, Rosenberg) institutional infrastructures (Carlsson). In the Technological System, the role of institutions is described in details the institutional infrastructures are four-part:

industrial R&D, academic infrastructure, other institutions and state policy. (Carlsson, 1992)

System of innovation approach is a '*conceptual framework*' rather a formal or established theory. (Edquist book pg2). But system approach to innovation is developed with the contribution of different theories such as interactive learning theories and evolutionary theories. There are no mentions of evolutionary theory is the national innovation system. But Carlsson approach in TS is based on an evolutionary perspective. System of innovation approach can be supranational, national, sub-national (regional/local) and at the same time sectoral and technological within their geographical demarcations.

Problems of System Boundaries

In the era of Liberalization, Privatization and globalisation, with the advent of Multi-National Corporations (MNCs) the system approach of innovation system took a grand leap by transcending national boundaries. Similarly, with the increased importance of interdisciplinary and transdisciplinary studies, emergences of biotechnology, nano-sciences, an amalgamation of different techniques, national, sectoral or technological system approach became inadequate to canvass the larger picture. The various author studied the openness of NIS, mostly in developed countries, to address the impact of globalisation in the innovation system (Niosi and Bellon, 1994, 1996; Bartholomew,1997). Innovation indicators/ parameters such as R&D investment of MNCs, International collaborations, cross-boundary technical alliances, international trades, international flow of scientific and technical personnel, FDI were developed to measure the degree of openness of the system.(Carlsson, 2006; Desai, 2008, Niosi and Bellon, 1994, 1996; Bartholomew, 1997)

There is large-scale variation in the degree of internationalisation. Not all innovation activities are internationalised. Explicit studies on the process of internationalisation show that skills, know-how, basic R&D activities are less internationalised than all other corporate activity. R&D still preferable at home is strongly influenced by the national innovation system. The country-specific factors such as the quality of basic research, workforce skills, finance system, education, training, corporate governance, local inducement mechanisms, abundant raw materials, the price of labour, private investment, public procurement, technological competitiveness of firms, governmental policies are building block on any NIS that give impetus to internationalize their activities. From the developing countries perspective (technological follower countries), country-specific law, learning and innovation

capacity, capabilities of local cluster determine the integration of translational corporation in the local system. (Mytelka, 2000).

Most of S&T resources in terms of R&D funding, S&T human resources, scientific publications, IPR, Laboratories and equipment, research institutions and top universities are concentrated in developed countries. There are other developing countries with advanced S&T infrastructure, and then the resources start tapering towards most of the developing countries having a significant share of the world population. Various collaborating partners (or unequal partner) in different system approaches interact within the given structure of ISI while the institutions play a crucial role in the transformation process. Internationalisation process is influenced by the NSI of both host national and destination country. The above interpretation shows the innovation, and its internationalisation process is a two-way process, where NSI and ISI interacts, overlaps, compliments and interdependent. But the directions of flow of innovation process from NSI to ISI or vice versa are solely dependent on the *context of innovation.*

The interdependence of NIS with the global system depends upon the character of the national system. Bartholomew (1997) in her study on biotechnology sectors of different countries such as the United States, United Kingdom, Japan and Germany argued that the "particular characteristics of national systems of biotechnology innovation form the basis for complex interdependence within the global system, through international technological cooperation and the cross border adoption and adaptation of institutional forms and practices. She concluded that tapping into foreign innovation systems through international cooperative alliances gives firms access to a wider range of solutions to technological problems. Forming cross-border alliances thus may be one of the most important means for firms to enhance their innovation capability in biotechnology. Internationalisation was aimed primarily at the wider exploitation in foreign markets of the basic competence they had already established at home. R&D activities were internationalised only to a limited extent and mostly oriented to adapting products to each market. In the 1990s, the rate of technological change speeded up, and it became increasingly difficult for firms to diversify their technology base at a sufficient pace. Firms began increasingly to rely on international networks to exploit the competence of foreign centres of excellence. A newly emerging complimentarily between competence accumulation and the diversification and internationalisation of corporate technology has emerged. (Cantwell,1997).Technological competition has increasingly become global in

scope, and related technology life cycles have shortened; firms have correctly responded to this new order by implementing multifaceted innovation strategies that reflect a new philosophy about the interdependence of competing firms. Speed in innovation is increasingly becoming the strategic benchmark upon which competitive survival are benchmarked. Hence, firms are partnering with other firms, organisations and institutions to survive and are thus trading off a loss in appropriability for timing". *Internationalisation process creates the analytical problem of defining system boundaries in Innovation framework. An innovation system can be national, regional, sectoral or supranational. (pg 11)*

System boundaries are treated as analytical problems rather theoretical one. System boundaries are context-driven and solely depend upon the research interest of analyst and objective of research.

Carlasson (2002) identified three major analytical problems in innovation system framework. First is the level of analysis, what is the focus of research a technology, product or clusters of activities or firms etc. The geographical boundaries depend on the unit of analysis. The second issue is determining the population and what relation or network or interaction to capture. Even a unit of analysis requires sets of population for analysis. System boundaries depends whether the population requires NIS, SIS, or RIS. The third issue is the method of measuring system performance. The context is important; what to measure, how to measure, rather focusing on component.

The complexity of biomedical innovation system due to involvement of different actors, institutions and organizations at different stages of translational research hinder framing the appropriate innovation framework for the study. To overcome this analytical problem in this study of innovation system we follow the framework purposed by Mina (2007). The study by Mina (2007) focuses on growth of medical knowledge its emergence, evolution and transformation while studying particular technology of PCTA that emerges in ophthalmology.

The author arguments are based on two major propositions. First, the innovation processes are systemic with involvement of multiple actors for specific context. Systems are not natural rather depends on the purpose and functions; hence actor can not only resides in the national boundaries. The second and most important argument made by the author is *'The purpose of the constructions of an innovation system is to solve a problem. The idea of problem sequence is the central concept or focal point to build an innovation framework'*. Innovation are not unique rather events of trajectory of improved sequences in the development of knowledge.

Irrespective of different system approaches, the system boundaries and level of innovation depends on two elements, i.e., ***Context*** and ***purpose*** of research. The focal point of this study is to study the biomedical innovation system in India through translational research. Biomedical innovation involves both drug development and diagnostic innovation. As practically it is impossible to study all the facets of biomedical innovation in a single study, a disease is taken as a unit of analysis. In the present study, the problem sequence is (diabetes), or knowledge field (Diabetology) and the innovation system is drawn around the problem sequences. All the drug development and diagnostic innovation in the area of Diabetology are under investigation in this study.

The preliminary focus is to find the action, institution at the national level but ignoring the international dimension or influences on a national system with undermining the context and purpose of this study. Innovative actors are rarely acting alone and depend upon the interactive processes of collaborations with and interdependence on the market organisation such as a supplier. The study required a System approach to innovation; the final analysis is done using the TIS framework. The rationale behind choosing TIS as a framework for this study discussed later in this chapter.

2.3 Relevance of TIS as the framework:

Biomedical research is a multiphase- complex innovation process where actors, organisations and institutions innovated in different innovation ecosystem with different objectives and purpose. The interactions are not just interdisciplinary in natures but cross institutional barriers. For that reason, boundary setting is problematic in BIS. The Science-based, Translational base and Clinical research and practice require constant feedback mechanism at multiple points to develop a product or artefact, a linear model of innovation are not suitable to capture innovation.

BIS involves high-end technological innovations in the field of biotechnology, nanotechnology, molecular biology, system biology, mechanical or chemical engineering for the development of drug, devices, diagnostic tool. Here, *technology is global*. The technologies are developed at a foreign nation (USA) and the knowledge transfers to technological follower countries at a later period. Hence, setting a spatial boundary around BIS is not appropriate, so NIS is ruled out for this reason.

TIS and SIS have similarities in structure and approach, where both give prime importance to the knowledge base, over the spatial boundary. But the perspective offered by SIS is different from TIS. While the concept of TIS look at networks of vertically as well as horizontally connected agents and organisations engaged in the development of specific technologies, the concept of SIS focuses on competitive relationships among firms by explicitly considering the role of selection environment. SIS works in a relatively homogeneous environment, consider the dynamic process of competition within a population of firms and products.

On the contrary, the concept of TIS is more technological specifics; industry and firms are not the only important element in the innovation process considered. It takes the evolutionary perspective to understand the source of knowledge and diffusion of knowledge. For biomedical innovation, knowledge formation and diffusion occurs at different stages. For Diabetology, The knowledge formation occurs at the clinical level, not at a firm or university level. The role of the hospital, university, firms are interlinked in the knowledge process.

TIS give prior importance to functions of innovation, rather the structure of innovation. The priority is on the context of analysis, rather setting system boundaries[4]. Further, TIS is a suitable framework for comparison and analysis of various components such as actors, organization, institutions not just the structure but how good or bad they functions in a particular system. TIS is an important policy instrument due to its capabilities in identifying blockage mechanism in a system, hence contribute to the policy argumentation in a specific sectors. Due to all these advantages and looking at the broader perspective of complex biomedical innovation and translational process, the TIS system approach is the most suitable framework for this study.

The objective of this study is to understand the biomedical innovation process from a system perspective. As the natures of innovation in biomedical research are multi-disciplinary or trans-disciplinary, biomedical innovations are often global, there is an analytical dilemma in picking the appropriate framework for this study. The purpose study is more interested in the biomedical innovation process, translational process; hence, the fundamental approach is to give prior importance to the functional of innovations over the structures of innovation.

Finally, ***Technological Innovation System framework*** *is being chosen for to address the issues of the biomedical innovation system and translational research in India. The following section an explicit study focus structure and functions of TIS, and rationale behind the TIS approach for this present study.*

[4] **Boundary setting in Technological System:** Nation-state constitutes natural boundary of many TIS, some time the same is done by regional or local technological system, although in most cases technological systems are international even **global**, extending well beyond any national or regional boundaries. Here, boundaries are drawn based on the state of affairs e;g the technological and market necessities, capabilities of various agents, degrees of interdependence and structure of interactions among agents are the factors to be contemplated before setting up the boundaries (Carlsson and Stankiewicz,1995:49)

2.4 Technological Innovation System framework:

The 'technological innovation systems' took a prominent position in the innovation literature and became a popular framework among researcher and policymakers in recent years. The term "technological innovation systems" was introduced in the innovation literature during 2008 (Hekkert, 2007); however, they are many publications under the notion of 'technological systems' exist since 1991(Markard, 2015).[5] The *'technological system'*[6] term was introduced by *Carlsson* that emphasis on specific technological field and its development, however, the approach of analysis was based on Sectoral System of Innovation rather National Innovation System. (Carlsson,1995).

The technological innovation system is a concept developed within the scientific field of innovation studies which serves to explain the nature and rate of technological change. It focuses on understanding the dynamics of an innovation system centred around a specific technology. However, the approach to technology can vary depending on the level of analysis. There are at least three levels of analysis to define technology in TIS. The three approaches are: '*technology in the sense of a knowledge field, a technology as a product or an artefact, or a set of related products and artefacts aimed at satisfying a particular (societal) function' (Jacobsson, 2000).*[7]The choice/ approach dictate what actors, networks and institutions will include in the innovation framework.

[5] A similar terminology *'large technical system'* used by Thomas Hughes in 1983 but the connotation has substantial difference from Carlsson's technological system. Hughes emphasized more on technological complementarities and interdependencies

[6] Technological System is defined as '*a network of agents interacting in a specific technological area under a particular institutional infrastructure for the purpose of generating, diffusing and utilizing technology'* (Carlsson and Stankiewicz, 1991). TS incorporate three constituent elements: economic competence (ability to identify and commercially exploit new technology), networks (buyer-seller relation, industry-academia relation, various bridging institutions) and institutions (tangible and intangible).

[7] Various analysts used TIS framework in different ways and the framework extended its scope and dimension over the period of time. For example TIS framework is used to analysis a product/ groups of product in the study of wind turbine or different components of wind turbines (Bergek, and jacobsson 2003), the machine tools (Carlsson & Jacobsson,1993). TIS also being analyzed as a technological knowledge field in stem cells, 'IT in homecare' or 'Microwave technology' (Holmen & Jacobsson, 2000) as a set of allied knowledge fields (biocompatible material – Rickne, 2000). From wind turbine, the scope become broaden as renewable energies or sustainable energies as knowledge field; with respects to the approach aimed at 'fulfilling a particular (societal) function', the TIS is used in investigating why and how the sustainable (energy) technologies have developed, advanced and dispersed into a society, or have not been able to do so.

Since its inception, the framework has seen several conceptual developments, including clarification of scoping issues, a tool for performance specifications for selected TIS functions, TIS from a system building perspective, international collaboration in TIS and TIS in context-specific analysis etc. The TIS framework is constantly evolving. In particular, the approaches are often used to assess the performance of TIS, to identify shortcomings and to derive recommendations for the design of policies in support of a specific technology. (Markard, 2015)

TIS can be analysed in terms of its structural components and functional components. Structural components are similar to the other system approaches in NIS and SIS as *actors, networks and institutions.* The key *technological factors* are important elements of TIS, similar to the *knowledge base* in SSI. *'Functions of innovation systems'* are the key processes that show the dynamic relationship between the structural components (actors, networks and institutions) of the system.

2.4.1 Functions of innovation system:

Functions of innovation allow the measure performance of (emerging/ existing) innovation systems by mapping how well each function of the innovation system fulfil. Applying the function approach will help us to gain insight into the relationship between structure and performance as well as the dynamics of the system. It helps policymakers in their assessment of the (desirability of the) direction of the research and innovation and providing guidelines for additional policy measures. Due to these functional aspects, developed in recent years by various authors (Johnson 2001, Alkemade 2007, Bergek 2008) innovation approach become widely used in various sectors. One of the major reasons for the popularisation of TIS framework in recent years is an emphasis on the functional dynamics rather than the structural dynamics of the system.

In the earlier system approaches *functions* (clubbed as 'over-all functions') were known as *activities* performed by the actors or organisation in the particular innovation system. The NIS, SSI others spatial based innovation system has structural elements as *actors/organisation, institutions,* and *networks*. There are a hint of functions of innovation in those system approaches but never specifically emphasised on them. Traditional literature often uses the term *function* of a particular institution or organisation or the system as a whole. The overall functions of actors, organisations and institution were to produce, diffuse and use innovation. (Edquist,1997).

A systematic approach to functions of innovation was needed as there is no *one-to-one* relationship between actors/ organisations and functions. One function can achieve by many actors, e.g., the function knowledge production could achieve due to the contribution of multiple actors such as University, Research institutes, R&D Firms. Similarly, one actor can contribute towards many functions – University can contribute to knowledge production and diffusion at the same time to help in resource mobilisation in the form of human capital. Similarly, the role of institutions to the functions is different from actors or organisations. The relation between functions and institutions are less direct them the former.

Liu and White (2000) indicate that the fundamental weakness of NIS is *'the lack of system-level explanatory factors'* for activities. The system only mentioned overall functions of actors are creation, diffusion, distribution and use of innovation. However, there is no sub-analysis of how the activities are performed or identified at each stage. Liu and White (2000) identify five activities related to various stages of innovation process not just limited to R&D stages: *Research (basic, development, and engineering), implementation (manufacturing), end-user (customer, product or output), linkages and educations.*

Johnson (1998) provides the first systematic studies on building basic functions of innovation systems. The first function in the functional approach is to *identify the problems or bottleneck in the system.* The next function is to *develop a solution* to the identified problem, a new technology, product or new knowledge. This function is directly related to the innovation process. There are external factors that do not directly influence the innovation process but helps in promoting specific function and support innovation process are identified as *support functions*.[8] Johnson and Jacobsson (2000) emphasis on "set of functions" and suggested that a TIS or SIS can be analyzed in terms of 'functional pattern'. Ricken (2000) discusses function as an indicator of performance in TIS.

[8] Johnson describes eight support functions similar to the TIS functions. The support functions (SF) are: *SF1- supply of incentives for companies to engage in innovation work, SF2- supply resources, SF3-guide the direction of search, SF4- recognize the potential for growth, SF5- facilitate the exchange of information and knowledge, SF6-stimulate/create market, SF7- reduces social uncertainity. SF8- counteract the resistance to change*

The functional approach in the innovation studies has certain advantages. (Johnson, 1998)

1. Functions help in setting system boundaries: System boundary is an analytical problem that exists in a system approach. Through functions, System approach focuses on all components that influence an innovation system. The boundary depends on the focal point (product, technology, knowledge field) and objective of the study. Border setting is not a priori to national, regional, local, or technological, rather different levels of analysis may combine.
2. Functions can be used to evaluate the present state of the system: Functions are used to identify the problems or a situation that induces or block the innovation process, and effectively tackled through policy or strategy.
3. The functional pattern helps in studying system dynamics
4. The function allows accessing the performance of an innovation system
5. Focusing on function, actors may uncouple from what happened in an innovation system. In comparative studies, two similar structures may have different functions or two systems may function wells equally even though structures are different. *This characteristic is useful in evaluating the context-specific biomedical innovation in India where strength and weakness of the structures and functionalities of biomedical innovation varies over global structure and function. Both systems have their own strength and limitations*.

Functions of innovation have many conceptual built up and clarifications over time to strengthen the system of innovation. **Table 1** summarises the contributions of different innovation scholars for development of each function.

There are seven main functions in an innovation system, namely:

Function 1: *Entrepreneurial experimentation*

Function 2: *Knowledge development and diffusion*

Function 3: *Influences on the direction of research*

Function 4: *Market formation*

Function 5: *Development of positive externalities*

Function 6: *Legitimation*

Function 7: *Resource mobilisation*

Function 1: Entrepreneurial experimentation

Uncertainty is a fundamental feature of technological and industrial development. For an emerging technology or science-based innovation like biomedical research, uncertainties are not limited to R&D stages but for all entire stages of the innovation process from the laboratory to the market stage. In TIS, the feature of uncertainty is associated with not only at an evolution or early stage but also at a later stage (Rosenberg, 1996). The presence of active entrepreneurs is the first and prime indicator of system performance. From a social perspective, entrepreneurial experimentation helps in uncertain reduction. Lack of entrepreneurial activities in an emerging innovation system affects all other system functions. The innovation indicator that contributes to this function is the numbers of new entrant/ startups, the number of diversification activities of incumbent actors and the number of experiments with the new technology, the breadth of technologies and characteristics of complementary technologies.

Table 1: Conceptualisation of functions of innovation in TIS

Bergek et al. (2008)	Galli and Teubal (1997)	Johnson (1998, 2001) and Bergek (2002)	Rickne (2000)	Bergek and Jacobsson (2003,2007)	Edquist (2004)	Carlsson et al. (2005)	Hekkert et al. (2007)
Knowledge development and diffusion	R&D diffusion of information, knowledge and technology	Create knowledge, Facilitate info and knowledge exchange	Create human capital	Create new knowledge	Provision of R &D and competence building	Creating a knowledge base	Creation of technological knowledge
Entrepreneurial experimentation	--	Create knowledge	--	Create knowledge	Creating & changing, organizations needed (Enhance entrepreneurship)	Promoting entrepreneurial experiments	--
Influences on the direction of research	--	Identify problem, Guidance, incentives for entry, identifying growth potential	Direct technology, market and partner technological opportunities	Guide the direction of the search process	Articulation of quality requirement, provide incentives Identify obstacles	Creating incentives	Articulation of demand. prioritizing public and private sources
Market formation	--	Stimulate market formation	Create & diffuse market knowledge. Facilitate regulation	Facilitate the formation of markets	Formation of new Product markets. Articulation of quality requirements	Creating markets & appropriate market conditions	Regulation and formation of markets. Articulation of demand
Development of positive external economics	Diffusion of Knowledge and technology. Professional Coordination	Facilitate information and knowledge exchange	Enhance networking	Facilitate the creation of positive external economies	Networking	Promoting positive externalities.	Exchange of information through networks
Legitimation	Design and implementation of institutions Diffusion of scientific culture	Counteract resistance to change	Legitimize technology and firms	---	Creating/changing institutions that provide incentives or obstacles to innovation	---	Development of advocacy coalitions for processes of change
Resource mobilization	Supply of scientific and technical services	Supply resources	Facilitate finance. Create a labour Market, create and diffuse	Supply resources	Financing of innovation Incubation activities	Creating resources (financial and human capital)	Supply of resources for innovation

Sources: Adapted from Bergek, 2008

Function 2: Knowledge development and diffusion

In the innovation literature mechanism of learning or *'learning by doing'* is fundamental to the innovation process. All the systems of innovation, NIS, RIS, SIS or TIS have given prime importance to the learning. The essential function of the structural elements networks in a system is knowledge diffusion or information exchange. (Carlsson, 1991). Networking also leads to new sources of information in the form of physical, financial or intellectual capitals that stimulate the market and diffuse technologies. (Rickne, 2001) The network helps in identifying intermediary organisations. *In the present context of biomedical innovation, where the focus is on translational research this functions helps in identifying an intermediary organisation that helps in translating from one base to other (science-translational – clinical trials – clinical practice) in the process.*

In TIS, the knowledge base is mostly *global*. This function analysis how well local TIS performed in terms of knowledge base and its evolutions. In the case of the biomedical innovation system, the USA is the global leader and intellectual centre of the world. Other developed countries, mostly European countries (Germany, UK), have developed biomedical innovation capabilities which are largely built upon the support and nourishment of the scientific community and industrial base. *India is a technological follower country, and the innovation capabilities are catching-up in recent years. The global knowledge base will help in understanding the biomedical knowledge formation and its diffusion to the latecomer countries like China and India.*

Knowledge is not one thing but many things. There can be different types of knowledge related to scientific, technical, production, marketing, logistic, devices etc. In biomedical innovation process the knowledge formations occur at a different stage, although for a disease-specific innovation system, *Clinical knowledge is core to the present TIS but Scientific (laboratory) knowledge, translational knowledge, clinical trial knowledge, clinical practices knowledges are very much essential to the system.* This function captures the breadth and depth of the current knowledge base also the evolution and diffusion of knowledge over the period.

Function 3: ***Influences on the direction of research***

The function influence/guidance of the search refers to the *activities* of the innovation system, which positively affects the visibility and clarity of the specific want among the actors.

(Hekkert, 2007) There must be sufficient pressure or incentives for the organisation to perform. The indicators for measuring this function are mixtures of qualitative and quantitative indicators. Some of the indicators are *vision, expectations, beliefs in growth potential, growth occurring in TIS in other countries, changing landscapes, incentive structures, development of complementary resources, actors' perception, actors assessment of future technologies, policy, regulations, technical bottlenecks, crisis management, articulation of demand* etc. (Bergek, 2008).

The guidance of search is not solely based on the market or government influences. There is several factors, actor- organisation- institution interactions and external factors influence this function. Biomedical innovation research from the laboratory stage to market stages undergoes various stages of innovations or translational process. The levels of interactions among actors and institutions have multiple roles in influencing the direction of search.

Function 4: *Market formation*

The market is crucial for the success of TIS. For, emerging TIS when the market is not fully developed, it is difficult to identify potential customers or to access capabilities, articulation, and performance of the system. There is a high rate of uncertainty associated with emerging markets, where institutional intervention is prerequisite (Hughes, 1983)

With the development and conceptual clarities on this function over the year, the stages of market formation became visible. Market formation goes through three distinct phase; '*nursing phase'* where the scope for learning space and entrepreneurial activities is open, but in terms of market size and number of actors are limited, the next phase is *'bridging market'* where the market grew in terms of volumes and involvement of the number of actors. The final stage is *'mass-market',* which is an indicator of successful TIS.

Accessing TIS from market formation perspectives, it is important to understand from the sequence of market formation (*timing, size and type of market*) and the driving forces behind market formations. The market formation can be analysed through quantitative measurement; however, to find the driving forces behind the market formation require san in-depth understanding of knowledge formation in the TIS. In TIS markets are often global, but local markets are still strategically important to test a new concept, products and learning.

In the present context biomedical innovation system in India, *Diabetology as knowledge field* where market formation can be examined from a sectoral point of view as whole lifestyle

segment or for the individual or groups of products (drug, device, artefact in the knowledge field) etc. Different product segment involves different trajectory of the development process, and the market formation and the driving forces behind market formation may vary from product to product.

Function 5: *Legitimation*

Legitimation is a matter of social acceptance and compliance with relevant institutions. The indicator of this function is mapping the rise and growth of interested groups and their lobby actions. Advocacy, lobbying, favourable tax regimes, institutional supports create technological for new product or process. In the biomedical process, Diabetology several products specific to India requires institutional support mostly related to herbal formulations. At the global level, the history of technological advances of different diagnostic and drug required social acceptance. (SBGM, insulin, new drug delivery methods etc.)

Function 6: *Resource mobilisation*

Apart from R&D involving core innovation process, TIS requires to mobilise different resources. They are like competence/ *human capital* through educations in the entire field of knowledge scientific, technological field, entrepreneur, management and finance, *Financial capital* through seed fund, venture capital, govt and private funds and *complementary assets* like products, services and infrastructures. This function can be measured through a quantitative measure like financial data, reports of agencies and organisations and also through a qualitative measure like interview and perceptions.

Function 7: *Development of positive externalities*

This function is an indicator of overall system performance. The positive externalities are drawn from other system functions. In entrepreneurial experimentations, the new entrant or new product, artefact and technological development by established or new firms help in developing positive externalities. The functions influence the direction of search, and market formation also contributes to the positive externalities. An improved legitimacy of innovation system has a positive influence on the resource mobilisation process. Overall, positive externalities capture the strengths of other innovation functions.

2.5 Summary of theoretical literature: The present study is going to analysis the biomedical innovation system in India using TIS framework. The study restricted its knowledge base of Diabetology. However, the level of analysis in the knowledge field is quite broad. The overall aim is to satisfying particular societal function, which is prevention and treatment of disease. Hence the technological component includes sets of related products such as drug development, device and artefacts. Apart from new technological innovations, the role of clinical trials and practices are important. How effective utilisation of health services through clinical trials, practices, policy and programmes also satisfy the societal function in TIS of prevention of disease.

The study includes mapping the structure and functions of the innovation system. However, the biomedical innovation process is a multi-step process that includes actors, organisations and institution at different stages of basic, translational and clinical stages. The study involves categorisation of structural elements at each stage of the innovation process that includes actors, organisations and institutions.

There are seven functions in the TIS framework, namely knowledge development and diffusion, Entrepreneurial experimentation, Influences on the direction of research, Market formation, Legitimation, Resource mobilisation, Development of positive externalities. In TIS, the knowledge base is global. In Biomedical research, USA and other developed countries global leaders in knowledge production in Diabetology. To understand the function of knowledge development and global diffusion perspective is inevitable. Functions are indicators of how actors or group of actors, institutions contribute to the development of the particular function in TIS.

Once the structure and function of TIS is established, it is important to access the functions and structure to find out the limitations of actors, organisations or institutions and their contribution towards the functional development in TIS. Hence, the TIS framework used to identify 'blockage mechanism' to identify emerging policy issues. The innovation literature refers to problems that hinder the development of innovation systems as *systemic problems, system failures or weaknesses*. The system problems are mostly related to *presence* and *capacity related to Actors, Institutions, Interactions, and Infrastructure.* (Klein-woolthuis, 2005)

2.6 Biomedical Research

Biomedical Research is conducted to increase fundamental knowledge and understanding of the physical, chemical and functional mechanisms of human life processes and diseases.'(National Library of Medicine, 2019) The endpoint of biomedical research is to generate knowledge in understanding and solving the human problem (disease).

The core knowledge field of biomedical research evolved around the understanding of the physiological and functional mechanism of a disease. The knowledge field has three major divisions as basic research, applied research and clinical research. Each division has a set of actors, a network connecting those actors and regulatory institutions serving the common purpose. The basic research is the understanding of core physical, chemical and functional feature of human-life and disease. The knowledge field is multi-disciplinary with the contribution of biochemistry, molecular biology, genetic engineering, protein chemistry works in a laboratory set-up. The applied research field harness knowledge from basic research to develop a product, artefact or process (drug, device or surgical process) involves disciplines like toxicology, animal studies. The clinical research executes the products or process developed through basic and applied research for treatment and an overall improvement in human health care in a clinical set-up. The three different knowledge fields serve a common purpose to cure a disease.

2.7 Translational research

The translational research is the interface between basic and clinical research, the process known as 'bench-to-bed' from laboratory research to clinical setup (Woolf, 2008). However, the concept of translational is being interpreted in different ways by scholars. There are two broader consensuses among the peer defining translational research. The predominant notion that defines translation is '*effective translational of new knowledge, mechanisms and techniques generates by the advances in basic science research into new approaches for prevention, diagnosis and treatments of disease is essential for improving health.*' Translating 'research into practices' is another way of interpretive translational work that focuses on *health services* that effectively implement new knowledge into the desired population for treatment of disease. *In a way, translation research is the connecting link between the three core knowledge fields of biomedical research.*

However, the two translational part 'basic research-clinical studies' (T1) and 'clinical studies-clinical practices' (T2) are the most challenge part of the implementation. The two spheres have distinct goal, objectives and requirements. The first part deals with the expertise of applied researcher molecular biology, animal house and toxicologist, the supportive infrastructure of capital, infrastructures, and skilled human resources. The T2 challenges are more related to implementation science; evaluating the interventions in the real-world setting. The disciplinary expertise such as epidemiology, community medicine, behavioural science, public policy, finance etc. is required for evaluation of T2 challenges.

2.7.1 Significance of Translational research

The scientific discoveries and its translational process is a time-consuming exercise, and the rate of failure is very high. In drug discovery, more than eighty per cent of projects fails before human trials. Out of more than ten thousand compounds, only five reach clinical trial stages and one approved for human consumption (National Library of Medicine, 2019). Most of these new molecules never reach Phase III trial stage. The journey from basic discoveries to the therapeutic development often faces many roadblocks, not related to just laboratory research but due to lack of funds, incentives, vision and technical expertise for further advancement. The lack of resources (capital, finance, infrastructures) and support moves basic science down the path toward treatments. That translational gap has come to be called by many the "Valley of Death." (Butler, 2008) Two empirical kinds of literature focus on finding translational gaps; however, their finds are merely related to time-gap not beyond that to find out the reason for failures. It takes 17 years for only 14% scientific concept enters the market stage with a rate of 50% use in the population. 24 year is the time lag between the concept (1st appeared in the article) to a useful product (Westfall 2007).

Models for identifying translational research problems (Translational Gaps)

Translational research models are instrumental in connecting different facets of the innovation process. In the knowledge field (biomedical research), research and innovation are not one thing, but many things. The process of development is context-specific. Drug and devices take a different trajectory of the innovation process; the problems and challenges associated with them are unique to the development process.

Sung model, one of the earliest models of translational research is a two-phase framework: first phase process is the period of laboratories studies to clinical research (T1 phase), the second phase is clinical research to clinical practices (T2 phase). The significance of Sung model is the identification of *'Blocks'*. (Sung, 2003) *Blocks, in the translational research, is similar to the concepts of system problems in a technological innovation system*[9]. The significance of Sung model is the identification of barriers (translational blocks) such as lack of wiliness in participants in the development of drugs, high cost of translation, financial & regulatory burdens, fragmented infrastructures, lack of human s (qualified investigators, research), practical limitation are few to mentioned. (Sung, 2003)

Westfall model is a three-phase framework **(Figure 2).**The first phase is similar to Sung's model (basic research to clinical research), but the second phase is subdivided into two-phase. The former is from pre-clinical studies to early clinical trials[10] (Phase I & II) *(T2 stage)* and later form Phase- III&IV clinical trial stage to clinical practices *(T3 stage).* The division of T2 and T3 again indicates the diversity of actors; institutions involves in the biomedical research. The earlier phase requires the involvement of Clinical Research Organisations, Toxicologist, Translational laboratories, basic laboratories while Phase – III clinical trials involve clinician, practitioner, hospitals, clinical setup, clinical guidelines, public health policy etc. The significant contribution of Westfall model is *bi-directional* dynamic nature of the translational process. The addition of T3 phase shows the significance of *'Practice-based research'* in the biomedical innovation process.

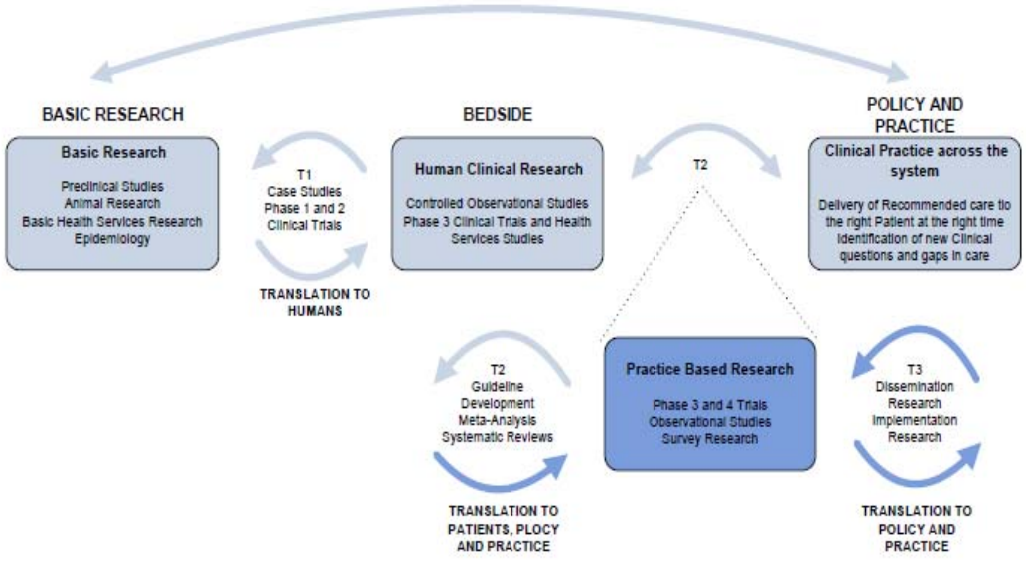
Two other translation models by Dougherty and Khoury further classified the complex process of clinical practices (Dougherty and Conway, 2008; Khoury,2007). Dougherty model, a three-phase framework, similar to the Westfall, 2007, however, the T3 stage takes the contribution of clinical practices for further to improve overall human health and population. Khoury's model is a four-phase framework, which makes a clear distinction

[9] System problems, or weakness, failures are the blockage mechanism that hinders development of innovation system in Technological Innovation System. In the process of biomedical innovation (drug or device), the translational gap are problems key elements that identifies the failure of translations from one stage to other.

[10] A new drug or a device undergoes safety, efficacy and validation process before approved as drug or device for treatment. The clinical trial phases are divided into Phase zero, I, II, III & IV, PMS. The earliest phases Zero to II are drug testing, safety, efficacy test with involvement of small sample of patients. However, Phase –III trials involve larger number of patients for comparative drug trials to measure the safety and efficacy and effectiveness of new drug with the standard treatment procedure already available for the treatment of disease.

between efficacy and effectiveness in clinical research.[11]Torchim, 2011 purposed a method for evaluation of translational process *('process maker framework')* from the basic research stage to the clinical practice and public health stages. The underline of the framework is to treat translation as a *continuous process*, not a separate knowledge field of basic, applied and clinical research field. There are many potential markers along the innovation process that can be evaluated to understand the innovation ecosystem.

Figure 2: Translational research, Different Phases of Innovation and Translational Gaps



Source: Blue highway- in NIH pathway - Westfall (2007)

[11] **Efficacy trials** in clinical setup are stated as a test to determine if a plan offers more good than harm when performed under *optimum conditions (standardized programs, homogeneous target population, controlled environment)* and **Effectiveness trials** are the tests to find out if a plan offers more good than harm when performed under *real-world conditions* (Glasgow, 2003)

2.8 Biomedical innovation

Biomedical innovation is the integration of modern biotechnological[12] processes in traditional pharmaceutical innovation that integrates for development of products (Ramani, 2002) Extreme diverse conditions underline the innovation process in biomedical innovation the traditional approach of 'one-size fits all'[13] strategy is not appropriate in the biomedical innovation process.

The first characteristic that evident in modern biomedical innovation is dependent on interdisciplinary research. The success of a biomedical product, artefact or devices requires co-operation among individuals with diverse but relevant professional background.[14] The second important observation in modern biomedical innovation process crosses institutional boundaries, highly dependent on the collaboration of knowledge base (science base) organisations with industry not only at the stages of knowledge formation but also at each stage of product development. The innovation process in biomedical research for a product or an artefact or process (from concept to final product) undergoes different stages of transformations. E.g. in biomedical innovation for drug development collaboration may or may not require at the R&D stage between university and industry. However, pre-clinical stages require collaboration with toxicologist, animal house facilities for validation of drug molecules. At this stage, a university–firm or laboratories – Clinical Research Organisations

[12] The modern biotechnological techniques are the advances in S&T in the fields of genetic engineering, rDNA technology, PCR based technology that manipulates the genetic material inside bodies and fusion of cells that was not part of traditional pharmaceutical innovation process.() The concept of modern biotechnology are drawn on two axis biotechnological products (sector) base and knowledge base. The products base includes combination of supply and demand sides, competing products, and production knowledge and demand side from the consumers. The knowledge base is the integration of knowledge, techniques and tools of different disciplines. (McKelvey,2004)

[13] Innovation is not one thing but many things. The innovation eco-system has lots of variations with in a sector and product ranges. A semi-conductor industries and aircraft industries have different approach. In pharmaceutical industry drug development and device has different approach. The sub sector in device manufacturing has diversity. Low- cost, inexpensive devices such as syringes, disposable needles to sophisticated invention of the computerized tomography (CT) scanner; the heterogeneity in products, and their research and development.

[14] Drug development process requires co-operation among molecular biologist, organic chemist, immunologist, chemical engineering etc. The interdisciplinary nature is more visible in device sector as the clinical knowledge transfers outside the medical domain to the field of engineering (physics, chemistry, material engineering, electronic, optics) and return back to the medicine discipline in a form of a product. The implementation of device may require varieties of medical specialists.

(CROs) collaboration is necessary, where two different organisations with different institutional set-up collaborate for a common purpose.

Biomedical innovation process:

The process of biomedical innovation is a complex, multiphase, multidirectional innovation method where actor, organisations, institutions involve various activities at different stages of innovation. There is the least interaction among innovation actors outside the core activities. E.g. interdisciplinary research is important characteristics in drug or device development process with the amalgamation of disciplines like organic chemistry, molecular biology, mechanical engineering, toxicology etc. However, when a device crosses the concept stages to technology developmental stages, or in drug development from applied/ translational stage to the clinical stages, the innovation crosses not only disciplinary barriers but also institutional barriers, where collaboration is critical for further development however most challenging part of medical innovation

Figure 3: Stages of Innovation in biomedical research

DEVELOPMENT STAGES FOR A NEW MEDICAL DEVICE

Idea → concept definition → proof of concept → prototype → lab validations → technology development → technology demonstration → technology integration → market lunch→clinical practices → feed-back mechanism on improvement of product

DEVELOPMENT STAGES FOR A NEW DRUG

(Steps and sub-steps in the development process)

Basic research → Translational research → Discovery of NCE/NBE → Pre-Clinical studies (Toxicological test, BA/BE,PK/PD, ADME) → Animal studies (testing of new drug candidates with different animal models: murine (rat or mice) canine (dog); higher order animal (primates) → Clinical Trials (Phase 0, Phase I, Phase II, Phase III, Phase IV) → market lunch → Post Marketing Survey (PMS) → clinical practices → feed-back mechanism on clinical efficacy and effectiveness.

Sources: Authors compilations[15]

[15] The concepts of development process for device and artifacts are taken from measuring innovation indicator-technological readiness index (DST), the drug development process (steps and sub-steps) are compiled from scientific drug development literature related to pre-clinical studies, clinical trials stages, etc. The terminology in

The problem-solving approaches in medical technology lead to some of the important inventions in medical history; those were nowhere having attached to the discipline of medicine. The application of laser in medicine, scalpels in endoscopy that further developed as minimally invasive therapy, cardiac imaging, the technology that provides echocardiography (ECG), cochlear implantation (electrical stimulation of the human ears) are the contribution of disciplines like nuclear technology, physics, mechanical engineering, electrical engineering to medicine.

The knowledge transformation and diffusion is a complex process in biomedical research, as the problem sequence travels from the discipline of medicine to another discipline then again returned in the form of products as an application for use in the treatment process. The process does not stop here, as the feedback mechanism of the performance of the device or drug creates new knowledge and new problems that help in the further development of the products.

The whole process is a non-linear model of innovation involves the constant feed-back process of improvement. This notion underlines the tone for context-specific innovation. The complex dynamism of biomedical innovation process and the application of other disciplinary knowledge (technology) in the medical field are being studied by various scholars.

Gelijns and Rosenberg (1994) observe three characteristics features of the biomedical innovation process. The knowledge exchange in biomedical innovation is bi-directional[16]. A linear model of innovation[17] is inadequate to capture the complex; the multi-phase, dynamic process involves in biomedical research. Uncertainty is an integral part of the innovation process. In most of the innovation, literature uncertainty is associated with earlier stage R&D

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the figure stands for: *New Chemical Entities (NCE), New Biological Entities (NBE), Pharmacokinetics (PK), Pharmcodynamics(PD), absorption, distribution, metabolism, and excretion (ADME)*

[16] The innovation process describes here is similar to the translational model given by Westfall in the previous section. The translational process connects all steps in biomedical research and bi-directional and relies on constant feedback mechanism.

[17] Linear model of Innovation is one of the earliest frameworks developed in STI field. According to this model basic research triggers the beginning of innovation, followed by applied research and development, finally culminating into product development and transmission. (Godin, 2005)

process or later at product development stages, related to market failure. The process of biomedical innovation from basic to applied research to product development requires constant feedback. What makes it unique about biomedical innovation is the role of *clinical practices*.

Clinical practice step in biomedical innovation is a mechanism to understand the physiological response of a new drug or devices in the human side body. The long- term clinical practices or use of the product (post-marketing drug trials) are important to understand the negative, side-effects of drugs. Clinical Practice is an important feedback mechanism to improve the innovation process. Practices not only verified a product but also create new- problems that help in incremental innovation and improving the product.

Only *open models*[18] can capture the biomedical innovation process as the inventions in biomedical at first place belongs to other disciplines. Major applications in biomedical researches such as ECG, NMR, X-ray, are a contribution from other disciplines. There can be multiple entries and exit point in the innovation process.

The third important characteristic is a complex non- linear understanding of role and dynamics of *demand* in biomedical innovation. Various factors affect the creation or introduction of new technologies. Hospital administrations, clinician, patients, insurance firms, policy and regulation influence the rate and direction of medical innovations. Policy priorities, disease burden, financial incentives, rate of diffusion of cost-reducing technologies can affect the rate and direction of the innovation process.

[18] Open innovation process is not limited by the organizational boundaries. It rather involves strategically managed sharing of knowledge and information with actors/players who are well situated outside the boundaries of an organization, with the aim of integrating their wherewithal and knowledge into the organization's own innovation initiatives. (Chesbrough 2006).

Role of clinical practices in biomedical innovation:

Gelijns (1998) elaborate on the characteristic uncertainty of medical innovations. Successful research and development puts an end to some uncertainties but opens new sets of problems because of the complexity of human limits the ability to predict the effect of a new intervention (new drug, device or a medical procedure). The emphasis was on clinical practice in the post-innovation innovation processes. Although development stages in biomedical innovation go through rigorous stages of validation and verifications, they are also a structural limitation to the innovation process. Clinical Trials are designed to test a narrow hypothesis. Randomised Controlled Trials (RCT) has a limitation in dealing with this uncertainty because the sample sizes are less, and the heterogeneity of patients limits the opportunity to find benefits of new research. Trials are often excluded many potential patients groups such as (elderly persons, pregnant women, children, and patients with complications). Clinical practice is essential to undermine the above limitations. Post innovation improvement is a strong indicator of the process of accumulation of medical knowledge, its trajectory of motion over the period in search of better solutions to clinical problems. (Metcalfe, 2005)

Clinical practices have positive effects and contribute to the development of basic and applied research. The use of laser in biomedical research is one of the biggest contributions of the field of physics/ optics, however, the effective usage, clinical implementation or complication of laser treatment for eye and skin in humans intrigues basic and applied researcher for further investigation related to the properties of light transmission, scatter, reflection, and absorption in diverse or controlled conditions.

Clinical practices broaden the scope of applications. Translational research identifies new drugs, treatment process and tracks the event from the laboratory to the bedside. The novel mechanism or mode of drug discovery, the physio-chemical treatment mechanism is intended to treat some particular clinical condition. However, clinical practitioners use the drug to treat disease with similar paths-physiological mechanisms and clinical condition. A drug for obesity can be used for control of diabetes. A drug for sleep deprivation can also be prescribed to deal with anxiety issues. The post-marketing studies or long term clinical

observations help in dealing with various complication and effective utilisation of drug in other clinical conditions.[19]

Brown and Duguid (1991) emphasised on organisational learning and communities of practice. Work practice is conservative and resistant to change; learning is distinct from working, and innovation is generally viewed as the disruptive but necessary imposition of change in practices. The ideas of working, learning, and sometimes innovating have a conflicting opinion but are interrelated and compatible. This eco-system of organisational learning is important loci for the development of new knowledge. Clinical practice offer solution to the current problems, validate the new concept and examine the new product in innovation, but the clinical practice environment also finds new problems, that acts as a feed-back mechanism for improvement of products. Consequently, scientific, technological and clinical knowledge co-evolve in which the process is embedded. The advancement of medical knowledge heavily relies on continuous feedbacks between science, technology and clinician and the nature and intensity of interaction across communities at different points in time are of great importance to the emergence, growth and transformation of medical micro-innovation systems.

[19] The antibiotics were used since 50 years, but its use in treatment of peptic ulcer is a recent discovery through clinical practices.

2.9 Biomedical Innovation in India: issues and challenges

In the case of biomedical innovation, the USA is the global leader and intellectual centre for learning and innovation. National Institute of Health (NIH), USA is the largest single funder of biomedical research in the world (Sampat,2012) Other developed countries, mostly European countries (Germany, UK) has developed biomedical innovation capabilities which are largely built upon the support and nourishment of scientific community and industrial base. Developing countries like China and India is technological follower countries are catching up with the process of developing biomedical innovation capabilities in recent years.

In India, the biomedical innovation system is embedded in the capabilities of systems under various developments for healthcare, biotechnologies, in-vitro diagnosis, pharmaceutical etc. The biomedical sector has drawn on technologies and socio/human capacities already established by the pharmaceutical and biotechnological sector that are traditionally focused on a process engineering model of innovation (Lander and Thorsteinsdotttir, 2011). The Indian health biotechnology and pharmaceutical sectors are closely linked as around 70% of all biotechnology firms are active within the pharmaceutical sector, and many of India's pharmaceutical companies have ventured into biotechnology

In spite of capabilities being developed in the pharmaceutical and biotechnological sectors post-reform period, India lacks the innovation capabilities for development of modern emerging biomedical innovations like regenerative medicines, stem cell research, RNA interference etc. (Chaturvedi, 2007). The transition is hindered by the path-dependent model of learning (reverse engineering) adopted by the generic firms with process innovation for the development of products. (Lander and Thorsteinsdottir, 2011)

In this context, Charturvedi (2007) argues to meet the specific need, challenges and demands emerging out the biomedical sector, there is a need to restructure innovation policies according to the sectoral requirement of prospective innovation chain and production system. Some of the specific suggestion includes *target-based research and innovation (a primary objective of translational research), a mechanism for providing financial support to new start-up entering biomedical sectors*. It requires a policy framework that takes account of the growing complexities of the innovation process and strengthens innovation systems at both the national and sectoral level. In the post-liberalisation period, the Indian Pharma and Bio-

pharma sectors increasingly took an interest in biomedical services such as bioinformatics, high throughput screening, contract research and manufacturing rather focuses on product development (Krishnan, 2003)

Acharya (2013) identified challenges related to biotechnology incubation centres (startup) in India. Biotech start-up companies require a very high amount of funds for R&D work compare to other startup and additional funds to establish, operationalise and stabilise the venture. The longer gestation period for commercialisation of Biotech R&D output is one of the biggest impediments for VC funding. There are also challenges in protecting IPR with limited resource and knowledge. Further, the process of licensing, commercialisation requires strategic alliances.

Thorsteinsdóttir*et al* (2007) worked on health biotechnology innovation in developing countries, has emphasised the importance of health systems to health-based innovation by demonstrating that user-producer relationships encourage developing countries to focus on local health needs. He also showed the importance of political will for biotechnology innovation and the importance of linkages between innovation actors. (Thorsteinsdóttir, Singer, &Daar, 2007).

Department of Biotechnology, GOI is nodal agencies to promote and assist translational research and help to develop the capabilities related to biomedical innovation in India. Dutz&vijayaraghvan (2012) analysed the policies and programmes on translational research of DBT. Their many policies initiatives and programmes like SIBRI, BIPP and Grand Challenge programmes are launched in the last decade. However, the capabilities are still underdeveloped. The programmes also lack impact evaluations.

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Visalaksh I (2009) has studied the commercialisation process in the biotechnology sector in India. Among the developing countries, India is one of the early investors in biotechnology. In the innovation process, commercialisation is a relatively costly and difficult phase. Some of the major reasons for failures in commercialization of biomedical innovation in India are due to the following reasons: Lack of capabilities of institutions involved in R&D beyond basic and applied research (no skill, funds or experience of up-scaling), lack of partnership between research institutes and industries, lack of reward system discourage investigators,

lack of industrial skill and production facilities, Lack of sufficiently strong patent protection discourages investment by industry in serious basic research.

NHSRC (2013) identifies barriers to the innovation care eco-system in India: lack of coordination between the different centre of knowledge, innovation and agencies at a different level of the value chain, 2. lack of synergy between basic research and prototype development, 3.poor access to access to information on technology patents and ongoing research 4. Lack of finance and organisational setup, govt rules related to procurement, audit, human resources, and innovation in the public system etc.

There has been considerable work in innovation system in different areas related to biomedical innovation such as pharmaceutical, biotechnology, agri-biotechnology and emerging technology such as nanotechnology, generic engineering, stem cells technology (Abrol, Prajapati, & Singh, 2011; Kumar & Desai, 2014; Tiwari & Desai, 2011) in India. Tiwari and Desai (2011) explore the emerging stem cell innovation system in India, where they study the role of social capital in terms of linkages for the co-evolution of technology and institutions that yet to emerge. Kumar & Desai (2014) mapped out the Indian nanotechnology innovation system and made an to identify the dominant actors, collaborative pattern and analyse the role of and interactions between the actors and institutions. Singh &Abrol (2017) explore on development of an ecosystem for innovation-making for in-vitro diagnostics (IVDs) technology for resource-poor settings in India. The literature reviews indicate that the studies are inclined to take a sector-specific approach either in a knowledge institution or firm-level analysis. The actors, organisation and interactions are more homogeneous.

There is only a few innovation literatures focuses on the understanding of complex dynamics of medical innovation the knowledge formation, development and diffusion. In biomedical innovation, clinical knowledge is core to the innovation process. Some of the innovation literature in the primary clinical care area are on ophthalmology, oncology, cardiology etc. (Metcalf *et al.,* 2000, Mina *et al.,* 2004, 2007).

2.9.1 Role of Hospital and clinical practices in the biomedical innovation process:

The scientific and innovation studies in biomedical research emphasised in the innovation in pharmaceutical industries, science- and a translational base such as research organisation, university and industries actors (firms and CROs). However, innovation studies have little focus on the role of hospital and clinical practice in the innovation process. The word innovation and the hospital do not seem incongruous. Hospital services have a particular position of social usefulness, symbolic importance (life and death), the capacity of research and innovation. Innovation in hospital is underestimated and some case unrecognised.

Djeall (2005) describes the contribution of the hospital in the innovation process is as a '*set of technological and bio-pharmacological capacity*'. The contribution can be categorised as medical innovations, a generic appellation for various types of (tangible and intangible) technological and bio-pharmacological innovations in the healthcare field.

The biomedical or bio-pharmacological innovation includes innovation related to the new medicine, new chemical entities, new biological entities. The tangible or hard medical innovations includes a technological system of providing healthcare and biological analysis of capital goods such as (MRI, Scanner), smaller groups (syringes, prosthesis), diagnostic and therapeutic equipment. The intangible or soft medical innovation includes invisible technologies, such as protocol, diagnostic, therapeutic strategies. The intangible medical innovations are related to clinical practices.

There are variations in utilisation of medical innovation by end-users. Several factors influence the use of medical innovation. Emilia (2005) identified some of the reason that influences the diffusion of new technologies is physician's understanding of the disease, physician's understanding of new technologies, patient consent, financial barriers, social characters, physician trust in the technology, political atmosphere, emotional quotient are a number of factors that influences clinical practices. [20]

In the innovation studies, much fewer attention were given to understand the interaction between biomedical innovation and clinical practices and what the factors are that influences

[20] The study was related to Breast Conserving Surgery (BCS) where the surgical skill required for the procedure is not vastly different from other, but physician understanding of disease in important.

innovations at the institutional level (Swan, 2007) The uptake rates of new clinical trial products in practices are poor. It is difficult to change the existing norms of clinical practices and convince medical practices to use a new product or new treatment methods. The problems arise due to the highly complex and iterative relationship that exists between scientific discovery and medical practices.

There is an absence of linkages between hospital/ clinician with science or translational based biomedical community in India (Lele, 2005). In the biomedical innovation process feedback mechanism, a continuous interaction among different disciplines and profession requires for the developing innovation capabilities. In India, there are both challenges and opportunities to explore biomedical innovation and its application to validate ancient medical wisdom, ayurvedic drugs using modern biotechnological techniques such as molecular biology, medical pharmacology and toxicology. The levels of interaction among different actor at different stages are limited.

2.10 Choice of knowledge field: criteria for selecting diseases

The current study is a context-specific innovation where the focal point is a problem sequence (Disease). The biomedical innovation system addresses the core problem around a particular disease. However, the choice of disease for the study is not random. The selection of a particular disease is based on the following criteria.

Types of Disease:

The dichotomy of India's healthcare system lies in its twin problems of higher prevalence and incidence rate for communicable and non- communicable diseases. The effective policy interventions and programmes in recent years somehow reduce the impact of communicable diseases, but non-communicable diseases have grown exponentially due to its demographic transitions. Along with the management at the overall healthcare system, there is a need for focusing on select diseases so that their impact can be reduced over the period.

Research and innovation activities not solely depend on the disease prevalence, rather driven by many markets and non-market factors that influence disease-specific innovation. Within the pharmaceutical sector, there is variation in approach and innovation preference for the

Type-I, Type- II and Type- III diseases.[21] The **table 2** below shows the variation in research and innovation activities in India and global level for a different type of disease. Chaturvedi (2004) suggested push-pull mechanism[22] to address the differential approach to innovation within pharmaceutical sector in India.

Table 2: Innovation indicators for different diseases

Type of Diseases	Global Patents (1)	Patents in India (2)	Global Publication (3)	Publications in India (4)	Global Clinical Trials (5)	Clinical Trials in India (6)
Type I Diabetes	85.623	2462	833,555	46,726	25,243	1580
Type II Tubercu losis	10,273	448	308,811	35,028	1,575	159
Type III Malaria	5, 842	306	115,420	16,193	1611	82

(Data Sources: 1. Patentscope-WIPO, 2. inPASS-IP India, 3&4- Scopus, 5. ICTRP & 6. CTRI)

[21] The types of diseases are the WHO classification of diseases based on the incidence rate at developed and developing countries. Type- 1 disease has prevalent in both developed and developing countries, type- 2 disease have more incidence rate developing countries and type-III disease have exclusively restricted to the under-developed or developing countries (WHO, 2012). Type I diseases receives maximum preference in terms of research and innovation in pharmaceutical sectors and least attention given to type –III disease.

[22] Push mechanism involves funding support for new drugs in type- II or type- III disease, while Pull mechanism is through eliminating R&D risk and creating demand, advance market commitment, eliminating regulatory hurdles etc.

Diabetes

In the contemporary scenario, diabetes is a major health problem in both developed and developing countries. China and India are leading countries in terms of numbers of diabetes patients in the world. There are more than 70 million diabetic patients' lives in India; every fifth diabetic in the world is an Indian. Diabetes is also associated with many complication and co-morbidities. The total global healthcare expenditure exceeds 54 billion in 2015 in the diabetes segment. (IDF, 2017)

In terms of health interventions, both communicable and non-communicable disease requires different institutional setups, management practices. Communicable diseases have disease-specific established programmes' in India (RNTCP- TB, NLEP- Leprosy, NACO-AIDS, NVBDCP- Vector-Borne diseases), while for non- communicable disease policies and programmes are in developmental stages.

There has been an incongruity between disease burden and clinical capacity/ policy measures to tackle the galloping figure of diabetes in India. Does the increased rate of diabetes imply a low amount of interventions on the part of Government or something else? Hence, the study attempts to find a solution to the problems by examining the knowledge field of *"Diabetology"***.** The select diseases include diabetes and its complication (DFU, retinopathy, neuropathy, etc.)

2.11 Summary

The empirical literature review on biomedical research, innovation and translational research shows, there is a limited number of research publications available in this emerging field in India. The approach of innovation scholars is sector-specific focusing on one or combinations of sectors like biotech, pharmaceutical, diagnostic, stem cells, nanotechnology etc. Sector-specific approaches are confined to address the sector-specific challenges; on the other hand, the entire biomedical innovation process is the combination of basic, applied and clinical research. A drug molecule, device or any artefacts goes through all the three stages before converted to a finishing product. Translational research process (bench to bed) covers the entire path of innovation. Within the pharmaceuticals or biotech sectors, the R&D priority and approaches of actors and organisations, institutions vary with a different type of disease.

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The literature review also indicates there is more focus to study firm-level innovation activities followed by science-based innovation (university, research organisation) etc. Hospitals, clinical practices and health services have a critical position in biomedical innovation but received the least attention from innovation scholar to address at the clinical level in STI studies.

The objective of this study is to analysis the biomedical innovation system in India from a translational perspective. Biomedical innovation involves innovation in both drug and device sector. The study focuses on the micro-level analysis of the entire biomedical innovation process (basic research- applied research- clinical trial – clinical practices) through the lenses of translational research (bench to bed). However, it is practically difficult to canvass whole biomedical innovation process in a single frame. Hence a disease is being taken as the unit of analysis, where Diabetology as a knowledge field and both drug and device innovation in the knowledge field being analysed.

2.12 RESEARCH QUESTIONS

Chapter Two discussed the brief theoretical perspective on TIS and review of literature on the complex process of biomedical innovation and translational research. The objective of the study is to understand the biomedical innovation process through the translational process from bench to bed.

Chapter Three will discuss the analytical framework and methodology for identifying structural component and functional elements of BIS in India. The BIS is a multidirectional, complex and multifaceted process where actors' organisations and institutions are identified at different stages of development. An obvious research question arise here is; ***what is an appropriate methodology for the identification of actors? What are the different methods followed at different stages and the rationale behinds adopting specific methods?*** We will address this question with a systematic analysis of the framework and connecting methodology with multiple methods to frame the structure and functions of TIS.

The theoretical discussions suggest that the knowledge formation in TIS is global. The USA is a pioneer in biomedical research and innovation, the knowledge transforms and diffuses to the technological follower countries like India and China at a later stage. Understanding the process of knowledge formation is important to analyse the functions of an innovation system in India. In that context, our next research question is ***how knowledge formation occurs in Diabetology globally? What are the different types of knowledge in Diabetology and how technological knowledge evolved?***

Chapter four will address this research question, through analysing technological progression in both drug development and diagnostic and device segment in Diabetology through a mixture of clinical literature and patent analysis of selected global firms.

Innovation systems at any level are not natural givens, their construction, purpose and functioning have to be explained; the idea of problem sequences is the central concept around which innovation processes are instituted. In the contemporary world, diabetes is a major epidemic *(problem)* in both developed and developing countries; India has worlds' 2nd largest pool of diabetic population; every fifth diabetic is an Indian. The innovation systems are constructed for the purpose to solve the problem. The *context* and *purpose* are two central themes of the Innovation system.

In the preceding context, the research question is; ***what is the structure of TIS in biomedical innovation system in the knowledge field of Diabetology in India?*** Biomedical innovation is a multi-stage innovation process, where actors, organisations and institutions contribute at different stages. The research question will further analysis ***who are the actors, what types of organisational set-up and institutions shapes biomedical innovation at different stages in the area of Diabetology in India?*** In an innovation system, actors, organisation and institutions contribute to the development of functions, one actor can perform multiple functions, and multiple actors can contribute to the development of single functions of innovations. Hence, from a functional approach in TIS, the research question is: ***How actors, organisation and institutions contribute to the innovation functions in shaping BIS in the knowledge field of Diabetology?***

Chapters five will address all the above research questions on the structure and function of the biomedical innovation system in India.

The literature reviews on innovation studies indicate that only few studies focus on the role of the hospital, clinical trial and practices in the biomedical innovation process. Translational research has two broader understanding of the translational process; former is related to 'basic research to clinical studies' (T1), and later one is related to 'clinical studies to clinical practices' (T2). T1 deals with novel product/ process innovation, while T2 is related to implementation science. In a resource-poor setting, effectively use of existing resources to control the epidemic/ disease contributes to the larger societal benefit is also an important translational process. Keeping in view the larger context the research question is, ***what the role of clinical practices, policy, programmers' and agencies in the management of diabetes in India is?***

Chapters Six will address the above research problem in detail.

Every innovation system has some structural and functional blockages that may have an impact on the whole innovation process. The knowledge field in BIS has three major divisions as basic research, applied research and clinical research. Each division has a set of actors, a network connecting those actors and regulatory institutions serving the common purpose to cure a disease. ***What are the systemic problems associated with all three stages of the innovation process in the Biomedical Innovation in India?*** The research question further investigates, ***what are the problems associated with the translation process from one***

stage to another? Translational research is the process known as 'bench-to-bed' from laboratory research to clinical setup. TR aims for effective translational of new knowledge, mechanisms and techniques generate by the advances in basic science research into new approaches for prevention, diagnosis and treatments of the disease are essential for improving health. From TR perspective, ***what are the different successful translational products in biomedical innovation system in India in the area of Diabetology? Their trajectory of development process and issues and challenges in involves in the innovation process for different categories of products?***

Chapter Seven will addresses both the above research questions by addressing systemic identification of problems at each stage and translational stages then identifying successful translational products in the area Diabetology in India.

CHAPTER THREE

ANALYTICAL FRAMEWORK AND METHODOLOGY

3.1 Introduction:

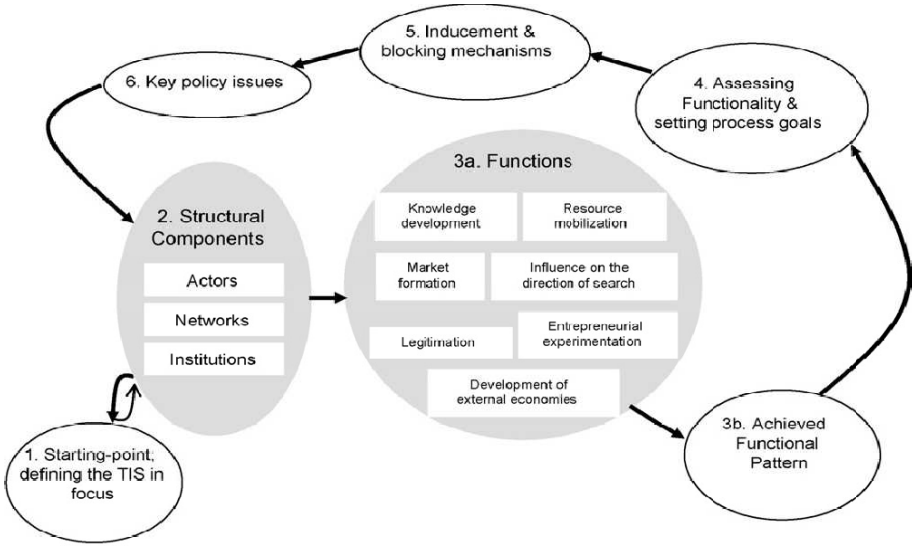
The review of literature on the theoretical underpinning of innovations from a *System* perspective, context-specific innovation (Diabetology as a knowledge field) and India specific issues and challenges indicate that the study requires a comprehensive framework for exploring the dynamics of the innovation process. In the current study of BIS, where the disease is a unit of analysis, the level of aggregation of the knowledge field is very broad. The problem sequence in the innovation system is a disease; a set of relatable products and artefacts includes both drug development and diagnostic innovation, as a diagnosis- treatment processes are an integral part in clinical practices and disease management. Hence, the study is not focused on a single artefact or product, but a set of related products to satisfy particular societal function. Each artefact, product and technology would have a different trajectory of development, diffusion and market formations. Again the process of development from basic stage to translational, clinical trial and clinical practice stage makes it a multifaceted, complex innovation system. Technologies are global. For a technology that is emerging in frontier countries, its successful catch-up by the follower countries will depend on capabilities of actors, the rate of the indigenous learning as well as the interaction of organisational, managerial and institutional aspects of the innovation process at a sectoral level. This aspects of technological assessment require a border perspective on policies, a comparative analysis of global and Indian TIS of both structural and functional elements. Since the innovation process, knowledge formation, development, diffusion, the technological trajectory of products are a highly complex and interactive process; the present study would follow a system framework to study the process of the biomedical innovation system in India.

The chapter has two major sections. This first part discusses the scheme of analysis that has been used in this study. The analytical framework gave a schematic representation on how to materialise systems function from both structural and functional point of view. The second section describes the methodology and different methods that have been used at various stages to identify and analyze the structure and function of the biomedical innovation system in India.

3.2 The scheme of analysis:

A system approach to innovation requires a basic understanding of the structure and functions of innovation in a TIS framework. The major reasons for the popularisation of TIS framework in recent years are due to a detailed subanalysis of various functions of innovations. In Hekket's word, *'scheme of analysis'* is the numerous steps and sub-steps require for the analysis of structure and functions in a TIS. The ***figure 4*** represents the detailed steps followed in this study during the operationalisation of this TIS framework.

Figure 4: The scheme of analysis



Sources: (Functions of innovation, Hekket 2008)

The system approach is a six-step; non-linear analysis process with multiple sub-steps involves numbers of iterations in between the process of analysis.

Step 1: Defining the TIS in focus

The first and foremost step in the system approach is to define the focal TIS. The outcome of TIS is depended on the context of analysis. Hekket outlined three major elements *(choices)* crucial for defining TIS. *First, choose between a knowledge field, product, a group of product or device as a focus of analysis. Second, once the focal element is decided what the breadth and depth of analysis are and at the end, what is the spatial domain of the TIS. The*

breadth of the study depends on the level of aggregation of the study. The choices made at the starting point determine the structure and function of TIS. Further, the framework is flexible enough to accommodate the scope of re-evaluation for choices throughout the analysis process.

The flexibility of choices and scope for re-evaluation are major characteristics of TIS, which makes it suitable for analysis in a context-specific innovation system. In biomedical innovation system analysis, the level of analysis might be sectoral approach (diagnostic, drug development, emerging areas of stem cell research, nanotechnology etc.), national (biomedical research in India), or technological (rDNA techniques, PCR techniques, POC devices). In the present context, where a disease is a unit of analysis, the context also varies among different diseases. E;g the structure and function of TIS will have a larger variation according to the disease pattern (type 1,2 or 3 diseases) such as diabetes, cancer, TB, malaria, or rare disease.

Step 2: Determining the structural component of TIS

Based on the focal point of TIS, the structural elements are determined. The structure of the innovation system consists of four components as *Actors, Institutions, Networks and technological factors.* Actors are organisations and individuals contribute to the development of TIS. They can be further categorised as *Knowledge institutes, educational organisations, industries, market actors, government and supportive bodies.* Institutions in an innovation framework considered as 'the rule of the game'. The *formal institutions* are the rules codified and enforces by the concerned authorities, while *informal institutions* are more tacit and organically shaped by the interaction and networking among the actors. Networks are the principal element of TIS, joins a different set of actors and institutions contributes to the development of TIS. The nature of the network, whether localised or globalised determines the strength of TIS. The last structural component technological factors investigate the technological infrastructure in a TIS, the technological trajectory of development of specific technology, the knowledge formation, diffusion and market formation due to the technological advancement.

In the present biomedical innovation system, the structure of TIS is a complex, multi-stage process includes innovation actors from science base, translational base, clinical trial base

then clinical practices and public policy actors. Hence the networking also varies within the domain knowledge base and outside between different stages of the innovation process. The actors and the network overlap at various stages of the innovation process.

Step 3: System function analysis

Functions of an innovation system are context-specific. Two different TIS might have similar structures but functions differently. Measuring innovation function is considered a big breakthrough in innovation system research. The functional pattern of TIS changes over time, space and geographical regions. The literature review chapter already covered the major functions of innovation. Functional analysis of a TIS determines by the structural component in the TIS.

The presence of new actors or new technological breakthrough by established actors determines the entrepreneurial experimentations and production of the system. The functions knowledge development, creation and diffusion, can be analysed from structural elements on the amount of patent, publications etc. Both formal and informal networks are indicators of knowledge exchange in TIS. Regulations, vision, the role of institutions, governments, international and national agency determine the direction and legitimacy of TIS. Both public and private players' determination and support to build physical resources, human resources and financial resources evaluate the function resource mobilisation.

In biomedical innovation, the above indicators are not sufficient to determine the functional characteristics; the methodological chapters' covers additional methods and indicator for assessing the functional pattern of TIS.

Step 4: Assessing the functionality of TIS

The objective of this step is to analysis functions and assesses the strength and weakness of TIS of a particular system. Step -3 indicates the entire functional pattern in a TIS framework, but unless a similar comparative model exists the evaluation is incomplete. There are two bases for assessment of functionality in TIS. First is to access *the phases of development in TIS, and the* other one is *System comparison.*

In the biomedical innovation system as a knowledge field, there is several products, artefacts, devices; drug molecules are part of the current TIS. The phases of development for all the

device or artefacts mentioned here have a different trajectory of the development process in knowledge formation, diffusion, market formation, across time and space. The challenges pertinent to the different device and drug innovation have an extremely diverse condition. Diabetology is a knowledge field will indicate multiple phases of development regards to the product and overall lifestyle segments.

The study also involves a comparison of global TIS in Diabetology with the current TIS, as technological innovation in biomedical research are global, the capabilities of indigenous actors can only be assessed through a comparative analysis with their global counterpart.

Step 5: Inducement and blockage mechanism in the TIS

In the TIS framework, the functional pattern is shaped by certain inducement and blockage mechanisms. These indicators do not always reside within a system but also affected by the external factors and influences by other sectoral issues. Bergek,2007 identified two inducement mechanisms as *Belief in growth potential* and *Government R&D Policy.* Both indicators have a positive influence on the functions of the innovation system. The *'blocking mechanism'* in the TIS framework receives large attention from innovation scholars due to its positive implication on the improvement of the system. The blocking mechanisms are the barrier to the development of functions in a TIS framework. The blockage mechanism further conceptualised as a *system problem, system weakness and system failure* mechanisms that hinder the development process in TIS due to both structural and functional barrier in the system. Klein-Woolthuis (2005) identifies system problems related to both structural and functional dimension of TIS. The system problems were related to the presence and capabilities problems in the structural elements of TIS such as *actors, institutions, interaction, and infrastructure.*

In the present TIS on biomedical innovation system, we attempt to identify the system problems in TIS and other sectoral issues that positive or negative influence on the development of current TIS.

Step 6: Key policy issues

The role of policy, programs' and interventions aims at remedying poor functionality in the relevant TIS by strengthening/ adding inducement mechanism and weakening/ removing the blocking mechanism. In the present TIS, we examine the policies and programs at different

stages, at basic research, translational research, clinical research stage, how clinical practices affect biomedical innovation positively or negatively. The policies are not exclusively for the current TIS, but many external factors have influences on the performance of TIS.

This section gives a schematic representation of analytical frameworks followed in this study of the biomedical innovation system in India using Diabetology as a knowledge field for analysis. The analytical framework provides a systemic approach to TIS framework and analysis. However, the implementation part is challenging as biomedical innovation system is a multistage process, where the structure of TIS have different actor, institutions, and networking at different stages. Similarly, analysis of functions occurs at different stages with the involvement of multiple actors and institutions. The next section gives methodology and various method used for this study for retrieving and analysis biomedical innovation system in India using TIS framework.

3. 3 METHODOLOGY

Biomedical research is both interdisciplinary and multidisciplinary, sometimes interaction does not just cross disciplinary boundaries, but it also increasingly involves the crossing of institutional boundaries. For e;g Drug development requires the expertise of various scientific fields such as molecular biology, organic chemistry, toxicology etc. at the research level. However, a potential drug candidate required association up with firms or CROs for validation and scale-up of the candidate and further development and validate through clinical trials before successful lunch as a product. Hence, the whole process involves unique sets of actors, institution and organisation at different developmental stages, along with complex interaction. These factors possess analytical problem for identification of relevant actors in biomedical research.

For a multiphase innovation system, the measurement problems are challenging as actor organisations are present at different phases. The single indicator is not sufficient to capture all actors and innovation activities. Therefore, several measures have been combined to address the magnitude and specificity of the problem. The ability of the innovativeness is assessed using various indicators such as patent data, publications & citation data, clinical trials registry data, portfolio analysis of companies, firms and organisation. Patent data was useful in delineating the major actors, mainly in firms & industries as patents suggest

commercial significance, whereas peer-reviewed article & citation analysis helped to explore the actors primarily in hospitals, a research organisation.

Identifying structural elements, actors, institutions, network and measuring functions of innovations performance in an innovation system is not a linear mechanism rather involves complex sets of indicators an analyst choose to access particular functions of innovation. Carlsson (2002) suggested it is preferable to use several indicators rather single in particular to assess the functions of innovation.

The complexity of the research problems demands the application of different methods simultaneously, as resorting to any particular method might render ineffective to address the problem of the research. Mixed methodology integrating both qualitative and quantitative analysis are the most suitable methods for addressing such research problems. (Teddlie 2009)

The use of mixed methods in health services & delivery research has increased significantly over the past decades. The use of combined methods in the larger research scheme of health-related issues appears to possess the flexibility of being fixed or emergent, as per requirement. (Bowers et al.,2013)

Rickne (2001) combined three methods in his study on biocompatible materials and related products due to the heterogeneous nature of the subject. The first step involved the identification of actors. The following steps encompass interview with the relevant actors (firms/research organisations), the interaction also helps in further identification of actors through the process of Snow-ball sampling. The final stage involves citation data analysis for broadening the range of actors and also access important inventions and contributions.

Holmén and Jacobsson (1998) methodology is an improved version of Rickne's method that supplement the snowball method with a patent-based method and citation method. The increased numbers of methods reduce the risk of the unaccounted population. Single indicators are never sufficient to identify and access innovation. Morgan's (1998) methodology involves all the above methods with complementary designs where qualitative & quantitative data were used for the analysis of preliminary & follow-up purpose simultaneously. (Teddlie &Tashakkori, 2009) Publication, patents and other scientometric studies are widely used in the operationalisation of the technological innovation system. The

indicator helps in identification of novelty, growth, impact, uncertainty and ambiguity related to the emerging system (Rotolo, 2015)

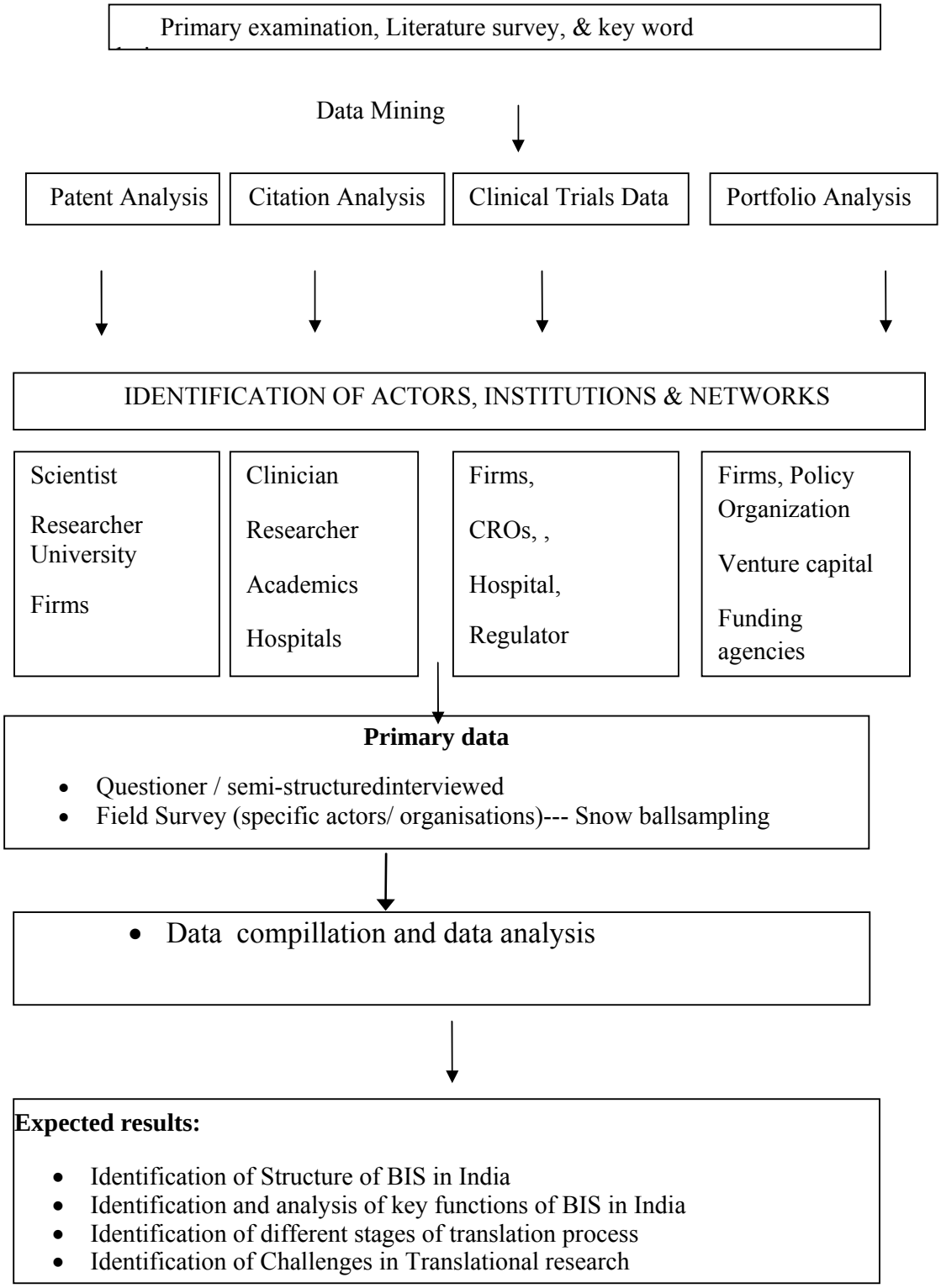
3.3.1 Identification of Actors, Institutions and Networks

The Biomedical innovation and translational research is a science-based phenomenon where a study of product development requires a great deal of time. Development of products in innovation sets in motion a complex array of the process that involves within its reach clinical trials and market delay, arising out of regulatory clearance. Thus, the diffusion process of products from the lab to the market seems to suggest a lengthy and complex course of development, which includes different actors and activity.

Many actors and institutions could be traced through these intermediate processes such as clinical trials, in-licensing, out-licensing, acquisition, collaborations etc. Companies profile, annual reports, financial reports, portfolio analysis & clinical trial databases contribute to finding out the contingent role of the different actors within the sphere of intermediate innovation activities. This study involves a combination of scientometric analysis, portfolio analysis and primary data analysis. The motives behind taking a wide range of indicators are to link and analysis both the quantitative and qualitative data.

The study also gathers information through primary data, semi-structured interview with the relevant actors and organisations identified through the scientometric studies. The interview aims to identify some subjective knowledge, including experience, perception, priorities, barriers and facilitators, finance and system problems associated with each sector. *The **figure 5** is a schematic representation of the sequence of methods and events that have been followed in this study.*

Figure 5: Identification of Actors, institutions and analysis of functions



(Source: Author's interpretation based on different methods followed in TIS)

A preliminary approach to the study:

Biomedical innovation is multi-stage innovation processes mainly consist of three knowledge domain basic research, applied research and clinical research. The study takes Diabetology as a knowledge field for the analysis purpose, where the purpose is to *satisfy a particular societal function*[23] . The choice/ approach dictate what actors, networks and institutions will be included in the innovation framework, what will be the shape, structure, and how it will function. In any medical innovation, the ultimate objective is to cure or management diseases; in this case, the disease is *Diabetes*. Managing diabetes can occur through *new drug development, diagnostic equipment, new devices, and through new scientific, clinical and technological advances, or effectively using the existing system through clinical practices, programmes, awareness drive, and community or practised based interventions*. In biomedical research, drug and device are relatable products because to cure a disease diagnosis-treatment processes both are an integral part of clinical practices. Without a diagnosis, there is no use of drugs and treatment process.

In this study, the knowledge field considers all the innovation in drug development, in diagnostics and devices, surgical procedure/ medical service innovation, in clinical trials and clinical practices related to Diabetology.

The study also aims to identify the issues and challenges in translational research, the sequence of events in the translational process *(as explained in the review of literature chapter)* helps in identifying actors (intermediary process) in different translational phases.

The methods should able to canvass the broader picture of basic, applied and clinical research along with the intermediary linking elements that can able to identify the gaps in translational research. The methodology and different methods used in this study take the broader objective of the study to identify all the actors, institutions in the biomedical innovation process from basic research to clinical practices and choose specific innovation indicators that not only just identified actor but also evaluated their performances.

[23] The study is similar toBergek (2003) where the scope broadens the approach as renewable energies or sustainable energies as knowledge field; with respects to the approach aimed at 'satisfying a particular (societal) function'. The TIS was used in investigating why and how sustainable (energy) technologies have developed and diffused into a society, or have failed to do so.

Identification of Actors, Networks & Institutions:

The study follows mix methodology, a combination of both qualitative and quantitative methods for identification of structure and function of innovations. The methodology involves a combination of four major methods mentioned below to identify actors, network and institutions. The methods are patent analysis, citation analysis, CTs data analysis and primary data through interviews. The mix methods (patents, publication and interview) are already being used in the various TIS framework for analysis (Bergek, 2004)

However, these four methods are not sufficient to address all the structural and functional elements of biomedical innovation in India. The other methods are mentioned at a different stage in their usages. The **table 3** is an indicator of major methods and their relevance to this study.

The patents, publications, clinical trials data are important innovation indicators not only useful for identification of actors and organisation but accessing and evaluating different functions of innovations.

Problems in Identification of actors: The above innovation indicators evaluate research or clinical output of actors and organisations. There are many actors and organisations those research outputs are not patent, publication or clinical trials but have a major contribution to the development of biomedical innovation system in India. Researcher and innovators in traditional medicine, AYUSH, generic firms the performance and capabilities cannot be accessed through these indicators.

The biomedical innovation process involves various intermediary steps or actors critical for translational research such as toxicologists, animal house, patent facilitation centre, they cannot be identified, and their performance cannot be evaluated through above methods. Separate methods are used in this study to identify and access the activities.

The structure of biomedical innovation system in India, phase-wise involvement of actors, organisation and institutions along with the network and collaborations in each phase, the innovation indicators and identification methods are mentioned in the chapter biomedical innovation system in India (Table 12: Structure of BIS in India)

Table 3: Study Design, sources of data and relevance of databases in the study

Methods	Data Sources	Purpose
Patent Analysis	***WIPO-Patentscope***	Identify global actors, organisations, global trend, knowledge development in global TIS, technological innovation in various sectors., collaborations
	inPASS - IP-India	Identify Indian actors, organisations, trends in R&D, knowledge development, collaborations
Publication data analysis	***Elsevier – Scopus***	Identify global actors, organisations, the global trend in research publication, knowledge distribution, types of knowledge, collaborations, networks, financial sources, sponsors.
	Global publication	Same as above in national domain
	Indian publication	
Clinical Trial data analysis	***ICTRP- WHO***	Global clinical trials trends, phase-wise CTs, CTs in children,
	CTRI- India	Registered CTs in India, active NCE/NBE under CTs of a foreign firm, domestic firms, phase-wise analysis, types of trials (interventional/observational), recruitment status, CTs sites and locations, sponsors, Linkages and collaborations (firms-CROs, CRO-hospital, firm-hospital, PI- hospital- firms)
		Evidence-based clinical practices, standard practices, knowledge formation in CTs, new treatment methods, drugs comparisons
Primary Data	***Semi-structured interviews***	Identification of relevant actors through the above methods along with new actors (through snow-balling)
		The interviews manual is meant for diverse sets of actors, at different stages of innovation activities intended to gather information about the structure, activities of the organisation and their collaborations, networking and linkages.
		The focus area of the interview is to identify issues, challenges, system problems in different stages of BIS, along with identifying challenges in translational research.

3. 3. 2 Analysis of the function of Innovations:

Analysis of functions in innovation is a critical component of TIS. However, functional analysis is difficult then structural analysis as multiple actors contribute to the one or more system function. Some functions do not have direct link with the actors and institutions, rather requires in-depth technological or background knowledge, critical thinking to access the functions. There is seven functions of innovation in TIS. The **Table 4** is an adaptation of Bergek (2008) indicates the different innovation indicator and how to evaluate the performance of TIS. However, every TIS is unique, and the sources of data, the use of data and innovation indicators varies in accessing the functions.

3.3.3 Data Sources and their Usages:

Patent databases:

WIPO-Patentscope database is used to retrieve data related to global knowledge field, the evolution of technological knowledge, progression, new technological innovations, technological trends, PCT applications, important MNC, firms or organization and their activities in global Diabetology research.

The reason for choosing the WIPO database is mainly due to its coverage and analytics. *Patent scope* has access to all the patent data of national and regional patent office in 152 contracting countries across the globe. The daily updating of bibliographic data, along with weekly updating of the new- application or PCT application are some of the features that help in accurate analysis of trends. The database has various analytical methods for retrieving or evaluating data such as simple search, advanced search, field combination and Cross-Lingual Information Retrieval (CLIR) search that helps in retrieving relevant document present in different languages other than English. Patent scope also covers national phase patents from 2017 onwards. However, their updates depend on the national patent office.

Table 4: Mapping innovation system functions, types of indicators and methods of data collection for analysis

TIS functions	*Innovation indicators for evaluation*	*Sources of Data/ Methods*
Knowledge development and diffusion	Numbers of patents, subject –an area of patents, numbers of publications, R&D proposals, Presence of network, the intensity of network	Patent database Citation database Institutional repositories
Influence on the direction of search	Regulatory pressures, technological policies, other policies that have an impact on the technology Production prices, (institutions affect pricing mechanism e;g tax) Future growth potential, Interest groups, articulation by consumers	Govt. policy documents International policy documents Market regulations, trends Trend analysis Primary data – interview
Entrepreneurial experimentation	Numbers of new actors and organisations and their nature of work. Diversification of activities by established actors, new technological experimentation or diversity in experimentations	No. of Startups, DIPP, Startup India, Patent database, Citation database, Secondary databases
Market formation	Number of the market, market size, various products, time of market formation, policies and institution that affects market formations (programmes and incentives)	Companies annual reports Financial reports, Market growth, Secondary data on specific segments, market associations, societies Interview with market actors
Resource mobilization	Seed funds and venture capital, R&D financing, number and qualities of human resources, number and qualities of infrastructures, international collaborations, joint ventures	Institutional repository Govt. policy &programmes PPP, Market support, Private investments
Legitimation	Perception towards the technology, interest group, lobbying, media and political interest	Subjective – depends on observation of the analyst Field studies – interviews with relevant actors
Development of positive externalities	Dealing with uncertainties, political will, interference, information and knowledge development, depends on the performance of other functions.	Subjective – depends on observation of the analyst Field studies – interviews with relevant actors

Adapted from: Bergek (TIS Framework used in the energy sector), 2008

Patent databases:

InPASS, IP- India is a search platform for granted patents and patent applications provided by Controller General of Patents Designs and Trademarks, DIPP, GOI has access to all national phase applications, published patents, granted patents, PCT application filled through the national patent office in India. This database is used to identifying Indian actors, organisations, domestic trends in R&D, knowledge development, co-patentees, entrepreneurial experimentation, new firms, new technological development etc.

Patent data was searched through keywords. Preparation of key terms is an important aspect of this study as scientific naming involves. Apart from the generic terms 'diabetes' new technological patents were retrieved through term like 'islet transplantation', designer insulin' 'islet transplantation', 'retinopathy', 'neuropathy', 'Diabetic foot ulcer' For extracting relevant and accurate information only abstract, key content and title of patent documents were taken into consideration. It is generally appreciated to take the full text for the search but more relevancy and decrease the level of precision; only keywords and abstract were taken for the study.

In the TIS, patents are important innovation indicators used by different innovation scholars (Bergek, 2008; Holmen &Jacobsson, 2000). However, there is an analytical problem associated with the patent classes and assessing functions of innovations when the unit of analysis is a product or artefact. The relation between patent class and product or artefact is questionable. (Berger, 2004) and even if a firm has patents in particular classes, that is not a clear indicator of masters of technology associated with that class. (Holmen &Jacobsson 2000). Patent analysis is most suitable for analysis of the knowledge field.

In the present context, where the analysis is based on 'knowledge field' patent classes might be useful; however; when the starting point is a disease *(Diabetes)* choosing a patent class might be problematic. For example, IPC class C07K belongs to 'peptide' useful for medical proposes, a search through patent class will reveal all the peptides in the line of the invention for different medical complications however using the keyword 'Diabetes' the data will only reveal inventions related to 'insulin peptide'. Similarly, A61P – 'therapeutic chemical compound' will data only about OADs (Oral anti-diabetic drugs) rather all oral consumable drugs. However, even the keyword method has certain challenges related to the accuracy and precision of data analytics. A keyword search at the level of abstract is preferable over the

title or full-text search — the detail accounts of patent classes in Diabetology given in the ***Annexure 1***

In a *'keyword'* method of search maintaining level of precession and accuracy is equally challenging. The accuracy of the analysis depends on the data extraction technique. *'Title'* is too narrow, and *'Full text'* is too broad as an area of analysis. Hence, *"abstract"* is taken for consideration for final analysis to maintain the level of precision in extracting accurate data. Abstract as an area of analysis also gives glimpses of co-morbidity (application not just related to diabetes but also related to the other diseases, lifestyle diseases, diabetes-TB/Diabetes-kidney failure/ Diabetes- Hypertension etc.) and related inventions that are hard to figure out with title search on contrary full-text search will lead to too much of *arrays.*

Publication databases: Research publications were analysis through a proprietary database Elsevier *Scopous*.

Scopous is one of the largest abstract and citation database. PubMed another citation databases the prominent in the biomedical research area; however, the analytics, methods of data retrieval method are not suitable for functional analysis. Hence Scopus database is used for retrieval and analysis of data.

Scopus database is used to identify and analyses global actors, organisations, the global trend in research publication, knowledge distribution, types of knowledge, collaborations, networks, financial sources and research sponsors

Clinical Trials databases: Two databases International Clinical Trials Registry Platform (ICTRP), WHO and Clinical Trial Registry-India (CTRI) databases are used for the analysis of clinical trial databases in India. However, the ICTRP data were limited to give overall ideas of clinical trials and the global trend of phase-wise clinical trials analysis. Most of the analysis in the current study is based on the Clinical Trial Registry-India (CTRI) databases.

CTRI database is used for identification and analysis of CTs in India, active NCE/NBE under CTs of foreign firm, domestic firms, phase-wise analysis, types of trials (interventional/observational), recruitment status, CTs sites and locations, sponsors, linkages and collaborations (firms-CROs, CRO-hospital, firm-hospital, PI- hospital- firms) along with finding innovation indicators for evidence-based clinical practices, standard practices, knowledge formation in CTs, new treatment methods, drugs comparisons etc.

Other innovation indicators:

The three major innovation indicators mentioned above are not sufficient for identification and analysis of BIS in India. There are specific actor and organisation have different output and objectives.

Indicators for herbal formulations:

Traditional Knowledge Digital Library (TKDL) database, a joint initiative of CSIR- AYUSH, GOI is used to retrieve traditional data on knowledge formation related to Ayurveda and other forms of Indian system of medicine (Unani, Siddha & Yoga). Research on traditional medicine, relevant actors, organisations and functions are analysed using institutional repositories of AYUSH.

Indicators for generic firms:

The Indian pharmaceutical companies have expertise in process engineering, and their main product portfolios are generic medicine. Patent analysis is not a suitable indicator of evaluating the performance of firms. A clinical trial partially indicates about R&D activities of any new drug molecule or BA/BE studies. The output of Indian generic firms can be evaluated through ANDA filling.

Apart from the above indicators various institutional databases, policy documents, reports, extramural research funding of various funding agencies, ministries, departments both related to health research and health services in India, programmes and institution that promote or hinders activities, market reports, trends, sector-specific issues and important that affect both structure and function of innovation. Development of products in translational research sets in motion a complex array of the process that involves within its reach clinical trials and market delay, arising out of regulatory clearance. Thus, the diffusion process of products from the lab to the market in translational research seems to suggest a lengthy and complex course of development, which includes different actors and activity. Many actors and institutions could be traced through these intermediate processes such as clinical trials, in-licensing, out-licensing, acquisition, collaborations etc. Companies profile, annual reports, financial reports, portfolio analysis & clinical trial databases contribute to finding out the contingent role of the different actors within the sphere of intermediate innovation activities.

Primary Data through Interview and Questioners:

The patent analysis, citation and publication data, clinical trials data helps in the identification of relevant actors at different stages of biomedical research and innovation in India. These methods also gave a prior knowledge about the activities and functions performed by different actors, organisation and institutions in India. The three stages of basic, applied, and clinical research are connected through intermediary actors and organisations in the translational processes. The prior knowledge and activities of various actors and the complexity of the translational research process and innovation stages help in formulating relevant questioners.

The primary data was gathered through semi-structured interviews with different experts and relevant actors at different stages of biomedical innovation. As biomedical innovation a multi-stage process, where actors have different objectives and functions, a common questioner is inadequate to address the pluralistic nature of research and activities

There are multiple sets of questioners for actors mainly as per their profession and contribution to the knowledge field. The multiple questioners have broader categories. They are science/ lab-based researcher, clinical researcher/clinical practitioners, firms (conventional and AYUSH), Policy actors and funding agencies, CROs professional etc. *The detailed interview manual is given in the* ***Annexure- V***.

The questioner has certain basic elements in all the categories regarding knowledge, experience, perception, priorities, network, research/clinical output along with with with the sectors specific issues and challenges, incentives and barriers to their activities. The questions are framed while keeping in view the TIS framework and Translational research. The objective of the studies is also to identify the issues and challenges pertinent to translational research and identification of translational gaps. Hence, the questioner also includes the questions that help actors and respondent to address the translational issues in their domain, the specific challenges or issues that address translational gaps.

There are 46 respondent in different categories includes scientist, clinician, policymakers, researchers, diabetic educators, grass-root *practitioner*, CROs, finance agencies, patent facilitators, animal house manager etc. The purpose is not to focus on the numbers rather different categories of actors to canvass the broader picture of biomedical innovation and addresses the translational issues through in-depth- interview and brain-storming. Apart from

the above 46 interview-based response, there are many online- questioner based responses to the researcher. However, for the analysis purpose, only relevant data were considered.

3.4 Summary:

This chapter addresses the analytical framework, detailed methodology and different method that will help in identifying the structure and analysing the function of the biomedical innovation system in India. This section also attempts to address the research question pertaining to the methodological issues and challenges in biomedical innovation system in India. The next chapter is the prelude to the BIS in India describes Global knowledge field of Diabetology, before analysis in the Indian context in the following chapters.

CHAPTER FOUR

DIABETOLOGY AS KNOWLEDGE FIELD: GLOBAL PERSPECTIVE

4.1 Introduction:

This chapter is a prologue to the analysis chapter on biomedical innovation system in India. Knowledge formation in the technological system is often global (Carlsson, 1995). The genesis of biomedical innovation system occurred in the developed world like the USA and European countries and later diffused to the technological catch-up countries like India and China. This chapter conceptualises Diabetology as a knowledge field and describes the origin, evolution of knowledge in this field. The chapter has focused on various developments on technological knowledge in drug development and diagnostic and device, those significant for diabetes management. The methods followed in this segment are a combination of clinical literature and patent analysis of select firms to focus on global technological knowledge formation.

4.2 Conceptualizing '*Diabetology*[24]*as knowledge field*' in TIS

The technological innovation system focuses on understanding the dynamics of an innovation system centred on a specific technology. However, the approach to technology can vary depending on the level of analysis. There are at least three levels of analysis to define technology in TIS. The three approaches are: '*technology in the sense of a knowledge field, a technology as a product or an artefact, or a set of related products and artefacts aimed at satisfying a particular(societal) function' (Jacobsson,2000).* The choice/ approach dictate what actors, networks and institutions will be included in the innovation framework, what will be the shape, structure, and how it will function.

[24] Diabetology is the knowledge field related to the clinical science of diagnosis and treatment of diabetes. The terminology is quite popular in USA, however, Diabetology is not a medical specialty rather considered as a sub- field of endocrinology. The rationale behind choosing this terminology is context of this study, where the focal point is the problem sequence disease (Diabetes). While endocrinology system is an umbrella term deals with whole endocrine system mechanism in the body the study focuses on diabetes only. Diabetes is associated with various complications related to blood pressure, cardiac disease, kidney and liver related complications. The knowledge field also includes: diabetic retinopathy (related to eye), diabetic nephropathy (related to kidney) and diabetic peripheral neuropathy (related to foot ulcers).

To study and explore biomedical innovation system in India, the present study took Diabetology as a knowledge field where the purpose is to *satisfy a particular societal function*[25] . In any medical innovation, the ultimate objective is to a solution to cure or management a disease; in this case, the disease is *Diabetes*. Managing diabetes can be through new drug development, diagnostic equipment, devices, scientific and technological advances, or effectively using the existing system through clinical practices, programmes, awareness drive, and community or practised based interventions.

The second component is the *set of related products*. In this study, both drug and devices are taken assets of related products. In biomedical research, drug and device are relatable products because to cure a disease diagnosis-treatment processes both are an integral part of clinical practices. Without diagnosis, there is no use of drugs and treatment process.

The knowledge formation process in biomedical research is highly interdisciplinary; crosses sectoral boundaries and established institutional structures. Technological development around an artefacts or product does not solely base on the technical knowledge rather involves scientific knowledge (scientific inventions, prototype at bench level) and clinical knowledge (at the practice level, post improvement level). Hence the knowledge field (Diabetology) captures a broader picture; where there is the integration of scientific, technological and clinical knowledge. In the sequence of events, how Diabetology discipline, related technologies have evolved and diffused in the system or failed to do so is the prime objective of this study.

[25] The study is similar toBergek (2003) where the scope broadens in approach as renewable energies or sustainable energies as knowledge field; with respects to the approach aimed at 'satisfying a particular (societal) function'. The TIS was used in investigating why and how sustainable (energy) technologies have developed and diffused into a society, or have failed to do so.

4.3 *Origin and evolution of knowledge in Diabetology:*

Diabetology is defined as the study of the diagnosis and treatment of diabetes. As the core problem is a disease, clinical knowledge about diabetes, its prognosis, epidemic studies, prevalence and incidence rates, various treatment methodology and clinical advances are core to its knowledge base. In ancient Indian literature, diabetes is described as "a mysterious disease-causing thirst, enormous urine output, and wasting away of the body with flies and ants attracted to the urine of people." The term was coined by Apollonius of Memphis which means "to go through" later "mellitus" joined the terminology as it made the urine sweeter (Das & Saha,2011)

How does Diabetology emerge as a discipline?

Citation analysis shows a glimpse of how Diabetology evolved as a discipline. The earliest academic literature a cited paper dated back to 1828 in the journal *The Lancet* in the form of communication letter on diabetes mellitus. Earliest forms of literature are in the form of academic correspondences, communication letter, case studies, clinical advances and various interesting treatment procedure. Before the discovery of insulin, these typical treatment procedures were morphine, tannin, vomiting wine, rubbing on the back of a horse, with Creosote, turpentine etc.

The late nineteenth century till mid-twenty century clinical advances are related to diabetes are published in prestigious journals like The Lancet, Journal of the American Medical Association, New England Journal of Medicine, British Medical Journal, American Journal of Medical Sciences, Annals of the Pharmacy etc. However, with the gradual increase in the prevalence rate of diabetes across in developed countries in the late *twentieth* century, more and more clinical evidence and research in this field, diabetes as a separate field of investigation evolved. Till date, diabetes is a very much a clinical subject and part of medicine/ endocrinology,

Growth of the knowledge field:

The growth of a subject can be noticed when specific journal or association, a society formed on a subject. APDP – Diabetes Portugal (Portuguese Diabetes Association) is the oldest diabetic association in the world established in the year 1926. In 1940, the American Diabetes Association (ADA) was formed, before the British Diabetic Association in 1934 and 1965, its European counterpart EASD also come into existences. In the meantime, International

Diabetes Federation (IDF) came to existences in the year 1950. Associations and society helped in establishing a formal network in the field and helps in growth and dissemination of knowledge through scientific journals, conferences and workshops etc. **(Table 5)**

Interestingly, the timeline also suggested most of these associations in the USA, European nations are established in the mid-*twentieth* century, however, in developing countries such as China, India, Brazil they are established late *twentieth* or early twenty-first century, also indicates diabetes is most prominent in developed countries initially then migrates to the developing nations and other countries.

In the contemporary scenario, Diabetes is global epidemics as all most all the countries in the global have diabetes subjects, association or society. As per latest data, IDF has a membership of 179 diabetes association/ society spreading in 115 countries across the globe. The European region has the highest numbers of 69 registered associations in 44 countries followed by South and Central American regions with 44 associations in 19 countries, North-America and the Caribbean region has 27 bodies across 24 countries. West Pacific region that includes China, Australia, Japan, Indonesia and various island nations have 28 associations in 22 countries. India is a major contributor in the South-east Asia regions where 11 accredited associations in 6 countries.

Associations, societies and bodies are not only contributing to the scientific, technical or clinical knowledge in a field but also works toward awareness (through magazines) drives and critical policy interventions. The further growth of a subject or knowledge field can be established when it makes a spin-off, more specialised branches within Diabetology emerged such as Pediatrics Diabetes, Gestational Diabetes, Diabetic retinopathy (eye), diabetic neuropathy (Diabetic foot) etc. There are some of the specialised journals such as Cardiovascular Diabetology, Diabetes and Vascular Disease Research Journal of Diabetes Nursing, Journal of Diabetes and Its Complications, Pediatric Diabetes; Diabetes Educator suggest the growth of the knowledge field.

Table 5: List of formal associations, societies, and scientific bodies in Diabetology

Year of Establishment	Associations	Journals & Year of Origin
1916	The Endocrine Society, USA	Endocrinology- 1927 The Journal of Clinical Endocrinology – 1941 The Journal of Clinical Endocrinology & Metabolism- 1952
1926	APDP – Diabetes Portugal (Portuguese Diabetes Association)	Oldest diabetes associations
1934	Diabetes UK/ British Diabetic Association	Balance (formerly The Diabetic Journal) – 1935 Diabetic Medicine - 1984
1937	Diabetes Australia - 3rd oldest	Diabetes Management Journal (DMJ) Circle - (Magazines)
1938	French Society for the study of Diabetes (SFD)	Diabetes and Metabolism
1939	European Society of Endocrinology(ESE)	Journal of Endocrinology
1940	American Diabetes Association	Diabetes – 1952, Diabetes Care – 1978, Clinical Diabetes – 1983, Diabetes Spectrum- 1988 (Translational-Research to Practice), ADA Standards of Medical Care
1973	American Association of Diabetic Educators (AADE)	Diabetes Educator - 1980
1974	International Society for Pediatric and Adolescent Diabetes (ISPAD)	Pediatric Diabetes - 2001
1953	Diabetes Canada	Canadian Journal Of Diabetes - 2006
1958 1961	Japan Diabetes Society Japan Association for Diabetes Education and Care (JADEC)	Journal Of The Japan Diabetes Society
1965	European Association for the Study of Diabetes	Diabetologia – 1965
1950	International Diabetes Federation, Amsterdam	Diabetes Research And Clinical Practice - 1985
1962	Diabetes New Zealand	Diabetes Wellness- magazine
1968 1995	Korean Diabetes Association Korean Diabetes Society	Diabetes and Metabolism Journal – 1972 The Journal of Korean Diabetes - 2000
1955 **1972** **2000**	**Diabetic Association of India** **Research Society for Diabetes in Developing Country (RSSDI)** **The Research trust of Diabetes India**	**International Journal Of Diabetes In Developing Countries - 1981** **Diabetes and Metabolic Syndrome Clinical Research and Reviews – 2007**
2007	Primary care Diabetes, Europe (PCDE)	Primary Care Diabetes
2009	Brazilian Diabetes Society	Diabetology And Metabolic Syndrome
2009	Chinese Society of Endocrinology	Journal Of Diabetes

(Sources: Compiled from publication data- Scopus, Institutional repositories)

4.4 Global technological knowledge in Diabetology:

Patent analysis shows the technological advances, breakthrough, firm competence, capabilities also technological trajectory of invention, innovation and development in specific knowledge field. As Diabetology is a knowledge field, major technological knowledge come under the ambit of two main categories: drug development (insulin and OADs) and device and diagnostics.

Historically, one of the earliest global patents in the area of Diabetology can be traced in the year 1888, **(Table 6)** a Canadian patent on medicine for the treatment of diseases of the liver, loins, bright's disease of the kidneys, diabetes, nervous debility, rheumatism, insomnia, dyspepsia, etc. *(Pat No.CA30232:1888).* Prior to the discovery of insulin the patent document shows the trajectory of inventions that lead the path of discovery of insulin with preparation of serum for diabetes inoculating blood of a dog *(Pat No. GB190209863:1903),*an injection prepared from the pancreatic glands of animals such as cattle, pigs, sheep, dogs, etc for treatment of diabetes in 1909 *(Pat No. GB190808514: 1909).*

Apart from insulin, oral antidiabetic drugs (OADs), salt-based biochemical formulation is an integral part of the diabetes treatment procedure in the modern medicinal system. The earliest evidence of new chemical entity for diabetes treatment is the process for the manufacture of saccharosonic acids and their salts in 1935 *(Pat No.GB430264:1935).* Sulphonyl Ureas (SU) is the oldest OAD drug class. The 1st generations SU drugs are manufactured between the periods of 1940s-50s. Some of the earliest patents in Sulphanilyl Urea drug classes are by *Boehringer &SoehneGmbh(Pat No. GB794552:1958)* the parent company of Boehringer Ingelheim GmbH, an oral formulation by *Hoechst Ag,* now part of Sanofi-Aventis*(Pat No.GB808073:1959)*, a new hypoglycemic sulfonamide derivatives by *Astra Apotekarnes Kem Fab (Pat No. GB826539: 1960)*, a sulfonylureas based formulation by *Pfizer(Pat No. US2979437:1961).* The earliest evidence of Biguanide classes of drugs where Metformin belongs to, the most successful OAD and the drug that uses in the first line of treatment for diabetes is by *U S Vitamin Corp.(Pat No. GB852584: 1960).* Similarly, the earliest evidencece of thiadiazole based compound by *Rhone Poulenc SA (Pat No. GB828963:1960).*

Similarly, the earliest technological development in the diagnostic innovation in Diabetology is an apparatus *"saccharometer"* for determining the amount of sugar in the urine *(Pat No. GB190412385:1905)*. Besides its clinical complication, diabetes is often associated as a life-style problem, hence inventions related to life-style improvement such as healthy dietary products, foods, exercises, nutraceutical innovation are also part of the system. Some of these inventions are related to dietetic food, nutraceutical such as improvements in proteid biscuits *(Pat No.GB189816115: 1899),* diabetic sugar-free milk *(Pat No.GB190016199: 1901),* improvement of cocoa preparation (starch-free) for diabetes patients *(Pat No.GB190012956:1900)* are the earliest patent associated with diabetes management.

In the present TIS, as discussed earlier where choices were made to have knowledge field as a focus point, where not just one product, a group of product and artefacts are taken into consideration the **Table 6** gives an indicator of a technological factor in this TIS.

Diabetology is better a choice as a knowledge field where innovation occurs at various scales such as diagnostic innovations, drug developments, medical procedural innovations, scientific or clinical innovation, major policy interventions etc. In the present TIS, Diabetology is considered as a knowledge field. Each development and innovation such as drug development (Insulin, OADs, other drug classes), Diagnostic innovation (from saccharometer to Glucometer and present-day App-based monitoring system), Procedural innovation (Islet Transplantation), major scientific discovery and its impact on technological innovation thereafter, major policy recommendation or intervention and their implications are described separately in this chapter. In biomedical innovation, clinical innovation and technological innovation occurs simultaneously sometimes hard to distinguish.

Table 6: Various forms of technological development in the knowledge field of Diabetology (through patent analysis)

Year of Publication	***Patents Number***	***Descriptions***
1888	CA30232	Medicine for the treatment of diseases of the liver, loins, bright's disease of the kidneys, diabetes, nervous debility, rheumatism, insomnia, dyspepsia, etc
1899	GB189816115	Improvements in Proteid Biscuits
1900	GB190012956	Improvements in Cocoa Preparation – *free from starch used for diabetes patients*
1901	GB190016199	Diabetic Sugar-free Milk
1903	GB190209863	A Process for the Preparation of a Serum for the Treatment of Diabetes and the like. *Medicines anti-toxines.-The blood of a dog which has been repeatedly inoculated with the juice of suprarenal capsules is used as an injection in the treatment of diabetes and complaints having their origin in imperfect action of the suprarenal capsules*
1905	GB190412385	Improvements in and connected with Apparatus for Determining the Amount of Sugar in Urine. *Saccharometers. - Relates to a fermentation "saccharometer" or apparatus for testing for sugar in undiluted urine, in cases of suspected diabetes & complications.*
1909	GB190808514	The Manufacture of a Pancreas Preparation suitable for the Treatment of Diabetes. *Injection for the treatment of diabetes is prepared from the pancreatic gland of an animal (cattle, pigs, sheep, dogs, etc.). The gland being removed while digestion is at its height or artificially enriched by ligaturing the veins. The gland after removal is left to self-digestion, albumens are precipitated by alcohol, and the filtrate is evaporated to dryness.*
1909	GB190817598	Pills for the Treatment of Diabetes Mellitus. *A pill for the treatment of diabetes is composed of a mixture of a vegetable enzyme, and an alkaline salt pressed together and coated with keratin.*
1921	GB159957	An improved remedy for diabetes and other diseases and a process for the preparation thereof - *A medicine for use in cases of diabetes mellitus is made by removing adherent flesh from ox tonsils and its preparation method.*

Year of Publication	***Patents Number***	***Descriptions***
1923	GB203778	A method of preparing extracts of pancreas, suitable for administration to the human subject *applicants: Frederick Grant Banting, James Bertram Collip, Charles Herbert Best*A pancreas extract to be injected intravenously or subcutaneously in the treatment of diabetes is obtained from fresh glands by extracting them with a solvent, such as alcohol, which inhibits the action of enzymes on the active substance or hormone and then removing toxic impurities by precipitation.
1923	US1469994	Extract obtainable from the mammalian pancreas or from the related glands in fishes, useful in the treatment of diabetes mellitus, and a method of preparing it *Applicant: University of Alberta/ University of Toronto, Canada* *Inventors: Frederick Grant Banting, James Bertram Collip, Charles Herbert Best*
1935	GB430264	Process for the manufacture of saccharosonic acids and their salts
1958	GB794552	Sulphanilyl Urea derivatives and compositions thereof *Applicant: Boehringer &SoehneGmbh* Pharmaceutical preparations for the treatment of diabetes by oral administration or otherwise.
1959	GB808073	Manufacture of new Sulphonyl Ureas *Applicant: Hoechst Ag - (now part of Sanofi-Aventis)*
1960	GB826539	New hypoglycaemic sulfonamide derivatives *Applicant: Astra Apotekarnes Kem Fab*
1960	GB828963	Pharmaceutical compositions containing 2-p-aminobenzenesulphonamido-5-t-butyl-1, 3, 4-thiadiazole *Applicant:* Rhone Poulenc SA
1960	GB852584	Biguanide compositions *Applicant:* U S VITAMIN CORP
1961	US2979437	Substituted styryl, and thienylethenyl, pyridylethenyl sulfonylureas and method of treating diabetes *Applicant:* PFIZER &; CO C

(Data Source: Patentscope-WIPO, Method: Patent Analytics)

(Search Method: Simple search→ keyword search→ Sort by→ Pub Date→Asc)

The **Table 6** shows the earliest evidence of various technological factors in the knowledge field of Diabetes. There are four major areas of technological knowledge field such as: Diagnostic & devices, Insulin, OADs and food and nutrition

Drug Development:

4.4.1 Insulin *(Evolution, contemporary research and future development)*

Insulin is a natural hormone and most potent drug for diabetes. Before the discovery of insulin, the clinical development and the scientific discovery of glycogen metabolism, the role of pancreatic cells in management of diabetes were significant milestones. In 1869, Paul Langerhans discovered insulin-producing beta cells in pancreases later; those cells are named after him as *'Islets of Langerhans'*. In 1889, Oskar Minkowski and Joseph von Mering strengthened the arguments of the decisive role of pancreases in regulating diabetes. Banting & Best's discovery of Insulin in 1921 is one of the greatest inventions of the century that changes the clinical management of disease after that. The first Human Trials occurs in the year 1922 on a 14-year boy named as Leonard Thompson. The infusion of insulin and successful survival of Leonard for the next 13 year creates new avenues of clinical and technological innovation in Diabetology in the following period of the late *twentieth* century to till date. First, prominent *Industrial- academic linkages* in Diabetology were between Eli Lilly and Toronto University in 1922 for production of insulin at the industrial level. Nordisk Insulin Laboratorium was established next year, that became Novo Nordisk one of the top firms in this insulin segment.

Evolution of Insulin:

Insulin therapy undergoes a paradigm shift in the last century. Insulin undergoes series of innovation and decades of development to achieve the status what we use today. The first decade of insulin development from the mid 1920s to mid-1930s is considered a period of slow-acting insulin. Most of those animal proteins are in impure form causes irritation and other complications. The search for a purified protein leads to the discovery of *Protamine*, a protein isolated from fish sperm by Hans Christian Hagedorn, the founder of Nordisk Insulin Laboratorium (Novo Nordisk) in the year 1936. The addition of protamine leads to the formation of clumps that delays insulin release. The mid 1930s onwards indicates a period of development on NPH Insulin and intermediary insulin followed by PZI (Protamine Zinc Insulin) along with acting insulin from mid-1940s onwards. (Deckert, Diabetes Care 1980 Sep; 3(5): 623-626.

Important scientific inventions can change the path of research and innovation and course of development. A similar event occurs with the discovery of partition chromatography techniques in the mid 1940s by Archer Martin and Richard Laurence Millington Synge. This discovery of chromatography techniques changes the method of separation and purification. This breakthrough technique leads to a decade of purified insulin (the 1960s) known as *'Monocomponent-MC/single peak'* insulin that significantly reduced the allergic reactions.

The 1970s onwards biomedical research and innovation took a giant step with enormous development in the fields of molecular biology, immunology, human genetics, genetic engineering, biotechnology makes series of scientific inventions in the following era have changed the courses of technological development in insulin.

Paul Berg's 1971 landmark gene-splicing experiment is the earliest step towards the development of Recombinant DNA technology. Paul Berg received Nobel Prize for this outstanding contribution in 1980 along with Walter Gilbert and Frederick Sanger.

The first successful experimentation of rDNA in a living organism was achieved by Herbert Boyer and Stanley Cohen in 1973. *rDNA technique became instrumental in the formation of a biotechnology firm in the coming year.* At the forefront was *Genentech*, founded in 1976 by Boyer and Robert Swanson. Synthetic insulin became the first biotechnology-based product. Later synthetic insulin renamed as 'human insulin' that are less allergic than the insulin from animal sources. 'Humalin' was the first biotechnology-based product launched in the market in 1982.

The success of Genentech is considered as the birth of the biotech industry. The Eli-Lilly and Genentech successful collaboration lead to a boom of biotechnology-based start-up backed by established pharmaceutical companies in the early 1990s. (Rosenburg-1995) The patterns of formation of the biotech industry in the technological follower nation are in line with the developed country. Eighty per cent of Indian biotechnological firms are backed by pharmaceutical companies.

Modern Insulin:

Modern insulin can be classified into various categories; however major categories are based on source of insulin, strength of insulin and time characteristics of their activities. **(Table 7)** Time-characteristics are measure through three components such as Onset, Peak and Durations. [26] Based on the sources, Insulins are of three types; *Insulin Pork/ porcine insulin* (extracted from pancreas of pigs), *Insulin Beef/ Bovine insulin* (extracted from pancreas of cows), *Insulin Human* (genetically engineered or chemical modification of porcine insulin. (diabetes india).

The modern day's designer insulin or analog insulin was based on the structural altercation of human insulin sequenceswith better pharmacokinetic properties. The advantage of designer insulin over conventional insulin is that the former can be adjusted according to the normal physiological insulin secretion. In contrast to the conventional once, modern short action insulin analogs *(Lispro, Aspart&Glulisine)*, long acting insulin analogs (*Detemir & Glargine*) or ultra- long acting insulin analogs (*Degludec*) are tweaked to adjust physiological insulin secretion. Animal insulin are currently being phased out for human use, however still available in selected market E.g*Hypurin*, is produced by Wockhardt UK. Most human insulin available now is recombinant

The detailed evolution of Insulin development is mentioned in the ***Annexure II.***

[26]**Onset** is the length of time before insulin reaches the bloodstream and begins lowering blood glucose.**Peaktime** is the time during which insulin is at maximum strength in terms of lowering blood glucose. **Duration** is how long insulin continues to lower blood glucose. *(American Diabetes Association)*

Tables 7: Types of Insulin in the contemporary scenario

Types of Insulin	Generic Name	Brand Name -Company	Onset	Peak	Duration
Rapid-acting	Insulin Lispro	Humalog - Eli Lilly Liprolog - Eli Lilly Admelog - Sanofi Aventis	10 - 30 minutes	30 minutes - 3 hours	3 - 5 hours
	Insulin Aspart	Novolog - Novo Nordisk Fiasp - Novo Nordisk NovoRapid - Novo Nordisk			
	Insulin Glulisine	Apidra - Sanofi-Aventis			
Short-acting	Insulin Human/ Regular (R)	Humulin R - Eli Lilly Entuzity - Eli Lilly Insulatard - Novo Nordisk Novolin R - Novo Nordisk Actraphane - Novo Nordisk Actrapid - Novo Nordisk Insuman Basal - Sanofi-Aventis Insuman Rapid- Sanofi-Aventis	30 minutes - 1 hour	2 - 5 hours	Up to 12 hours
Intermediate-acting	Insulin Human NPH (N)	Humulin N- Eli Lilly Humulin L - Eli Lilly Novolin N - Novo Nordisk NovolinsetGe NPH-NovoNordisk	1.5 - 4 hours	4 - 12 hours	Up to 24 hours
Long-acting	Insulin Glargine	Lantus – Sanofi- Aventis Toujeo - Sanofi- Aventis Basaglar -Eli Lilly Abasaglar Eli Lilly	0.8 - 4 hours	Minimal peak	Up to 24 hours
	Insulin Detemir	Levemir - Novo Nordisk			
Ultra-Long-acting	Insulin Degludec	Tresiba- Novo Nordisk	0.8 - 4 hours	Minimal peak	Up to 48 hours
GLP-1 Receptor Agonist (Insulin Analog)	Lixisenatide	Adlyxin - Sanofi-Aventis Lyxumia - Sanofi-Aventis			
	Liraglutide	Victoza Novo Nordisk Saxenda Novo Nordisk			

(Sources: DrugBank& Joslin Diabetes Centre, Harvard Medical School)

4.4.2 Oral Anti Diabetes Drug (OADs), drug classes other then insulin:

The ease of administration, low cost (with exception of DPP-IV and newer drug classes), ability to control blood glucose level in about 60% of type 2 diabetes patients at any given point of time in a clinical setting and apprehensions to use insulin due to several misconceptions, have made oral blood glucose lowering agents immensely popular among patients.

Earliest evidence of global patent for novel formulation for manufacture of saccharosonic acids and their salts is in the year 1935 *(Pat No. GB430264:1935).* One of the earliest oral formulations developed by pharmaceutical companies on Sulphanilyl Urea derivatives and compositions is by *Boehringer &SoehneGmbh(Pat No. GB794552:1958),* followed by other companies on the same drug classes such as *Pat No.GB808073:1959 by Hoechst Ag (now part of Sanofi-Aventis*, *Pat No. GB826539:1960 by Astra Apotekarnes Kem Fab* and *Pat No. US2979437:1961 by Pfizer & Co.* **(Table 6)** During the following period, around 1960s other drug classes such as Thiadiazole *(Pat No.GB828963:1960 by Rhone Poulenc SA)* and Biguanide classes of drugs came in to existence (*Pat No.*GB852584*:* 1960 *by U S VITAMIN CORP).*

The history of oral anti diabetic agent therapy long antedates insulin, the first validated report being by Muller in 1877 on the effect of sodium salicylate on urinary glucose. In 1918, the blood sugar lowering influence of guanidine was described along with series of toxic guanidine derivatives. Less toxic derivatives such as *Synthalin A* and *Synthalin B* are used diabetes treatment process for some period; however discovery of insulin and its rapid successes ceases the use of these toxic guanidine compounds. The modern oral anti diabetic drugs era began with the accidental discovery of the hypoglycemic activity of the Sulphonamide, Sulphonyl thiadizole in 1942 by Marcel Janbon and their systematic study establishing their structure- activity relationships two years later by French endocrionologistAuguste-Louis Loubatières. The clinical introduction of sulphonylurea therapy followed in 1955 and two year later biguanide therapy became available.

History of Metformin: *Biguanides -Metformin* was first described in the scientific literature in 1922, by Emil Werner and James Bell. Slotta and Tschesche discovered its sugar-lowering action in rabbits in 1929. However, other guanidine derivative *Synthalins*, received more attention and research interest at that time.Meanwhile, success of insulin ceases the oral

diabetic drug formulation research between 1920s- 50s. Only after 1950s, Oral anti diabetic drugs research revived. During early 1950s along with 1st generation SUs two other *Biguanides (Phenformin, Buformin)* were discovered in 1957. French diabetologist Jean Sterne published his human trial result of metformin in 1957 and coined the term "Glucophage" (glucose eater), later it became its trade name. Metformin became available in France in 1957 and became part of British National Formulary in 1958. Broad interest in metformin was not rekindled until the withdrawal of the other two biguanides *(Phenformin, Buformin)* from market in the 1970s due to risk of lactic acidosis. Metformin was approved in Canada in 1972 but only after a long period *Glucophage* -the first braned formulation of metformin by Bristol-Myers Squibb received USFDA approval in 1995. Today metformin is the gold standard treatment for diabetes, uses as 1st line of treatment for type- 2 diabetes patients across the globe. Generic formulation is available globally and it also included in the WHO-list of essentinal medicine along with national list such as NPPA- DPCO in India. Metformin has survived for more than 90 years in the diabetes drug market is believed to have become the world's most widely prescribed antidiabetic medication.

OADs are in use for almost seven decades, however till mid nineties only two pharmacological classes of OADs were available namely *Sulphonyurea* and *Biguanides.* Subsequently, in mid nineties*Acarbose* that delay digestion of carbohydrates, was lunched. In late nineties, *Repaglinide*, first non suphonylurea insulin secretogogue came into the market. Around the turn of century thiazolindindiones, namely *Rosiglitazone and Pioglitazone* were on the market. In 2008, *Sitagliptin,* the first DPP-IV inhibitor was lunched followed by *Vildagliptin* and *Saxagliptin*. *Rosiglitazone* later removed from Indian Market in 1910 due to its cardiac toxicity. For detailed historical and chronological development of different anti diabetic drug classes see *Annexure*.

The recently introduced molecules are not merely ‘me too’ molecules but they represent totally different pharmacological classes of anti diabetic medications having a mechanism of action distinct from the older classes of OADs. These new agents have mechanisms of actions which are complementary to traditional agents with they can be judiciously combined. In the meantime while new molecules were being rapidly introduced in clinical practice, these alternatives sometimes confuse a generalist, a pertinent challenge to clinical practices. (Talwalkar 2014)

Numbers of anti diabetic drug classes other than insulin are evolved over the period in the market. Most of these drugs are follows oral route of administrations hence, also known as Oral Anti Diabetic Drug (OADs), except Glucagon-like peptide-1 (GLP-1) agonist which follows Subcutaneous Route via injection. Currently, Anti Diabetic Drugs belongs to eight major drug classes. There drugs are available in different permutations and combinations. OADs with proper administration up to its maximum capacity, could potentially delay the usage of injectable products. In addition, the pharmacotherapeutic armamentarium seems well equipped with different classes of anti-diabetic drugs. (Thomas N. , 2012).

Besides insulin many anti diabetic drugs classes are evolved in the last century. The evolution process of anti diabetic drugs classes mentioned in the ***Annexure IV***. Although the drugs classes can be classified in many ways however, based on the the mechanism of action/ site of action the anti- diabetic medication is of following types;

1. **Centrally acting agents**: These agents act directly at the site of pancrease to stimulate release of insulin from beta cells. They are also known as Secretagogues[27]. Major anti diabetes drugs classes are *Sulfonylureas* and Non-sulfonylurea (*Meglitinides*).
2. **Peripherally acting agents**: These agents increase tissues sensititvity towards insulin hence also known as Insulin Sensitizer. Sensitizer addresses core problems of *insulin resistance*[28], prominent in Type-2 diabetes patients. These peripheral acting agents are sub-divided into (*Bigunides*- acting mainly at liver,*Thiazolidinediones (TZD)*- acting at striated muscles and adipose tissues)
3. **Agents acting at instestinal mucosa:** These class drugs slow down digestion of carbohydrates in the body and thus the abostoption of glucose. Only OADs in this class is *Alpha- Glucosesidase Inhibitors*
4. **Agents acting through incretin axis**[29]: Two major groups in this category are *Dipeptidyl-peptidase-IV (DDP-IV) inhibitors/gliptins* and *Glucagon-like peptide-1 (GLP-1) agonist.*

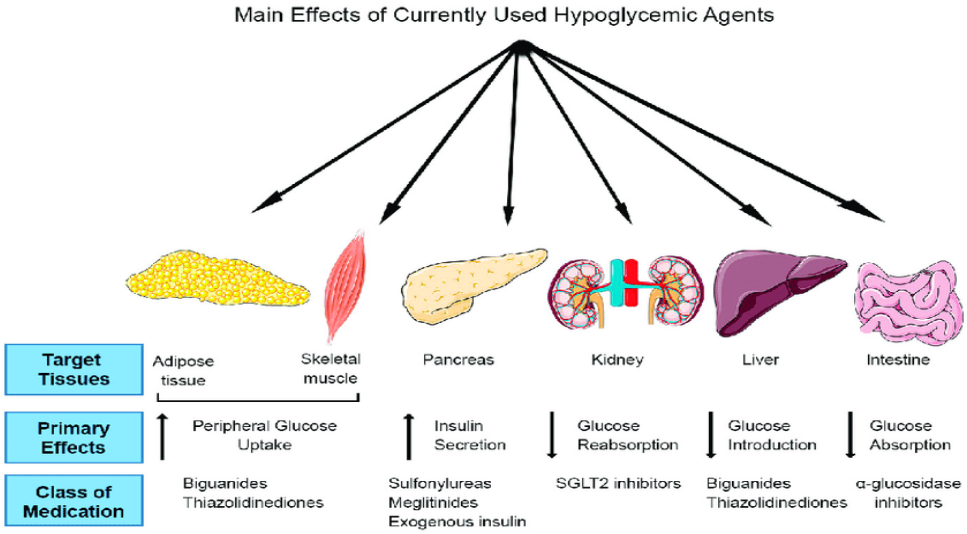
[27]**Secretagogues** are substance that causes another substance to be secreted. Here, Insulin Secretagogues drugs increases insulin output from pancreas.

[28]**Insulin resistance (IR)** is a pathological condition in which body cells fails to respond to hormonal insulin. In case of Type-2 Diabetes Mellitus (T2DM), body does not use insulin properly, although insulin are produced in the body.

[29]**Incretin** hormone stimulates insulin secretion in response to meals, as it stimulates insulin hence also called as Insulin Secretagogues. Two main candidate molecules are glucagon like peptide (GLP-1) and gastric inhibitory peptide (GIP). Both candidat are rapidly inactivated by enzyme dipeptidyl peptidase (DPP-IV).

5. **Agents acting on supra charismatic nuclei in hypothalamus**: The only drug *Bomocriptine* act by resetting the lowered dopaminergic tone in type 2 diabetic patients.

Figure 6: Different Anti- Diabetes Drug classes and their site and mechanism of action



Source: Naimi M et al (2017), Nutrients 9(9):968

Important scientific invention and technological innovations in OADs:

Important scientific inventions creates new avenue for drug discovery often changes the path of technological innovation and course of development. 1970s onwards biomedical research and innovation took a giant steps with enormous development in the fields of biochemistry, molecular biology, immunology, genetic engineering, biotechnology etc. Series of scientific inventions in the following era have changed the courses of development that further expedite in 1990s with advances in human genetics, genomics, proteomics, bioinformatics etc. In Diabetology innovation new path way of drug delivery, noble mechanism of drug action, new target sites were invented through research in protein chemistry. Three such scientific discoveries in the field of oral diabetic formulation are:

1. The first evidence of distinct glucose- transport protein is provided by David James in 1988. The transporter (GLUT-4) an insulin-regulated glucose transporter protein discovers the mechanism novel method of transferring glucose to muscle and fat cell. Understanding how glucose is transported from the bloodstream into cells to be used as

fuel is significantly improve clinical management of type-2 diabetes along with open avenue for new drug classes.

2. This protein Glutamate decarboxylase (GAD) is an important enzyme involved in cellular communication in the brain and pancreas was discovered in 1990. The 64K autoantibody associated with type 1 diabetes is identified. The clinical knowledge leads to new drug class.
3. The incretin hormone Glucagon-like peptide (GLP-1) is discovered in mid 1990s. Incretin hormones are secreted from the gut in response to food, and the stimulates the body to produce insulin. Discovery of GLP-1 later lead to a new class of diabetes drugs.

Generic Formulations:

Generic formulation is available for the following drugs - Sulfonylureas *(Glimepiride, Glipizide, Glyburide),* Biguanides *(Metformin),* Thiazolidinediones *(Pioglitazone, Actos),* Alpha-glucosidase inhibitors (Acarbose), Meglitinides (Nateglinide), Dopamine agonists (Bromocriptine) and combination drugs in these classes. However, no generics medication available for drug classes Glucagon-like peptide-1 (GLP-1), agonist Dipeptidyl-peptidase-4 (DPP-4) inhibitors/gliptins and Sodium glucose cotransporter 2 (SGLT2) inhibitors, due to their drug are recently discoved and patent protected.(Table- OAD evolution) and their combination drugs. *Indian pharmaceutical firms have competence and expertise in generic medicines patent protection to these new drug classes are major blockage to the biomedical innovation system in India.*

Out of all drugs only *Metformin* and *Glipizide* are included in the WHO- list of essential medicine, NPPA- India. Hence other drugs are unaffordable for weak section of society.

Table 8: Anti Diabetic Drugs, Mechanism & their complications

Drug Classes	Mechanism of action & administration route	Drugs- Generics name (Brand name)	Side effects
Sulphonylureas (SU)	Stimulate the pancreas to produce more insulin *Oral Route of administrion*	**1st generation :** Tolbutamide (Orinase), Chlorpropamide (Diabinese) Tolazamide, Acetohexamide (Dymelor), Carbutamide **2st generation :** *Glibornuride,Glisoxepide, Glipizide* (Glucotrol) *Gliquidone* – (Glurenorm), ***Gliclazide* (Diamicron)** *Glyclopyramide* (Deamelin-S), ***Glibenclamide/Glyburide*(Diaβeta/ Micronase)** **3rd generation:** *Glimepiride* (Amaryl/ Zoryl/ Geminor), *GliclazideMR*(Diamicron MR60)	Hypoglycemia (lowering blood suger) & weigh gain
Meglitinide / Glinides	Stimulate the pancreas to produce more insulin *Oral Route*	***Repaglinide* (GlucoNorm/ NovoNorm/ Prandin)** ******Nateglinide* (Starlix)	Hypoglycemia
Biguanides	Reduce the production of glucose by the liver *Oral Route*	*Metformine*(Glucophage) **-1st in group** *Phenformin* (DBI), *Buformin*	Lactic acidosis Diarrhea, Nausea
Alpha-Glucosidase Inhibitors	Slow the absorption of carbohydrates (sugar) ingested- *Oral Route*	*Acarbose* (Glucobay/Precose/ Prandase)- **1st in group** *Miglitol* (Glycet) *Voglibose*(Voglib)	Bloating Diarrhea, Abnormal pain
Thiazolidinediones (TZD)	Increase insulin sensitivity of the body cells and reduce the production of glucose by the liver*Oral Route*	*Troglitazone* (Rezulin) - **1st in group** *Pioglitazone* (Actos) *Rosiglitazone* (Avandia).	Edema, Swelling, Weight gain
Glucagon-like peptide-1 (GLP-1) agonist	Mimic the effect of certain intestinal hormones (incretines) involved in the control of blood sugar *Subcutaneous Route (Injection)*	*Exenatide* (Byetta) - **1st in group** *Exenatide extended-release*(Bydureon) *Liraglutide* (Victoza) *Dulaglutide* (Trulicity) *Lixisenatide*(Lyxumia, Adlyxine) *Semaglutide*(Ozempic)	Nausea, diarrhea, vomiting Gastric mortility Weight loss
Dipeptidyl-peptidase-4 (DPP-4) inhibitors/ gliptins	Intensify the effect of intestinal hormones (incretines) involved in the control of blood sugar- *Oral Route*	*Linagliptine*(Trajenta) *Saxagliptine*(Onglyza) *Sitagliptine*(Januvia) *Alogliptin*(Nesina, Vipidia) *Vildagliptin* (Galvus)	Upper respiratory tract infection Pharyngitis, headache
Sodium glucose co-transporter 2 (SGLT2) inhibitors	Help eliminate glucose in the urine Oral Route	*Canaglifozine*(Invokana**)** *Dapagliflozine*(Forxiga**)** *Empagliflozine*(Jardiance**)** *Ertugliflozine*(Steglatro)	Genital and urinary infections, more frequent urination

(Source: Compiled from Thomas, 2012& Schwanstecher, 2011, Diabetes Canada, 2018, Drugbank, Genebank)

Collaboration in drug developments in Diabetology:

In the biomedical innovation process especially drug development due to its long incubation period, high risk of drug failure, high capital requirement collaboration is somehow necessary at various stages of drug development. The collaboration are not limited to research or innovation stages or drug discovery but at various stages from clinical trial to market formation. Most of the new drugs in last 10 years (SGLT2- all drugs) are developed through collaborations. The **table 9** below gives a glimpse of collaborative activities of successful anti-diabetic drug molecules

Table 9: Drug molecules and nature of collaborations

Name of the drugs	***Nature of Collaboration***
Glibenclamide/ Glyburide	Jointly developed by Boehringer Mannheim (now part of Roche) and Hoechst (now part of Sanofi-Aventis) in 1966
Repaglinide	Initially developed by Boehringer then out-licensed to Novo Nordisk
Nateglinide	Initially developed by Ajinomoto, Japan then out-licensed to Novartis
Exenatide	Developed by Amylin Pharmaceuticals but commercialized by AstraZeneca
Lixisenatide	Developed by Zealand Pharma , then out-licensed to Sanofi
Taspoglutide	Jointly developed by Ipsen and Roche (underdevelopment process)
Linagliptine	Developed by Boehringer Ingelheim but commercialized jointly by BI and Lilly
Saxagliptine	Jointly developed by Bristol-Myers Squibb and AstraZeneca
Canaglifozine	Developed by Mitsubishi Tanabe Pharma but commercialized by Janssen(Johnson & Johnson)
Dapagliflozine	Jointly developed by Bristol-Myers Squibb and AstraZeneca.
Empagliflozine	Jointly developed by Boehringer Ingelheim and Eli Lilly

(Sources: Complied from secondary sources)

4.4.3 Diagnostic & Devices development in Diabetology:

The first clinical evidence of diabetes in ancient time was the attraction of ants to the sugar in diabetic patients' urine. During that period uroscopy (a practice that study urine to dignose medical condition) is a prominent method of diagnosis. The urine flavour chart describes the sight, smell and taste of urine. Diabetes became successfully diagnosed through the chart due to presence of glucose in urine that gives a different texture, colour and taste. The first clinical test for sugar in urine was developed in 1841 by Karl Trommer, which involved subjecting a urine sample to acid hydrolysis. The self testing of urine using benedict's reagent requires heat for colour development, However, as the test involves liquid reagent it was difficult to transport. This problem leads to the invention of dry reagent strips. The early 19th centrury became the period of development in Dry-Reagent Chemistry. The first ever dryreagent test strip developed in the 19th century was the litmus paper. Clinitest (a modified copper reagent tablet) introduced by Ames Company, (a division of Miles Laboratory) in 1941 was the first conveninent tablet test for measurement urine glucose followed by Clinistix (Diastix) a'dip and read' urine reagent strip introduced by Miles-Ames Laboratory1956. Urine glucose testing is clinically inaccurate as it can measure only the urine output rather the glucose presence inside the body. The correlation between urine and plasma glucose were inconsistent. The clinical problem leads to invention of blood glucose dry-reagent test strips (visually monitored blood glucose test strips) in 1964. For detailed chronological evolution of different diagnostic methods and technology in Diabetology see *Annexure.*

Technological development:

1.SMBG (Self Monitoring of Blood Glucose)

The concept of SMBG faces stiff resistance during the period 1955 to 1970s from big diagnostic firms. During 1970s diabetes became major clinical problems in the developed countries. The priority of health management leads to various clinical trials in the mid 1970s. The clinical trials data revealed that close control of blood glucose reduces the clinical complications. Glycated haemoglobin (HbA1c) was introduced as an index of the quality of glycaemic control during the same period. The requirement for mass screening and testing of blood sugar for prolong period leads to gain in the concept of self monitoring of blood glucose (SMBG).

1st generation blood glucose meter: Ames Reflectance Meter (ARM) was the first blood glucose meter developed by Anton Clemens at Ames- Miles Laboratory in 1970 to produce quantitative blood glucose results followed by Reflomat (Stat Tek) in 1974, a reflectance meter using a modified reagent strip produced by Boehringer Mannheim requiring comparatively smaller volume of blood (20–30 μL). Dextrometer was the first meter with a digital display and could be operated by battery/power was came to the market in 1980. A series of blood glucose meter were introduced by Lifescan in the following years under the brand of Glucochek, Glucoscan. However, 1st generations glucometer are bulky, expensive, narrow haematocritic range and take longer period for calibaration, test and analysis.

Next generation blood glucose meter:

The automated digital read out meter with photometric test strips became available in 1987 leads to the birth of 2nd generations BGMS. During the second and third generation the technology at various platforms evolved to address the 1st generation problems. The benefits are became evident like real time recognizing blood sample, simpflying procedure by eliminating blood removal step, separation of plasma from RBCs, correcting for blood colour in colorimetric devices, improvement in electrochemical reactions and incorporation of checks to identify defects and user error in procedure (software development). All these improvement leads to simplfing procedure and improve accuracy in result. *OneTouch* Meter by *Lifescan is a* 'second generation' blood glucose monitoring system (BGMS). Use of biosensor technology in diagnostics leads to the birth of third generation BGMS. The enzyme based electrode strip improves accuracy, precision reduces error. *The ExacTech System,* by *MediSense is* the first blood glucose biosensor system*.* From 1990s onwards smaller glucose meters became available.3rd generation glucose meter focuses on contineuous glucose monitoring. New technological development occurs in this period on minimal invasive techniques (intravenous sensors, micropores and microniddles) and non- invasive techniques such as transdermal. 4th generation glucometers are focus on alternate mode of delivery or diagnosis, non-invasive methods such as (optical detection methods, thermal detection etc.) Chronologically, each developmental stages brought improvement in developing capillary methods for blood sampling, improving the error detection routines, decreasing the test time down from minutes to seconds, decreasing the sample volume required to 1μl or less, addressing pO2 effects in electrochemical sensors with change to GDH enzyme, improving dynamic range, improving haematocrit range

Contemporary research on blood glucose monitoring devices has focused on data management through cloud based technologies; the trend is connectivity of information technology systems, especially for glucose systems for the hospital market, personal computers, games consoles, phones or personalized devices. Special focus also given to the agronomics of devices or diagnostic equipments, in the design of meters, operation and data management, rubber grips for smooth handling, larger display panels, meters with minimal operating steps, auto calibration, colored sampling ports, and haematocrit correction etc. with more advanced data handling capacities also became available.

The evolution and progression of blood glucose monitoring devices, is combination of many scientific and technological progressions and assimilation of different technologies. They are Test strips techniques, SIP-IN technology; Cartiage based multi-strip systems, Lancet devices, No Coding technology, and biosensor technology in the Point of Care device manufacturing.30

Technological development and progression in a particular artifacts or device however, does not obsolete the previous or older technology. For e;g the advances in biosensor based enzymatic test trips does on completely replace the dry reagent test strips. The dry reagent test strips evolved from urine test strips to blood test strips for determining blood sugar level, however, that technology further evolved as Multistix, a reliable front- line test for detection of broad range of clinical conditions such as urinary tract infections (UTI), diabetes and kidney disorders etc.

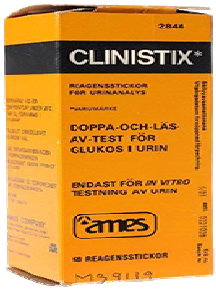
Insulin pump is a device use for continuous subcutaneous insulin therapy. This device is generally applicable to Type 1 diabetic patients where a daily dose of insulin is required. Compare to the SMBG device insulin pump is relatively new technological innovation as the 1st prototype of insulin pump was developed in 1963 by Dr. Arnold Kadish. The first

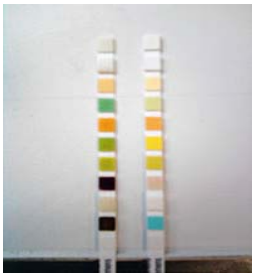
[30] A ***blood lancet (lancet)*** is a small medical implement used for capillary blood sampling. Lancets are used to make punctures in the fingers to obtain small blood specimens. They are generally disposable. A blood-sampling device or **lancing device** is an instrument equipped with a lancet. It is also most commonly used by diabetics during blood glucose monitoring. The depth of skin penetration can be adjusted for various skin thicknesses. ***Cartilage based- multi-stripsystem*** will eliminate the use of testing and lancet device. ***SIP-IN Technology*** is designed to make applying blood to the strip fail-safe, to minimize the chance of having failed tests due to not enough blood being put on the strip. Glucometers with ***No Coding Technology*** will automatically code the test strips, hence reducing the human error in manual coding. A ***biosensor*** is a biological detection system consists of a biological component combined with a transducer to perform measurement of a biochemical quantity. A typical biosensor includes a bioelement such as an enzyme, antibody, or a cell receptor, and a sensing element or a transducer.

bedside, computer controlled closed-loop insulin pump (Biostator) was developed by Miles Laboratory Inc in 1974. Biostator is an important technological innovation is instrumental for development of artificial pancreas or bionic pancreas.

Bionic pancrease is the most recent invention in this field is a cellphone-sized wearable device monitors blood sugar 24/7 and releases the hormones insulin or glucagon to keep levels steady, just like a healthy pancreas would.

Figures 7: Diagnostics technologies and devices in Diabetology



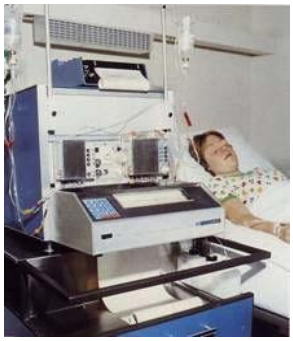


Row A **1** **2** **3** **4**

Row A: Development in Test Strips: *1- Urine Flavour Wheels, 2- Clinitest introduced by Ames (a division of Miles Laboratory) - the first conveninent tablet test in 1941, 3- Clinistix (Diastix) a'dip and read' urine reagent strip (1956), 4- Mulitistix*

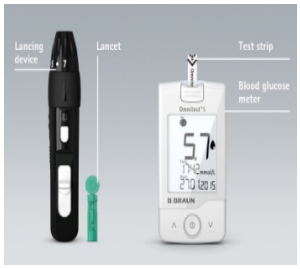
Row B **5** **6** **7** **8**

Row B- SMBG Develpment: *5- Ames Reflectance Meter (ARM): The first blood glucose meter -1970, 6- Reflomat (Stat Tek)-1974 7- Onetouch glucometer 8- Alternative BGMS- wristwatch)*

Row C **9** **10** **11** **12**

Row C- Insulin Pump Development: *9 -11 - Insulin pump (1st generation), 12- Artificial pancreas/ Bionic pancreas),*


Row D 13 14 15 16

Row D- Lancing Devices*: 13- representation of SIP-IN technology,14- Lancing device and mechanism 15. Insulin pen 16- BGM through IT devices*

4.5 Global TIS through Patent analysis:

In Diabetology, most of the patent belongs to the **three major IPC classes *A61K, A61P* *and* *C07D*** gives an indication of core technological knowledge base in this knowledge field. C07K class represents peptide, in Diabetology it is related to the technological knowledge related to insulin peptide, peptide analogs, drug class belongs to GLP that mimic insulin, A61P class indicates therapeutic chemical compounds for medical preparation, here the technological knowledge associated with the development of oral anti diabetic drugs (OADs) and medications. Similar class such as C07D for heterocyclic compounds and C07C for acyclic/ carboxylic compounds gives ample indication about technological bases in OADs. IPC classes

A61M and A61B represent diagnostics and devices that describe technological innovations related to devices such as glucometers, lancet devices, insulin pump and other forms drug delivery method, C12Q stands for measuring or testing process using enzymes, micro assays and test strips. The drug class also shows the evolution of testing methodology from dry urine based test strips, blood glucose test strips to modern day, enzyme based electrode used in glucometers. Interestingly G06F is a new class in this sector, only two decades old in the time frame, represents electronics data processing used glucometers, insulin pump for reading and analysis also diabetes app based management techniques.

IPC classes are very informative in terms of technological knowledge base however, alone does not cover the entire spectrum. *Analysis through Patent Classification System is somehow problematic; the division of classes and sub-classes in IPC are sometimes confusing, repetitive, does not give an objective pictures. It also requires subject expertise for analysis (see Annexure). Hence, possesses an evident methodological challenge for analysis.*In the present study both IPC search and keywords search used harmoniously for desired result.

Globally more than 82,000 published patents[31] applications are available in the field of Diabetology shows the enormous amount of research, activities and competence among the actors in this sector. Here, the actor includes all major biopharmaceuticals & biotech companies, leading research organisations, universities and individual inventors.

Based on the published patents data contribution of national patent offices are as follows: USA (15343), China (13377), European Patent Office/ EPO (8296), Patent Co-operation Treaty/ PCT (10661), Australia (5683), Canada (5136), Republic of Korea (3677), India (2447), Mexico (2370), Japan (2322), Russia (1779), Brazil (1349), Spain (1260), Argentina (1234), Denmark (888), Germany (745), Chile (546), UK (304), Eurasian Patent Organization/ EAPO (231), African Regional Intellectual Property Organization/ARIPO (23) etc.

However, patent application through national patent office should not be confused with the number of patent belongs to an assignee country. A foreign patent can also be routed through national patent office or PCT mode. Patent Co-operation Treaty is an important institution in biomedical innovation system. An international patent application shows the coverage, competency and capability of a firm or an assignee holder at global level. Most of the pharmaceutical organisations, MNCs routed patent application through PCT mode for wider coverage of patent protection also to save time and resources. Role of PCT will be discussed at a later stage.

[31] The total numbers of global published patents applications are 82,911 till 2018 on 22.01.2019 through WIPO-Patentscopus. The total number of patent varied from database to database. Although WIPO database updated every weekly, it depends on the respective national patent office databases for data. The numbers of data retrived here are based on the publication date at WIPO. The application date of a patent document is generally prior to the publication date registered at the national patent offices. Methodologically, it is an uphill task for referring to individual national patent database to check application date, rathers here analyst prefer a single database with publication data at WIPO. The published patent application forms should not be confused with the granted patents. As not all the published application became patents in future, however, this application trend shows the research trends in a subject area.

**Method: Patent analysis, DB: Patentscope- WIPO; Search Strategy - ('Simple search': Keyword/ Sort by: Pub Date Desc)*

Table 10: Patenting by global firms in both drugs and device segment in Diabetology

Firms (Global)	**Numbers of patents**	**Firms (Global)**	**Numbers of patents**
Drug Developments		***Diagnostic & Device***	
Merck	3181	Roche (both)	3469
Eli Lilly	1425	Abbott(both)	2432
Sanofi	1385	Bayer (both)	800
Pfizer	1116	Medtronic	167
Boehringer Ingelheim	1078	Lifescan Inc. (Johnson & Johnson 1986-2018)	162
Novartis	940	Boehringer Mannheim (merge with Roche)	62
Novo Nordisk	887	Animas Corporation	56
Astrazeneca	747		
GlaxoSmithKline	287		
Genentech	152		

(Method: Patent analysis, DB: Patentscope- WIPO)

(Strategy:-field combination (keyword + applicant name: Limit search to front page)

Here, selective global pharmaceutical firms are taken into consideration for the detail analysis. *The rationale behind choosing selected global firms are based on their presence in diabetic segment, technological history of association with diabetes research, market dominance in life-style segment and global leaders in pharmaceutical research. The study also has to limit its level of analysis because its focus on national perspective (TIS in India) not global perspective, however a comparison between the two is inevitable for the analysis.*

4.5.1 Selected Global Firms in Drug segment:

As per the diabetes market segment Novo Nordisk, Sanofi and Eli Lilly are considered as big 3C of diabetes market, dominates more than 85% market of global insulin segments. Patent analysis of these three firms shows similarity in their technological competences such as Eli Lilly (Major IPCs: A61K, A61P, C07D, C07K, C12N), Novo Nordisk (Major IPCs: A61K, C07D, A61P, C07K, and C07C) and Sanofi (Major IPCs: A61K, A61P, C07D, C07K, C07C). Eli Lilly was the first firm to sign a commercial agreement with the Toronto University in 1922 for development of insulin immediate after discovery of insulin in 1921. Similarly, Nordisk Insulin Laboratorium (now Novo Nordisk) was established in the year 1923. Novo Nordisk brought innovation to insulin research with discovery of NPH/Protamine based intermediate acting insulin in 1936. *Dominance of these firms in the insulin segment also has historical significance due to their first-mover advantages.*

Currently all these firms have patents and products in all forms of Insulins (short acting, intermediate, long acting), designer insulin, insulin analogs etc. Eli Lilly has patents related to GLP-based insulin analog- Dulaglutide (Trulicity) in 2014 and DPP-IV agonist-Linagliptine (Trajenta) co-developed with Boehringer Ingelheim. Novo researchs was dominance with proamine insulin till 1973 then there is eviences of insulin analogs (GLP-based) other drugs classes such as SUs and DPP-IV etc. Sanofi's patent analysis through field combination shows more than 1300 patents. The research base here no just limited to core diabetes research (GLP based – lixisenatide) but also associated co- morbidities such as hypertension, obesity, overweight, CVD etc.

Merck & Co (Major IPC: A61K, C07D, A61P) has earliest patent dated back to 1962 a sulphamides class OADs. This firm has patent in all major anti-diabetes drugs classes (GLP-1, GPR-120 in 2019) alongs with somatostatin analoges, PPAR- gamma that address diabetes co- morbidity. Boehringer Ingelheim (Major IPCs: A61K, A61P, C07D) current focus is on kidney related diabetes complication SGLT-2 (Empagliflozin), along with DPP- IV (linagliptin), co-developing amylin analoge with Zealand pharma. Pfizer (Major IPCs: A61K, C07D, A61P) ealiest diabetes patents is on a SUs molecules in 1960s and current research based is focus on kidney related complications (SGLT-2), co-morbidity related to CVD. Novratis (Major IPCs: A61K, A61P, C07D), relatively new in this segment that shows patent data only after 1990s. The core research base of this firm is not diabetes, rather its address its co-morbidity, diabetes related complications, medication related to diabetes neuropathy,

Peripheral Nervous System, neurogenerative disorders, Alzheimer and diabetes (BACE1& BACE2), gestational diabetes (synthetic apelin fatty acid/ APJ receptor), Wnt pathway (colon cancer), heart failure (LIK066), myostatin or activin antagonists, antibody cytokine engrafted protein – realted to T1DM) One of the successful diabetes product of Novartis is galvus (vidagliptin) Similarly, other relatively new entrant in this segment are Astrageneka (1st patent in 1994) have research base related to amylin analogs, diabetic neuropathy, anti obesityetc, GlaxoSmithKline (1st patent in 2003) focuses on co morbidity, obesity related complication in diabetes.

The current research trend suggests that all major pharmaceutical firms' significant numbers of patent in Diabetology drug segment. There are many established firms that are relatively new in this segment, where patent only traced to late 1990s. The reason for this overwhelming research interest in this segment are due to increase rate of prevalence rate and incidence rate of life-style disease during last decade in both developed and developing countries, life-style segments is a profitable segment not just limited to drug development but to the broader development of life-style modifications related to neutraceutical, food, agricultural segment. The very nature of diabetes, that associated with a lots of co-morbidity and complications such as (CVD, Hypertension, arthritis, renal failure, obesity, retinopathy, neuropathy, Peripheral Nervous System etc.) also indicates shift of established firms (Novartis, AstraZeneca, GSK) having competences in different research area such as CVD, Hypertension, Obesity somehow draw to this segment due to its co-morbidity associated with diabetes.

4.5.2 Selected Global Firms in Diagnostic Segment:

The other important segment in Diabetology is the diagnostic and device segment mostly focuses on the research related to blood glucose monitoring devices, HgA1C test kits, insulin delivery devices such as insulin pump and artificial pancreas. **Table 10** indicates that three major firms such as Roche (3469), Abbott (2432) and Bayer (800) have maximum patents in this segment.[32]

Historically, the Ames Company (Miles Laboratory), Boehringer Mannheim, Japanese firm Kyoto-Daiichi, Lifescan and MediSense are pioneer in diabetes diagnostic technologies. However, in the late 1980s and early 1990s significant changes occurred at market level with acquisitions of Ames, MediSense and Boehringer Mannheim by Bayer, Abbott and Roche respectively during 1995-98 and LifeScan by Johnson & Johnson in 1986. The whole scenario changes then leads to patent consolidation and make the respective firms as market leader of this segment. During earlier period of dry reagent chemistry in 1950s, *Clinitest* the *first convenient tablet test* for measurement of urine glucose was introduced by Ames Company in 1941 followed by *Clinistix (Diastix)* a*' dip and read'* urine reagent strip in 1956 and then *Dextrostix, the first blood glucose test strip* in1964. Similarly, Glucotest/test strip developed by Boehringer Mannheim1954, followed by *Combur-Test* in 1964 and *ChemstripbG (blood glucose strip*) in 1965.

1970s is the decade of first generation Self-Monitoring of Blood Glucose (SMBG). The Ames Reflectance Meter (ARM) is the first blood glucose meter introduced by Ames Company in 1970 followed by Eyetone Blood Glucose Meter by Japanese company Kyoto-Daiichi in 1972, Reflomat (Stat Tek) produced by Boehringer Mannheim1974 and Glucochek by Lifescan1980. Most of the first, second and early third generation SMBGs are manufactured by these firms. Similarly, in device segment the first prototype of an 'insulin pump' was developed by Dr Arnold Kadish in 1963. Dean Kamen invented the first wearable infusion pump in 1973. AutoSyringe Inc begins manufacturing Kamen's version of insulin pumps by 1976. Another important invention occurs in 1974, with the development of the Biostator that enabled continuous glucose monitoring and closed loop insulin infusion, a

[32]*Roche, Abbott* and *Bayer* are three major MNCs have patents in both drug segment and device segment in Diabetology, however, these three firms are categorized in the devices segments due to its historical association with diagnostics research and role in consolidating patents related to the diagnostic technologies.

critical technology for the development of artificial pancrease. In early 1990s Medtronic released its first MiniMmed insulin pump in the market.

Identifying technological knowledge through IPCs- the case of Abbott

Patent classes are sometimes become problematic in identification of specific knowledge field however, in this case of Abbott firm; the IPCs have clear and distinct indication of the core knowledge and competence of the firm, which is different to others firms. Abbott's technological competence shows through its patent classes (Major IPCs: A61B (Diagnostic), G01N (testing devices), G06F (electronic digital processing), C12Q (biochemical testing), A61M (Device introduction in body/media/animal etc) shows firm competence in diagnostic equipments. Even within the classes, the inventions related to G06F classes are newer (mostly in last decade) rather than others classes, shows the journey of technological advances from analogs to digital data processing and smart sensor.

One of the earliest patent shows how to determination of glycosylated haemoglobin in blood, HgA1C reagent and test kit in 1980s, electrochemical analytical sensor (2000), biosensor (2000), diabetic nutrition, technology related to in-vitro analytic sensors, combining glucose measuring and insulin pump combination (US20040254434/2004), lancing device (US20040267300/2004), fluid delivery with auto calibrations (US20050235732/2005) Biosensor (US20050258052/2005) Subcutaneous glucose electrode (US 7462264/2008), Artificial Pancreas Integrated CGM Architectures and Designs (WO2019005686/2019) Universal Test Strip Port, (IN201848019880/ 2018), RFID tags on test strips, vials and boxes (EP3467796/2019), nano- particle based electrodes etc. *Patent consolidation and firms competences in a particular field are not just depends on the research and innovation capabilities of them, but also on the acquisition and market formation.* Abbott enhance its capabilities with acquisition of Medisense (1995), Therasense (2004) and Alere (2017). This function is further elaborated in details later at market formation.

Other diagnostic firms:

Roche (Major IPCs: C07D, A61K, A61P) competences with 3469 patent applications established it as a major actors in both drug and device segment. The earliest patents dated back to 1972 a SU -OAD molecule, followed by a biguinide (1977). Most drugs development in the recent year address the co- morbidity aspect of diabetes research. The earliest evidence of diagnostic research can be traced to the year 1997 a patent related to in-vitro diagnostic technology later technological development related to diabetes management system (2003), lancing actuator(2015) , insulin pump, Blood Glucose Meter Strips (2019) etc.

Medtronic (Major IPCs: A61B, G06F, G01N, A61M, C12Q, A61K, A61N) is a established firm in Insulin pump segment. The earliest patent was related to Continuous Blood Glucose Monitoring devices (CBGM devices) and medical data management system in 1997. In the following years technology related to virtual patient software system, model predictive method and system for controlling and supervising insulin infusion developed around 2008, glucose sensor (2011), microarray electrode(2014) added further. Apart from blood glucose monitoring, alternate method of diagnostic using colorimetric sensor for non-invasive screening of glucose in sweat/tear (2018), insulin patches (2018) are also prominent technological advances.

Animas (Major IPCs: A61M, G06F, A61B) is also an insulin pump manufacture firms has patent in Decision Support System for patients (2002) to automatic diabetes management basal manual insulin control (2018), close loop insulin management system(2018) and hybrid control to target and predictive control to range model artificial pancrease(2018)

LifeScan (merge with Johnson and Johnson in 1986 now separated) - (Major IPCs; A61B, G06F) is also a diagnosis and device firms have patents in the area of glucose monitor and infusion pump, bolus dosing feedback management of diabetes, multirisk indicator (hypoglycemia/hyperglycemia) in 2018, computer programme for diabetic management (2009), Implantable Pouch Seeded With Insulin-Producing Cells To Treat Diabetes (2004), Amniotic fluid derived cells (2006)

Boehringer Mannheim Gmbh (merge with Roche) (Major IPCs: A61K, C07C, C07D, A61P, G01N) have patents with bigunide class OADs in 1970s, followed by Thiazolidinediones and insulin analogs. In Diagnostic research, patents realted to diagnostic testtube in 1970,

followed by diagnostic market Humaner T-Zell-Marker HT6 in 1993, Invivo diabetes test in 1997.

Bayer (Major IPCs: A61K, C12N, C07D,A61P, C07K, G01N, C12Q) have similar invention trend. 1969/70- SUs at the early phases followed by amylase inhibitor (1971) and G-protein receptor (2000). Also have research in nutrition sector through probiotic -2018. In Diagnostic research some prominent achievement are lightswitch indicators, voltometrics(2016), strip grabber (100-112) in 2016, indexing test sensor cartridge, Replaceable multistrip cartridge and biosensor meter, electrochemical biosensor, lancing device etc.

Recombinant DNA Technology in 1980s was an important inventor that leads to the formation of biotech firms. At the forefront was Genentech, founded in 1976 by Boyer and Robert Swanson. Insulin became the first human protein to be manufactured through biotechnology in 1978; Humulin became 1st JV product of Eli Lilly and Genentech. Some of the important inventions related to advance biotechnologies and genetic engineering are;- Human pro-insulin and analogs (Patent No. EP0055945/ 1982), Therapeutic methods for IDDM during 1993/94, Low molecular weight peptidomimetic growth hormone secretagogues (AU1996041644/1996) composition comprising insulin and insulin-like growth factor-I (IGF-I) (CA2261799/1998), Elisa for VEGF (CA2387390/2001), NPH-insulin (2002)

Co-patenting at Global Level:

The patent analysis (Global) not just indicates the research trend, firm competence and capabilities also shows the networks and collaborations among different actors. The following **Table 11** shows co-patenting trends that indicates collaboration at the early stages (basic research /translational stage).

Table 11: Co-patenting at Global level in Diabetology

Parent Firms	**Collaborative firms**
Pfizer	Merck
Astrazeneca	Amylin pharmaceutical
Novartis AG	Xenon pharmaceuticals inc
Boehringer Ingelheim	Zealand pharmaceutical
F. Hoffmann-La Roche AG	Vernalis research limited
F. Hoffmann-La Roche AG	Siena biotech s.p.a
Novo Nordisk	Ontogen corporation
Bayer	Ascensia diabetes care holdings ag
Genentech	Forma therapeutics
Genentech	Aventis Pharma
Genentech	Biogen Inc.
Pfizer	Covx technologies, Ireland

(Source: Patent analysis- global patents- WIPO Patentscope)

4.6 Summary:

Diabetology as a knowledge field is major portion belongs to clinical knowledge. However, the solution to the problem, in larger biomedical innovation framework the knowledge can be categorized mainly at three levels mainly scientific, technological and clinical. All the three knowledge co-evolved. Scientific inventions have the ability to change the path of research and innovation and course of development. Chromatography Technique and Recombinant - DNA technology became instrumental for the next generation insulin development.

In a biomedical innovation, clinical inventions, innovation and technological innovation or advances goes hand in hand, many times overlaps and complementary in nature. New clinical discovery leads to change in technological trajectory of invention and innovation. The evolution and progression of blood glucose monitoring devices, is combination of many scientific and technological progressions and assimilation of different technologies Technological development and progression in a particular artifacts or device however, does not obsolete the previous or older technology

In this chapter we analyzed selected global pharmaceutical firms active in diabetes segment in both drug development and devices and diagnostic sectors. The rationale behind choosing selected global firms are based on their presence in diabetic segment, technological history of association with diabetes research, market dominance in life-style segment and global leaders in pharmaceutical research. The study has to limit its level of analysis in global segment because its focus is on national perspective; however the global technological knowledge is inevitable analyzing technological factors or functions of innovation in a national system. .

In the biomedical innovation system, Collaborations can be identified at various stages of development from co-patenting to over all drug development process. In Diabetology, generic formulations for new drug classes not available, that will have an impact on national innovation system in India. The following chapter is the analysis of BIS in India where Diabetology is a knowledge field.

CHAPTER FIVE

BIOMEDICAL INNOVATION SYSTEM IN INDIA

(TIS -STRUCTURE AND FUNCTIONS IN DIABETOLOGY)

5.1 Introduction:

Biomedical Research is the knowledge field that concern with the fundamental understanding of the physical, chemical and functional mechanisms of human life and diseases. The scope of biomedical innovation is to help in prevention and control of diseases through novel interventions in the form of new drug, device, diagnostics equipment, surgical procedure, medical treatment and practice. The categorization of biomedical innovation is vary vast such as drug development, diagnostic, emerging areas of research like stem cell, nano sciences, synthetic biology etc. (Charkrobarty 2010). Innovation scholar have given prime importance to the firm-based or science-based research, however, clinical research, trial and practice have prominent role in the development of knowledge field as well as technological field in medical innovations. The present studies focuses on innovation in process that passes through many stages (basic research- applied – translational- clinical trials – clinical practice). There are multiple entry point and exit point and scope for innovation at every stage. The innovation process, translational process, the different types of innovation and their trajectory of development makes the system complex and vast, and analytically difficult to assess and measure performance of all the actors, organisation and institutions under one system framework.

Focusing on one diseases and innovation around that specific field helps in setting boundaries that excludes the biomedical innovation and applications that are useful for treatment of other disease. When disease is taken a unit of analysis, it serves dual purpose of covering all related innovation (drug, device, procedure, practices) in specific field, and analytically possible to canvass the bigger picture of biomedical innovations as a whole. In this study Diabetology is the knowledge field. The conceptualization of Diabetology in TIS framework was already described in the previous chapter. This chapter provides the structure and function of innovation in the knowledge field of Diabetology in India using TIS framework.

The chapter follows the sequences of events as explained in the analytical framework in Chapter 3. (For detail see pictorial representation of scheme of analysis in **Figure 4.**

5. 2 Setting purpose and boundaries to the study in TIS:

The empirical operationalization of the TIS is not always straightforward. Laying the foundation for TIS is a critical point where an analyst has several choices to make. However, the ability to pick up the right choices defines structures, functions, the purpose and the outcome of TIS.

The choice between Knowledge field / Product as a focal point:

The starting point of analysis is depends on the aim and objective of the study. The study focuses on the knowledge field '*Diabetology*'. Through the knowledge field the study will implicate the structure and function of biomedical innovation system in India and the various phases involved in the process at each stage (basic- translational – clinical stages). The study also gives ample attentions to the translational process (bench to bed) that helps in understanding the phase-wise transitions. The sub-step in the choice requires defining the *'technology'* in TIS. This part is already been explained in detail in the conceptualization of Diabetology as knowledge in TIS.

The choice between Breadth and Depth of analysis in a knowledge field:

This choice helps in restricting the system boundaries and setting realistic target for the study by choosing the *level of aggression* and *range of applications* in this study.

Level of aggregation: The definition of knowledge field is may be very narrow or much broader. It might be a specific knowledge field or a set of knowledge field. The subject biomedical innovation is very broad due to the multiple application of biology in the medical innovation e:g drug discovery, diagnostic innovation, medical process innovation, new technological advances in nanotechnology, molecular biology, tissue engineering etc. Focusing on a single technology or an artifact will not be able to give a clear picture of biomedical innovation system, however to canvass the entire horizon of BIS is practically difficult in a single study. There is a need for a fine balance between the scope of the work and feasible, achievable targets with in a particular time-period. By focusing on a single disease makes the study practically viable.

Range of application: When a knowledge field is selected as a point to start, analysis could be focused on some underlying technologies (specific drug/ diagnostic/ medical procedure) or all of them. Further the system boundary could be around specific application.

In biomedical innovation focusing on a single artifact or technology can limit the scope and objective of this study however covering all the technological advances will not be feasible. Hence, this study sets a boundary to focus on studying biomedical innovation taking a reference point of all the technological advances in a particular area of healthcare innovation. Here we set a *'Disease as a knowledge field'* to define the boundary of this study. While analyzing biomedical innovation in India taking a particular disease as a focal point, it improves the feasibility of this study by restricting all other innovations or technological advances that are not in the ambit of curing that particular disease, however this does not restrict the scope of this study by focusing on a particular advances or technology.

The *Choice of the disease* is also an important indicator because the structure and function of TIS may varies with different diseases. For a life-style disease or a tropical disease/ neglected disease the actor, organization, network and its structure and function might have great variation.

The Choice of spatial domain:

Technology is global in nature. In the case of biomedical innovation the knowledge creation, development first occurs at developing countries. Countries like India and China are technological follower nations. While, it is inevitable to take the global perspective to understand the technological knowledge, the study restricts its boundary at the national level. The geographical limitation helps the TIS to focus at national level hence fulfilling the objective of this study.

5.3 Structure of Biomedical Innovation System in India*:*

In the system approach, the structural elements are common to all different innovation frameworks. *Actors, Network* and *Institutions* are three basic components of structure. Another element *technological factor* is unique to TIS system similar to the concept of *knowledge base* in SIS.

5.3.1 Actors

Biomedical research is a multi–faceted research and innovation process that is amalgamation of basic research, applied research and clinical research, where research and innovation occurs at different stages. There are multiple, and diverse actors with different agenda, objective contributes at different stages of innovation process. Mapping the whole process is a difficult task. The innovation process here measures through the lenses of translational research. The **Table 12** gives schematic representation of the structure of biomedical innovation in India. The actors, organisations, institutions are involved at different stages of innovation processes engage in different activities. Identification of actor is methodologically challenging as different actors have different objectives and works at different innovation eco-system. Multiple methods are being used to identify the actors.

There are no clear boundaries between stages. Actors are not mutually exclusively belongs to one phase of innovation. A single actor may have multiple functions; a university or knowledge institute can engage in both basic and pre-clinical studies or a medical research institute can engage in both research and clinical activities, similarly, multiple actors can contributes for the functioning of innovation system; in the process of knowledge creation and development, university, hospital, firms, market and individual actors can contributes to the knowledge development process in TIS.

Multiple methods of identification and analysis are essential as the objectives, requirement and output of actors are different at each stage. The indicators mentioned in the **Table 12** are used for identification of actors as well as analysis of their functions. Identification of actor is a crucial step, because structure influence functions in the innovation system.

Table 12: Structure of Biomedical Innovation System in India

Stages in BIS	Actors and Organisations	Institutions	Networks/ Linkages/ Collaborations	Identification Methods/ Indicators
Basic Research Stage	Researcher Institutes-(Central & State) Autonomous organisations Universities (Public & Private) Colleges (Govt. & Private) Individual Patentee, Group of Patentee Inventors/ Scientist/ research labs Medical Research Institutes & colleges	**Agencies:** DIPP, OCGPD&T, MCI, MHRD, UGC, DST, DBT, ICMR, **Rules**: GLP- Guidelines, Ethical guidelines Indian Patent Acts WIPO (PCT Rules)	Formal network – associations, societies Co-patenting, co-authors, co-publications, Collaborations	Patents analysis Bibliometrics analysis Govt. Databases Interview & Snow-ball samples
Pre-Clinical Research Stage	Researcher Institutes (applied res) Universities (Public & Private) Toxicology Researcher Animal Houses Pharmacology (PK/PD) researcher Firms (biotech & pharmaceutical) Contract Research Organisations Clinical Research Organisations	**Agencies:** MoEF&CC, NABL, CPCSEA- AWBI DST- NGCMA **Rules:** The Breeding of and Experiments on Animals Rules GLP manuals , OECD Manuals	Formal network – toxicology associations, societies Academia- firms Academia- CROs Collaborations, outsourcing In-licensing/ out-licensing	Bibliometrics Bibliometrics: Keyword - Country- - Subject (Pharma/toxicology) Interview/Snowball Clinical Trials phases Zero, I and II
Clinical Trial Stage	Hospitals, Clinics Medical Research Institutes, Clinical Research Organisations Firms (Foreign/ Domestic) Contract Research Organisations Clinical Research Organisations	**Agencies:** MOHFW, CDSCO, DCGI, ICMR CDTL/RDTL, IPC Indian Pharmacopeia Commission **Rules:** Drugs and Cosmetics Act (1940) Drugs and Cosmetics Rules (1945) Ethical Guidelines of the ICMR (2006) Indian GCP Guideline (2001)	Firms- Hospitals Firms- CROs Hospital – Clinics Doctor- Patients CT Sponsor – Clinical Investigators	Bibliometrics Clinical Trials data Secondary sources Govt. Database Interview/Snowball Clinical Trials phases III, IV and PMS
Clinical Practice Public Policy	Doctors, Practitioners, Para- medico, Diabetic Educators, ASHA workers, PHC, SHC, THC Policy Makers, Funding Agencies Regulators	**Agencies:** MOHFW, DGHS, NHM, DCGI,CDSCO ADA, RSSDI, WHO, DHR **Programmes**: SDG, NPHCE, NPCDCS, DPCO, WHO-EM	Formal network – medical associations, societies International health collaborations, partnerships,	Interview/Snowball Policy documents Govt. programmes Secondary methods

(Sources: Author's compilations based on the analysis)

5.3.2 Networks

The second structural component of the TIS is the network formation among actors. The network can be either informal or formal one. Formal networks are easier to recognize and have clear spelled objective and nature of collaborations. Most of the recognized formal associations, societies and bodies in different field of studies are part of formal network. In biomedical innovation formal network are in the field of medicines at clinical stages such as diabetes associations, endocrinological societies (**Table 5)** or at basic stages different scientific associations, technologist associations, at pre-clinical stages toxicology associations etc. The other network, collaboration or linkages are identified through interaction between domain experts, co-patenting, co- publishing, co- authorship, research sponsor- project investigators, firm-hospital, industry- academia, funding agencies – research or clinical organisations, public-private partnership (PPP) programmes, firm- firm interaction, NGOs-public institutions, policy making agencies with policy implementing agencies, international regulatory bodies with national regulators etc. The type and nature of linkages, networks in biomedical innovation requires multiple methods for identification of networks and nature of network depending upon the level of collaborations at different stages. The informal networks are identified through the interviews with different stakeholders in the system. The collaborations and networks are described at different level in the following chapters.

It is also important to understand sign of existence and non-existence of networks as network helps in identifying system blockage or inducement mechanism and contribute to the knowledge of system problem. Non- existence or weak existences of network are indicators of system problems.

From translational research perspective, network and linkages are important between science base- translational base and clinical base for successful translation of a product. Network is an important indicator for identification of Translational gaps. The nature of linkages and network varies with their motto and agenda. All these linkages and network along with the nature of collaborations are discussed in the following chapters.

5.3.3 Institutions:

The final structural component is identification of institutions. Institution can be categorized into two types: Soft institutions are sets of common habits, routines and shared habits used in a repetitive sequence, where as hard institutions are organized by rules, norms and strategies. (Wieczorek, 2012). Hard networks are easy to recognize with secondary literature, institutional databases, government regulatory bodies, but soft institution are recognized only through interaction among the actors and organisations. As biomedical innovation are multi-stage innovation process, the different institutions regulates and shapes biomedical innovation in India at different stages.

Institutions shaping biomedical innovation at different stages in India

The process of biomedical innovation governs by complex sets of actors and institutions at different stages. Any product innovation in biomedical research either a bio molecules or a device from concept stage to the final product travels through various stages. Each stage has its own sets of rules, regulations, practices and guidelines. For different product with in the basic or laboratory stages rules and institutions may varies. For e;g a stem cell research (follows national guidelines for stem cell research –ICMR-DBT, 2017) , for herbal formulation (AYUSH guidelines), a research on neutraceutical follows FSSAI Act 2007. Each process of translational activities is governed by different sets of rules. The **Table 13** gives a glimpse of institutions; set of rules policy influences the research and innovation at each stage of development process in biomedical and translational research in India.

Table 13: Policy, rules and guidelines at different stages in BIS in India

Stages of BIS	Policy, rules & guidelines	Implementing agencies	Purpose
Basic research Stage	Good Laboratory Practices (GLP) Institutional biosafety committee (IBC) Institutional Ethics Committee (IEC)	DST-NGCMA DBT ICMR	Regulates Lab and pre-clinical Ethical issues
Translation/ Pre-clinical Stage	Toxicology guidelines – OECD Animal Studies – CPCSEA Prevention of Cruelty to Animals Act – 1960 Breeding of and Experiments on Animals (Control & Supervision) Rules of - 1998 Institutional Animal Ethics Committee (IAEC)	DST-NGCMA DAHD- Min. of Agriculture	Pre-clinical studies Animal experimentation and ethics
Clinical Trial Stage	Drug & Cosmetic Act -1940 Drug & Cosmetic Rules- 1945 Ethical Guidelines for biomedical research for human participants 2006 Indian Good Clinical Practice Guideline – 2001 Indian Medical Device Rule - 2017	ICMR CDSCO ICMR CDSCO CDSCO	Cinical trial Regulations Similar to ICH-GCP guidelines For regulation of medical devices and invitro-dignosis
Market Stage/ ***Clinical practice Stages***	Good Manufacturing Practices, Post Marketing Trials evaluation Standard of Medical Care in Diabetes, Clinical Practices Guidelines	CDSCO ADA, WHO, EASD, RSSDI, ICMR IMA	Long-term drug evaluation Clinical Practices

(Sources: Authors' compilation from secondary and primary sources)

What makes this process looks more complex, and difficult both from the stages of innovation perspective or as analyst indentifying innovation indicator are the involvement of institutions and regulatory bodies. In a laboratory stages GLP process is regulated by Dept. of Science and Technology. The nodal agency for implication of GLP in India is National GLP Compliance Monitoring Authority (NGCMA). GLP and toxicological guidelines are important as most of the new drug candidates and molecules failed to cross at pre-clinical stages of development.

However, GLP registration process in India is ***Voluntary***. There are 47 GLP registered test facilities; industrial laboratories are present in India till 2018 as per the data of NGCMA. Apart from the certification and regulation, the role of NGCMA is to sensitize and capacity building through workshop and training programmes. Biomedical research involves process like transfer of biological materials that comes under the regulatory guideline of ICMR and handling of biomaterial, waste under the regulatory guidelines of DBT and multiple institutional committees in the science-base organisation regulates various facets of scientific innovations.

The pre-clinical study involves use of experimental animals for drug testing. Committee for the Purpose of Supervision and Control of Experiments on Animals (CPCSEA), under Department of Animal Husbandry and Dairying, Ministry of Agriculture and Farmer Welfare, Govt. of India is the nodal agency regulates and approves experimentation on animals in India. The main functions of CPCSEA includes Registration of establishments conducting animal experimentation or breeding of animals, Selection and assignment of nominees for the Institutional Animal Ethics Committees, Approval of Animal House Facilities, permission for conducting experiments involving use of animals, recommendation for import of animals for use in experiments. National Institute of Animal Welfare (NIAW), Ministry of Environment, Forest and Climate Change, GOI is the nodal organization fulfills the statutory requirements that laid down the Prevention of Cruelty to Animals Act, 1960.*CPCSEA has 1748 registered animal facilities in India; however most of these animal facilities are small in size. Only 122 larger animal facilities are regulated by CPCSEA mostly include biopharmaceutical firms, national research organization, state- research organisations, clinical research and contract research organisations'.*

The translational stage of biomedical innovation process involves multiple actors and institutions. The network and linkages are within the sectoral level and sometime beyond the sectoral boundaries at the vertical and horizontal process. The regulatory institutions are operates at different level. 'There are several regulatory bodies involved in pharmaceutical regulation in India such as Drug Control General India (DCGI), Indian Council of Medical Research (ICMR), Genetic Engineering Approval Committee (GEAC), Department of Biotechnology (DBT), Central Drugs Laboratory (CDL), Central License Approving Authority (CLAA), Drugs Technical Advisory Board (DTAB) etc For e;g the toxicology studies guided by OECD guidelines, laboratories works are regulated by GLP protocol, research involving experimental animal are regulated by Committee for the Control and Supervision of Experiments on Animals (CPCSEA) act, 1960." Clinical trials are registered at CTRI at NIMS- ICMR, trials are regulated by CDSCO. At institutional level, the process goes through bio-safety committees and institutional ethical committees. All the guideline comes under the ambit of different ministry and departments.

5.3.4 Technological factors:

Actors, organization and institutions are common elements of TIS. Technological factors are unique to TIS similar to the knowledge base in Sectoral systems of innovation. Technology is global in nature in TIS. The previous chapters have a detailed analysis of technological development in drugs segment (Insulin and OADs) and devices and diagnostic segments (SMBG, Insulin pump, reagent strips). There are also component level technological progression such as blood lancet device, SIP-IN Technology, biosensor based detection, cartilage based- multi-strip system in diabetes segments. The global technological knowledge will helps in analysis the Indian biomedical innovation eco-system and technological development among Indian actors.

The unique factors to the Indian biomedical innovation system, that could not be traced at global level is herbal based formulation in Ayurveda, Unani, Homeopathy, Siddha based formulation. Yoga system are related to life-style management, have contribution in managing life-style related diseases including diabetes. There are evidence of combination of treatment with yoga in clinical practices to manage diabetes.

5.4 Function of Innovations:

5.4.1 F1: Knowledge creation, development & diffusion

In the Technological Innovation System knowledge, creation and development is a fundamental and most important function that affects all other functions. Knowledge bases are global in nature, how local TIS performs in term of adopting, creating or contributing new knowledge or existing knowledge is basis of this function. The function captures the contemporary knowledge both at global and local level to analysis the functions, however, evolutionary perspective on the breadth and depth of knowledge, its development over the time period contribute to

From Galli and teubal (1997) to Bergek (2008) seven TIS model defines this function in a different manner. Johnson (1998,2001), Bergek (2002), Carlsson (2005) includes creation of knowledge base, new knowledge, facilitation of information & knowledge exchange, Rickne (2000) describes knowledge creation regards to human capital, Hekkert (2007) includes technological knowledge and Galli and teubal (1997) focuses on R&D diffusion of information, knowledge and technology. Overall this function describes the creation, evolution, diffusion of a knowledge field, type of knowledge created and spill-over of new knowledge in TIS.

This function describes the knowledge creation and development in the field of 'Diabetology' Knowledge can be distinguish in various forms such as; scientific knowledge, technological knowledge, knowledge related to production, market, logistic, design etc. as described in various previous models. However in the present TIS on biomedical innovation a new category evolves as 'clinical trial knowledge'. Clinical trials are integrals part of a biomedical innovation process, in contrast to other innovation processes that does not involves direct human health. It is the crucial intermediary stage between the technological development of a product/process and final product/process before the consumption by the consumer.

Diabetology as a knowledge field in India

Comparing to global knowledge field, the earliest research papers in India through citation analysis can be traced back to the periods 1928-30, the papers related to new chemical compound and biochemistry from Allahabad University and Nagpur University. Earliest clinical paper can be traced back to 1950 in British Medical Journal on cause of death due to diabetes and in 1955 on diabetic retinopathy in AMA proceedings. Earliest evidence on pharmacological papers is in 1962 on oral hypoglycemic agent from BITS, Pillani. The innovation indicators patent and citation analysis has its limitation to study the knowledge formation and diffusion processes in Indian context.

Contrary to the global knowledge of discovery of insulin or glycogen metabolism, in India the ancient formulation of treatment of diabetes is more than 1000 years old. Some of the ancient Vedic literatures describe the clinical symptoms, diagnosis techniques and medical formulation for treatment of diabetes. The *Prameha* as a disease entity has been recognized since long in Ayurvedic medicine. *Madhumeha*is fairly common and is one of the chronic diseases. The earliest references of *madhumeha (Prameha)* are found in Vedas, which is oldest documented knowledge of universe. The description available in *'Atharvaveda'* is considered as the first ever on this topic and mentioned in *Kaushika Sutra*, *Sayana* and *Keshavabhatta*. Prameha is not clearly mentioned as a separate disease in Vedas but the description of a disease associated with *Bahumutrata (*excessive urination) is clearly found. The commentators of Vedas have interpreted the word *'Asrava'* mentioned in Atharvaveda in different ways. Vedic commentator Keshavabhatta and Sayana interpreted Asrava as Mutrasrava (excessive urination). Prameha is of twenty types classified on the basis ofdosas. Among them *Madhumeha* or *ksaudrameha* is taken as type of *VatajaPrameha*. Acharya Charaka defined Madhumeha as "the disease in which the patient passes urine characterized as astringent, sweet, yellowish and rough" (Chaudhary, 2017). Apart from ayruvedic literature, the clinical knowledge of diabetes in also mentioned in other medical system such as Siddha formulation, Unani formulation and ancient Yoga literatures. Most of those literature describes the treatment procedure as oral formulation either single or compound formulations from the plants and plants parts. **(Table 14)**

Table 14: Ancient formulation for treatment of diabetes in AYUSH system

S. No	*Name of formulas*	*Document Sources*	*known since (in years)*	*Description*	*Sources of Literature*
1.	Neerizhivukku Kasayam	GP08/84	1000	Single/compound formulation from plants and plant parts *Oral formulation*	*Agathiyaramuthakal aignanam1200* :Agasthiyar**Siddha formulation*
2.	NaavalKani	SR06/54	500	Single/compound formulation from part of plants*Oral formulation (Karpam Drugs)*	*TherayarKappiyam*: Therayar**Siddha formulation*
3.	KaanthaChendooram - 2	PD04/07	1000	Plant based formulation *(CenturamDrug)*	*Agathiarvaithiam600* :Agasthiyar**Siddha formulation*
4.	NilavagaiChooranam	PD03/29	1000	Prepared as *Churanam*	*Bogar700* :Bogar**Siddha formulation*
5.	NeerazhivuKudineer 3	BS01/71	1000	Prepared as *Kudineer*	*TherayarKudineer*:Therayar**Siddha formulation*
6.	M¢¾¢dic¦r´am (2)	RS/161	500	Prepared as *Powder*	*Gadanigraha*; Vaidya Sodhala*Bhava Prakasha* - Acharaya Bhava Mishra *Yoga Ratnakara Bharat Bhaishajya Ratnakar*
7.	QursZiabetus	MA3/473	50	Prepared as *Qurs*	*Kabiruddin: Bayaaz-e-Kabir *Unani formulation*

(Source: Compiled from Traditional Knowledge Digital Library (TKDL) Database,CSIR- AYUSH Collborative project, Govt. of India)

Formal networks and growth in the knowledge field in India:

The growth of a subject can be noticed when specific journal or association, society formed on a subject. APDP – Diabetes Portugal (Portuguese Diabetes Association) is the oldest diabetic association in the world established in the year 1926. ADA and EASD, the most active and influential global formal network in Diabetology were established in mid 1950s. Associations and society helped in establishing formal network in the field and helps in growth and dissemination of knowledge through scientific journals, conferences and workshops etc. Comparing to the developed countries, in developing countries like China, India & Brazil the formal networks are visible during late *twentieth* or early twenty-first century. This trend shows diabetes was a first world disease, more confined to the developed world then. Only in late 1990s due to demographic and socio-economic transitions diabetes became a major problem in developing countries.

One of the oldest formal networks in Diabetology in India, Diabetes Association of India was found in 1955, Research Society for Diabetes in Developing Country (RSSDI) is most prominent society excusive for diabetes established in 1972, and the Research trust of Diabetes India is a recent inclusion in formal network category established in 2000. Diabetes is a clinical subject, the roots of knowledge formation lies not exclusively in Diabetology domain rather in the broader domain of medicine. Before, Diabetology field was established knowledge creation and diffusion occurs through other relevant clinical network[33] such as Association of Physicians of India (1944), Endocrine Society of India (1971) Indian Medical Associations (1928),

Diabetology is a clinical subject, hence major portion of knowledge resides in clinical domain, but in biomedical innovation there are two other knowledge bases science and translational or applied research contribute to the innovation process. As a multi-phase system, formal network can be formed at various stages for fulfilling specific goal and objective. During citation analysis, we were able to find out some of the networks and their journal that contributes and help in growth of the knowledge field. The networks like Association of Clinical Biochemists of India (1975), Indian Pharmacological Society (1966), Indian Association of Clinical Medicine (1992), Indian Drug Manufacturers' Association

[33]Read as *Name of Network (Year of Establishment)* e.g. Endocrinology Society of India was established in the year 1971.

(IDMA)- 1961, Indian Association of Biomedical Scientists, Indian Pharmaceutical Association (1939) Indian Association of Pathologists and Microbiologists (1949) Indian Association of Preventive & Social Medicine (1974) Indian Association of Medical Microbiology (1976) Associations, societies and bodies are not only contributes to the scientific, technical or clinical knowledge in a field but also works toward awareness (through magazines) drives and critical policy interventions.

Knowledge development in the contemporary scenario: *(Through research publications)*[34]

India's Contribution in global literature in Diabetology:

Diabetes became a global epidemic in the recent past engulfing both developed and developing countries. The research publication in the area of diabetes show exponential growth in last two decades due to global attentions received by the clinician, policy makers and researcher.

Globally the number peer reviewed research articles in diabetes has increased from below 15,000 before 1960 to more than 2.4 lakhs in last decade (2000-2009) clearly showed the emergence of this discipline. An additional amount of research articles 3.7 lakhs in last 9 years (2010-18) indicating research publication in Diabetology will further increase in the future. **(Figure 8)**

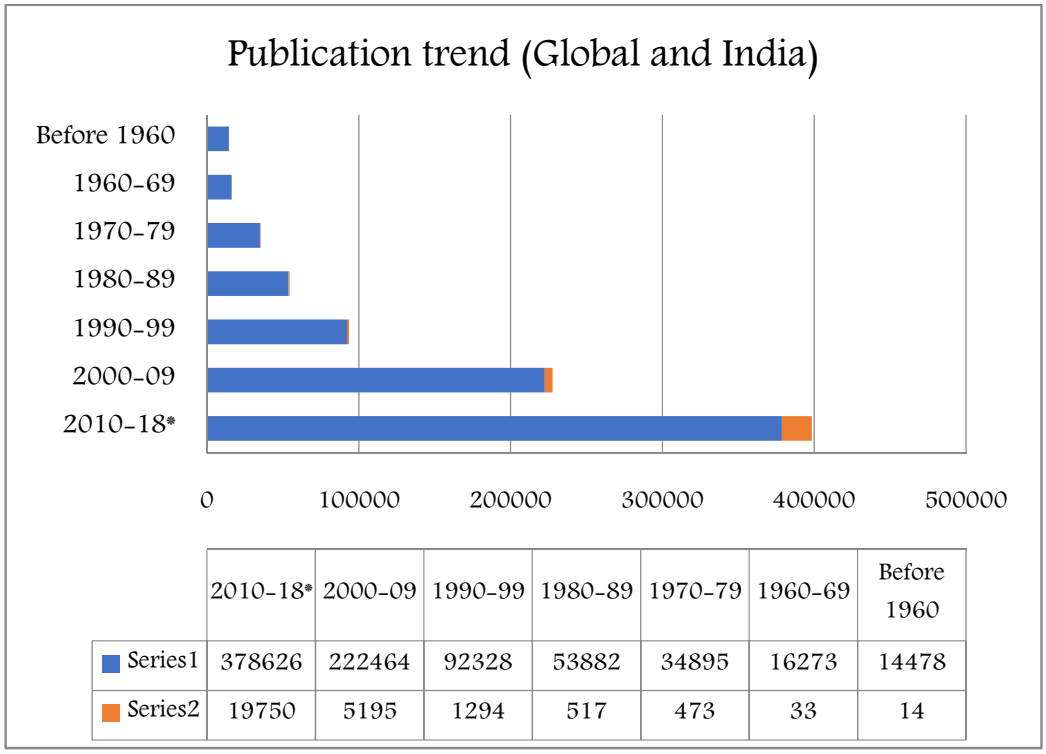
[34] Research publication trend analysis is an important innovation indicator. The number of publications varies from database to database depending on the coverage. The analysis was done through Scopus database. The total numbers of global publications are 8,12,073 in Diabetology, out of which 6,01,090 are in between the period of 2000-2018.(access to database feburary 2019) Only that period was considered for the details analysis. Apart from the number of publication, Scopus analytics provides information regarding document type, year, author, subject, sources, keywords, funding sponsors, country of research publications. These indicators are useful of analysis purpose, however, data retrival and search strategy is very important for the accuracy and precesion of the data.

**Method: DB: Scopus, Elsevier – Search query: 2 major query sequences are:-*

Global research publication data –query sequence : (TITLE-ABS-KEY(diabetes) AND PUBYEAR > 1999 AND PUBYEAR < 2019)

publication data(India)–query sequence: ((TITLE-ABS-KEY(diabetes) AND AFFILCOUNTRY(India)) AND PUBYEAR > 1999 AND PUBYEAR < 2019)

Figure 8: India's contribution to the global literature in the area of Diabetology



	2010-18*	2000-09	1990-99	1980-89	1970-79	1960-69	Before 1960
Series1	378626	222464	92328	53882	34895	16273	14478
Series2	19750	5195	1294	517	473	33	14

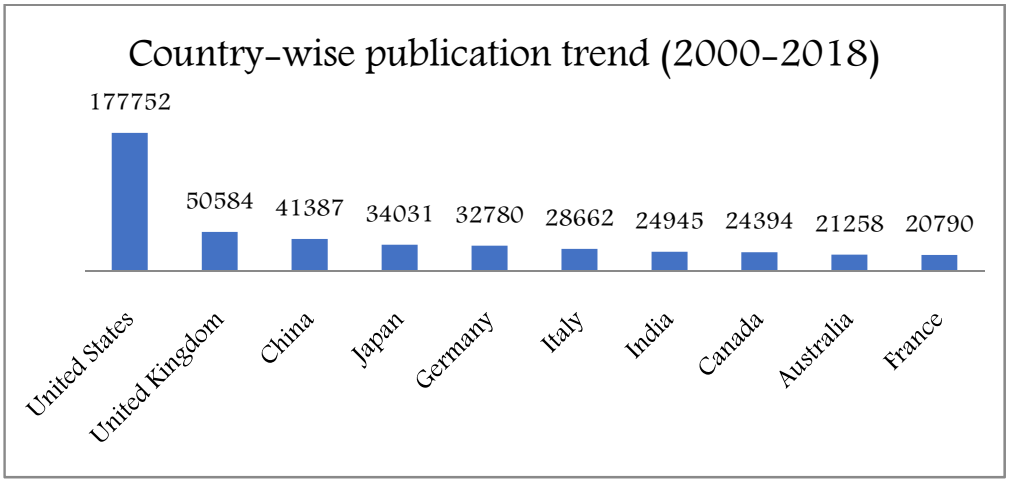
(Source: analysis through Scopus database, Elsevier)

Contributions of Indian actors, organisations and institutions in the global pool of research publication have shown steady progress from 0.09 percent before 1960 to 2.3 percent during the period from (2000-09). Most interestingly, in the last 9 year 2010-18 the contribution to the global pool of research publications is 5.2 percent, double the amount of publication from previous period. The total research publication trend shows growth in literatures after 2000, however, contribution from the India actors are maximum recently during the period from 2000-2018

Numbers of universities, hospitals, firms, scientists, researchers, clinician and policy makers have significant contributions to global Diabetology pool of research publication. India's contribution to these global innovations has increased many folds in last two decade. Globally, India stood at 7th position in terms of total number of publications from 2000-2018 **(Figure 9)** United States of America has hegemony in terms of research publications with more than 1.7 lakhs research publications that accounts for 3 times of total publication of United Kingdom, which stands distinct 2nd in the list. India's total publication during this

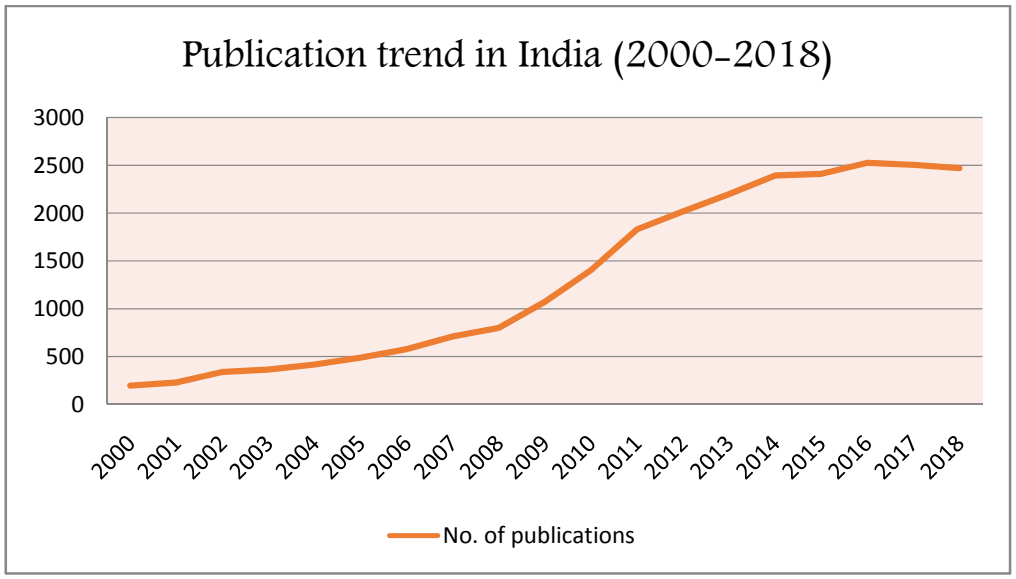
period is less than 1/7th of USA and less than half of UK. The country wise trend shows both developed and developing countries have research publication in Diabetology.

Figure 9: Top ten countries for research publication in the area of Diabetology



(Source: analysis through Scopus database, Elsevier)

Figure 10: Growth in research publication in the area of Diabetology in India



(Source: analysis through Scopus database, Elsevier)

The research publication pattern in India (2000-2018) shows an upward trend from below 200 per year publication in the year 2000 to more than 2400 for last four consecutive years (2015-18)

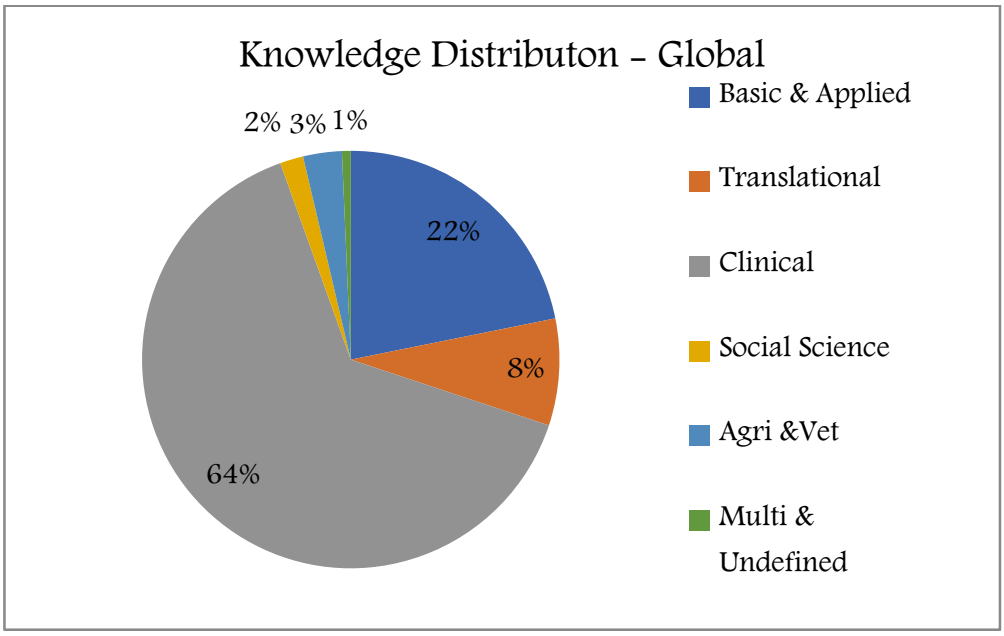
Distribution of knowledge field in Diabetology

The TIS function *(F1: knowledge development and diffusion)* emphasized on different types of knowledge and sources of knowledge in a system. The **Figures 11 & 12** are representation of different sources and types of knowledge in this biomedical innovation system. These two figures represent different sources and type of knowledge in Diabetology research and innovation at global and national level. From the prospective of biomedical innovation and different stages of translational research and innovation process, the classification is attempt to distinguished between basic, applied, translational, clinical knowledge by categories different disciplines under different category. However, the classification is a bit problematic and a major methodological issue.[35]

Diabetology is the clinical science of diabetes mellitus, its diagnosis, treatment and follow-up. The core subject area is medicine and endocrinology. In both, global and India's literature in diabetes the maximum contributions are in the clinical subjects (64% and 44% respectively), followed by basic and applied science subjects (22% and 27%) and then translational research areas (8% and 23%). Diabetes is a life-style disease, diet and nutritional are part of management. Agriculture and *veterinary* science contributes to Diabetology research. Diabetes is associated with financial and social burden, generates research interest among social sciences researchers. However, from biomedical innovation and translational research point of view, the most difficult part of this classification is distinguished between basic, applied and translational knowledge. The problem has been further discussed in the following chapter on issues and challenges in translational research.

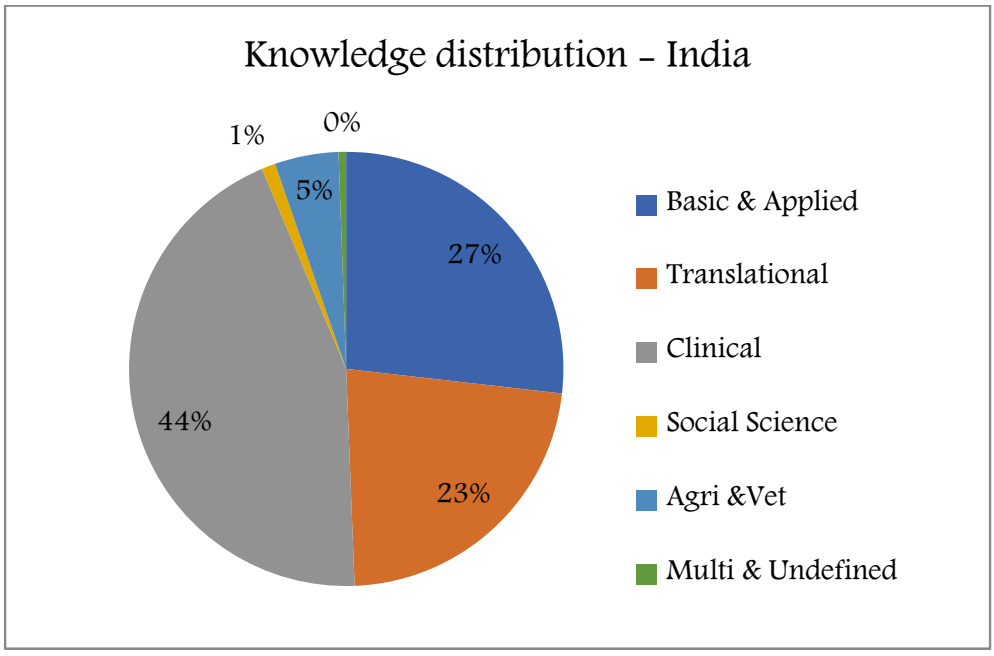
[35] To analyze the knowledge distribution in various fields in Diabetology, the subjects are being classified into following categories. Category 1- Clinical: (Medicine, Nursing, Neuroscience, Dentistry, Health Professions) Category 2- Basic & Applied: (Biochemistry, Genetics and Molecular Biology, Immunology and Microbiology, Chemistry, Mathematics, Physics and Astronomy, Earth and Planetary Sciences & Computer Science) 3. Translational: (Pharmacology, Toxicology and Pharmaceutics, Engineering, Chemical Engineering, Materials Science) 4- Agriculture *&veterinary:* (Agricultural and Biological Sciences, Veterinary, Environmental Science, Energy) 5- Social Science: (Psychology, Social Sciences, Arts and Humanities, Business, Management and Accounting, Decision Sciences, Economics, Econometrics and Finance) 6. Undefined area

Figure 11: Knowledge distribution in Diabetology at global level



(Source: analysis through Scopus database, Elsevier)

Figure 12: Knowledge distribution in Diabetology in India



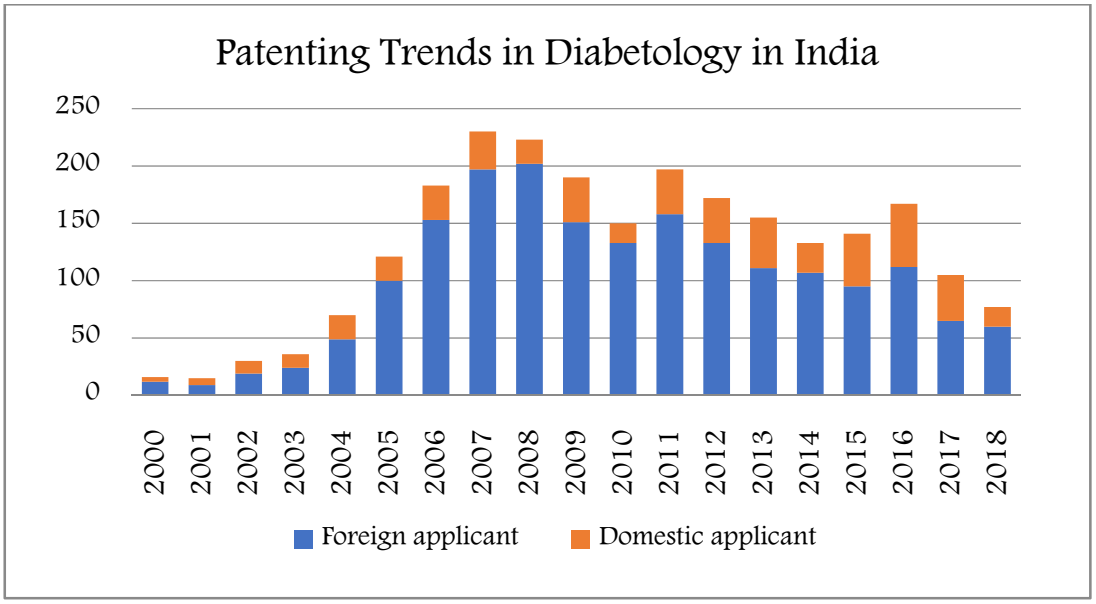
(Source: analysis through Scopus database, Elsevier)

TIS in Diabetology in India: through patent analysis

Compare to the global trend, only 2425 patents[36] are registered at the national patent office in India in Diabetology. However, the total number should not be confused with the domestic applicants. It is the total number of patent applications received at Indian patent office that seeks patent protection with in India consists of both domestic and foreign applicants.

Out of 2425 patent 14 patents belongs to the period before 2000 and rest 2411 patent application are belong to the period from 2000- 2018. This also shows the growing research and innovation in the field of Diabetology in recent year both global and national level. **Figure 13** describes detailed years wise patenting trends in India from 2000-2018[37].

Figure 13: Patenting trends in the area of Diabetology in India



(Source: patent analysis through In PASS, IP-India)

[36]The total numbers of patents registered at national patent office are 2411 till Feb 2019. The data were accessed through IP- India INPASS (Indian Patent Advanced Search System). For patent analysis, the reasons for selecting two databases are that, through WIPO-Patentscope only global patenting trend or domestic patent application routed through PCT mode can be analysed, but it excludes other domestic patent application, which are not intented for global protection. When the research focus is to analysis biomedical innovation in India, it is inevitable to analysis the domestic trends. IP- India dataset have clearly met our objectives and demand.
**Method for obtaining total number of patents: Patent analysis, DB: IP- India INPASS;*
Search Strategy - ('Simple search': Keyword/ Sort by: Pub Date Desc, restricted search area to Abstract)

[37] Year wise trend analysed manually by limiting time period (e.g. 1/1/2008 to 31/12/2008) and restricting search area to abstract for both the published and the granted patents.

From the total patent applications 78.3% (1890) are foreign applicant and only 21.6% (521) are domestic applicants. *At one had that shows the dismissal trend of national actors and their innovation capabilities at least at patenting level on the other hand the larger foreign applicants show the future emerging markets in India, a positive signal, where firms and actors seeking patent protection for their innovation.*

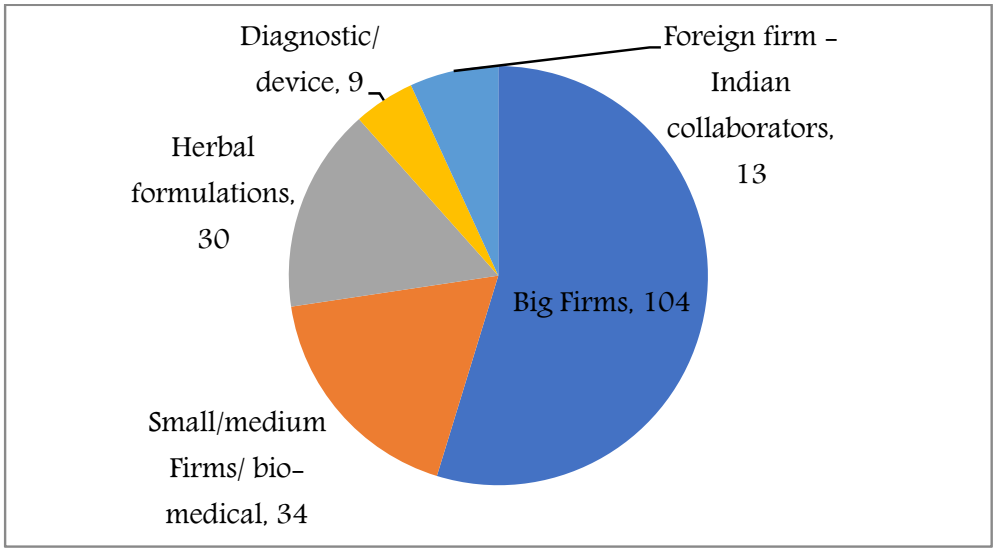
Year wise in total 2007 has maximum applications (230) followed by 2008(223) and 2009(190). However, while observing separately foreign application trends with the domestic applicant it shows foreign applicant have maximum growth in the period between 2006-11 precisely 2008 (202), 2007(197), 2006(153), 2009 (151) and 2011(158) and domestic application trends have maximum growth in the period between 2013-17 precisely 2016(55),2015(46), 2013(44) and 2017(40).

The global trends through PCT at IP- India could not solely reflect the global trend, however comparing patenting trends through WIPO- Patentscope data shows 2009-11 have maximum application then the slightly decreased thereafter. *These data shows research in Diabetology in India is catching up and shows positive growth in recent years comparing to the global trend*

Research and innovation of domestic firms in Diabetology:

The detailed patent analysis of the entire patent application of Indian applicants shows an interesting trend. They are 64 firms in total, have registered patent applications at Indian Patent offices. For analysis purpose we divided these firms into following categories. Big Firms (14), Small & other firms (17), firms based on herbal formulation (15), firms related to diagnostics (9), foreign firms (9). The following **Figure 14** shows category wise numbers of application in the categories of firms.

Figure 14: Number of Patent application by different categories of firms in India



(Source: patent analysis through In PASS, IP-India)

A. Big firms:

(14 firms in this category with 104 applications)

In this category we considered top 20 India firms and their performance in Diabetology research and innovation in India. Dr. Reddy's Laboratories Ltd. is one of the pioneer firms in NCE research in India. The first successful drug candidate molecule *'glitazones [DRF 2593 (Balaglitazone)'* was discovered in 1996, then by 2005 the molecule out licensed to Novo Nordisk. Dr. Reddy's patent portfolio does not have any patents related to Diabetology after 2000. Maximum numbers of patent application are from erstwhile Ranbaxy Laboratories Ltd. (now Sun Pharma) (29), followed by Wockhardts Ltd (24) and Cadila Health care (20).

Area of research: Most focused research area is OADs where most of the patents belongs to the older drug class such as SUs or biguinides, only few patents in the recent years belongs to new drug classes (SGLT2 inhibitors: Sun pharma: Ertugliflozin- 2017, Dapagliflozin - 2016 GPR120 Agonists: Nicholas Piramal India Ltd. 2016, Wockhardt Ltd. Saxagliptin- 2012 and Sitagliptin-2013) Only two firms have research focus on Insulin. Biocon: (Full length peptide expression (2006-07) and Wockhardt (long-acting insulin- 2008). Others than OADs and Insulin, diabetes is associated with various co-morbidity and complication such as BP, Nephrology, CVD etc, hence many research also have patents related to its complications (Ranbaxy, Panacea biotech, IPCA Lab). Reliance Life Science Pvt. Ltd. has patent on lipase-

based drug delivery system. Cadila has wider area of patent portfolio in both old and new drug classes, and peptide analogs related to insulin.

Collaborations: Top Indian firms have limited collaborations at the invention level/ basic research level (two collaborations can be noticed at this stage. Cadila Pharma with Synzyme and Lupin – collaboration among the inventor of different countries and institutions)

Issues: One interesting trend is that there is a period of time lag from 2005-15, these is no new patents for any new molecules by Indian Firms in Diabetology (exception – Cadila Healthcare Limited). This perception is also echoed in the National Pharmaceutical Conclave in 2019, that no new molecules/ innovation occurred by major big Indian firm in last 15 years, there focus more on fixed dose combinations rather innovations.

B. Firms (Bio pharmaceuticals, others small and medium):
(*21 firms in this category with 34 applications)*

In this category we considered 21 India firms and their performance in Diabetology research belongs to chemical and pharmaceutical sectors, biotech, drug discovery service companies, CROs, research based pharmaceutical companies. This category of firm's comparatively smaller to the 1st category in terms of size and volume however, the composition they are more as a research cum production oriented firms, which are typical characteristics of biomedical firm. Hence, Interdisciplinarity and collaborations are evident. Interestingly, out of all applications 31 are in last 10 years (2009-2018).

Area of research: The areas of research are same somehow, with big firms (OADs, Insulin etc), however a positive trend is research focus on new drug classes (DPP-IV, alpha glucosidase inhibitor, sitagliptin, empagliflozin, teneligliptin). Apart from the drugs new novel methods of drug delivery system by Reliance Life Sciences, a chewable solid OADs by Bafna pharmaceuticals, Stem cell encapsulation by DiponEdBiointelligence, Chennai and industry scale production of stem cells Kasiak Research, Mumbai are also present in the list of patent applications.

Collaborations: Four collaborations can be noticed in this category at the invention level/ basic research level Synzyme with Cadila Pharma (CRO-pharma) on insulin analogs, Aurigene discovery technologies limited with Novartis (International collaborations – DPP-IV molecules) and Impetis Biosciences limited with advinus therapeutic (tata group) –CROs

(NCE molecules), Transgene Biotek Ltd., Medak, AP (insulin analogs). The last two collaborations occurred at the inventor level.

Issues: The development in this category is a positive influence on the Diabetology innovation and market in India. Most of the patent applications are filled in last 10 years, shows diabetes became priority areas for research and innovation also have a positive market a head. Although with in industrial structure collaborations among big-small firm or CROs-firms are evident, however, through patent analysis in this category industry- academia linkage is not evident at patent application that does not ruled out any other forms of collaborations among industry and academia. These are many promising innovation in this category both by new entrant and established firms, however, number of PCT application are less.

Methodological challenges: Due to these recent inventions, the translation of these new inventions into a successful product cannot be accessed at present context, because in biomedical innovation especially drug discovery, the incubation period is minimum 7 years for a new product. There is also some minimum time period require for PCT application to process before publish, hence, these international patent application are not traceable at this stage.

C. Firms- Herbal formulation:

(*15 firms in this category with 30 applications)*

Traditional medicine, herbal formulations have unique role in medical innovations. Specially, in life-style diseases such as diabetes, hypertension, where a diseases can only be managed rather cured. In India, many firms explore their research capabilities in this sector, due to positive future market. There are 15 India firms belongs to ayurveda, unani, siddha, herbal formulations, FMCG companies, firm engaging in neutraceutical, food and nutritional products etc. The patent applicant includes established ayurvedic firms such (Patanjali, Dabur Research Foundation, Himalaya) and FMCG firms Mysore sandal (choornam), nutraceutical/ functional food based firms (Lalianeutraceuticals, AvesthaGengraine Technologies, Innoveda Biological solutions, Holy Crystal, Arjun Natural Extract etc.) Out of all applications 20 are filled in last 10 years (2009-2018).

Area of research: There are two major research areas of the firm in this category. One category belongs to herbal based extract or formulations (mostly consists of AYUSH firms) and other category is functional foods and nutrition (FMCG firms and neutraceutical firms)

Collaborations: One industry- academia linkages at innovation level notices in this category between Sentiss Pharma Pvt. with Delhi Institute of Pharmaceutical Science and Research (DIPSAR) and Promed research centre, Gurgaon. The patent application invention in 2011 is related to "A synergistic herbal composition for preventing and treatment of diabetic retinopathy and cataract". Sentiss pharma has product portfolio related to ophthalmic, ENT and inhalation products, but any products development related to the above patents specification cannot be determined.

Issues: There are no PCT applications in this category. There are also sectoral issues related to AYUSH products and research and innovation. This study also has methodological challenges in tracing translational activities of AYUSH product, as the methods such as patents, publication, clinical trials, market reports are not characteristics of AYUSH firms.

D. Firms- (Diagnostic & Device)

(6 firms in this category with 9 applications)

Diagnostic and device is a key segment to the medical innovation. For diabetes, screening or early detection of diabetes is important for management of disease. In this category 6 firms have 9 applications; most of these applications are in last five years. The major focus are of these patents are Point-of-Care (POC testing devices) and healthcare mobile Aap. Interestingly, established IT firms such as TCS & HCL has entered this segment of POC testing devices recently. Other patent are related to Omni active Health Technologies diagnosis on diabetic retinopathy and ZUM HEILEN m-health applications.

The translational process and the time-period of translation are different for different product segments. The time period for translation or innovation process (Idea -concept - product development) is least in this category compare to the other segment. Within the segment, IT related applications such as health app, software development related to device, software programming connecting device with database or cloud based monitoring tele-medicine progrmmes a product can be developed within months. But for the POC device, the innovation process takes usually longer time then IT based development, however the time period is less in compare to drug developments.(OADs, Insulin or herbal formulations).

ZumHeilen Healthcare Pvt. Ltd has a M-health application products called as tele-diabetology service.

E. Foreign firms

(*7 firms in this category with 13 applications)*

The purpose of this category is to identify and map contribution of the individual actors, innovator and firms in research and development in Diabetology innovation of a foreign firm. In this categories two types of contributions of Indian actors can be identified, one as a co-inventors in a patent application other as a co-applicant in a patent application. *(as mentioned in the **Table no 15)***

Role of Research Organisations: *(through patent analysis)*

Patent analysis also reveals innovation among premier research institutes in India. In this category, there are 57 patent applications from 14 different organization, maximum from in house R&D institutes of CSIR (39) followed by DBT (5), DST (3), ICAR(2), DRDO (1), KIRTADS, Govt. of Kerala(1). Apart from the above attached research organization, they also support research and innovation through extramural funding to independent research. In this category, there are 6 patent applications are retrieved that are supported by CSIR (3), ICMR (1), DBT (1), CCRAS (1).

CSIR:

There are 14 CSIR research institutes have 39 patent applications in Diabetology, CDRI-Lucknow has maximum patent applications (10) followed by CFTRI-Mysuru & IICT - Hyderabad (7 each), IICB-Kolkata (3), NBRI-Lucknow & IGIB-Delhi (2), CIMAP-Lucknow, CLRI-Chennai, CEERI- Pillani, NCL-Pune, NPL- Delhi, CCMB- Hyderabad, CGCRI-Kolkata , IIIM- Jammu (1) each.

Area of Research: The innovations among CSIR institutes vary as each organisation has different expertise. The range of products and process involves new process, animal model, NCEs, herbal formulations, diagnostics and devices and other products related to diabetic complications. CFTRI-Mysuru have patents related to food, nutrition and neutraceutical products such as (low fat cake, fiber enrich rice, fiber enrich biscuits, cereal bars etc.), Both CDRI and IICT has similar areas of patents on New Chemical Entities (NCEs) and herbal formulation. IGIB and CCMB are premier institutions in biochemical, molecular, cell and

integrative biology; hence the patent of IGIB is related to genetics and molecular biology. CCMB has patent related to transgenic knockout animal model and islet transplant procedure in diabetes. NCL, Pune has patent related to diagnostics markers of HgA1C biomarkers. Both CGCRI and CEERI have patent related to diagnostic sensors and POC non invasive device respectively. CLRI- Chennai has an innovative product to deal with diabetic foot related complications. There are many collaboration patterns (inter-departmental, inter-institutional, between different research organization, research organization and academic research organisation) are observed in these innovation activities. The research and innovation activities in the area of biomedical research especially Diabetology is diverse, different products, process and artifacts are developed at different institutional setup for solving common problem of the disease.

Issues: Most of the institutional patents of CSIR, DBT have PCT applications. There are two successful translational products by CSIR institutes are one a herbal drug 'BGR 24' co-developed by CIMAP and NBRI and another 'foot ware for diabetic patients' developed by CLRI. Apart from these, there are many products and process are at different stages of developments. The details case will be discussed in the next chapter. Similar to the big firms, there are less patent applications between the periods of 2005-15.

Other research institutes: There are 18 other application belongs to different research organisations. DBT organisations NCSS- Pune and NII- Delhi have patents related to insulin mimicking while NIPGR- Delhi has patent on herbal formulations., most of other patents are in herbal formulation except one DST patent on Self- monitoring blood glucose meter. There are other patent of NIPER, UCMS-Delhi, ICAR- NDRI etc. There are collaborations at the institutional level between DBT-NII with IISc in insulin analog research and research on herbal formulation with joint effort from CSIR, DST and Government of Kerala based tribal instituteKIRTADS. .

Role of Universities and Institutes: ***(through patent analysis)***

Apart from research institutes there are many universities such as DU, JNU, IISC, BHU, IITs, AMU, MS-Baroda, JU, Jiwaji, ICT-Mumbai, Annamalai and Chandigarh University have patent applications in the area of Diabetology. There are many private universities AMITY (**10**), SRM, Integral university, LPU, Manipal Academy, Deccan, VIT, SASTRA University and private engineering colleges and institutions have patents in this Diabetology. Most of

these patents are in the recent 5 years. Many emerging areas of research such as cloud based management of data of hyperglycemic conditions, biomedical engineering and instruments related to POC device.

Individual patentee:

There is a good numbers of patent applications (124) are from individual inventors, grass root innovators. Most of these applications are in the herbal formulation, traditional knowledge, natural treatment procedures and life style managements, yoga, diets, naturopathy etc.

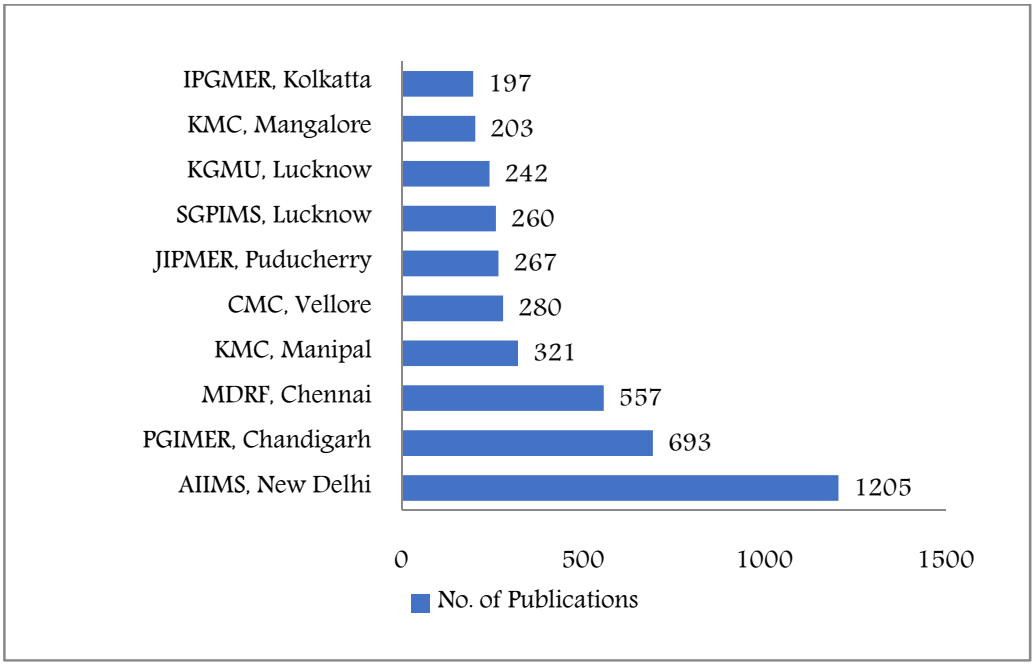
The patent analysis shows that not all the patents are meant for translational purpose. Yoga, naturopathy, treatment procedure using traditional methods are way imporving life-style and diabetes management does on yield a new product or process from concept through innovation cycle, however, these intervention are helpful in existing interventions.

Role of hospitals and medical research organisations in knowledge development:

As the core knowledge field of Diabetology belongs to clinical knowledge the contribution of hospitals and medical research organization are maximum in terms of publications compared to other knowledge bases of science or translational research. The publication data reveals **(Table 15)** that only one organization (AIIMS) in India has more than 1200 numbers of peer reviewed research publications, followed by PGIMER and MDRF in the area of diabetes research in India. Publication data is an important innovation indicator to access the output of research organization, academia and medical organization. Out of all the publication data, hospital or medical colleges based research publications consists of 55% of total publication, university and academia based publication consist of 34% and rest only 13% belongs to publication by specific research institutions in India. Within top 58 institutions having more than 100 publication lion share of publications are by top 27 medical college and institutes in India, followed by 23 universities based research and rest only 8 research organisations. The citation data also pointed out the nature of work been done in the field of Diabetology in India.

Issues: Specialized research organisations exclusive for Diabetology research (except MDRF and DRC) are less in number in the higher echelon of the pyramid. In the biomedical innovation process, the publication in the knowledge field of Diabetology is more focused on the clinical trial, clinical efficacy or effectiveness or epidemic studies in India rather drug development or discovery and translational research.

Figure 15: Research publication of hospital and medical research institutes in Diabetology in India



(Source: analysis through Scopus database, Elsevier)

Collaborations:

The publication trends of hospitals and medical research organization shows collaborations with medical organization depends on the function and activities with research organisations, CROs, policy organisations, and firms. In biomedical innovation system, collaboration occurs at various levels. The three important phase's science, translational and clinical stages, intra-level collaboration is evident but from translational perspective the collaboration need to cross the institutional boundaries. The *Academia- Industry* collaborations, *Clinical-Academia* or *Clinical- Industries* collaboration are important in translational research. The

Table 15 indicates some of these collaborations in India.

Table 15: Co-patenting and collaboration at research level in Diabetology in India

Patent Organization	***Collaborating Partners***	***Nature of Collaborations***	***Area of research in Diabetology***
CSIR	DST- SCTIMST, KIRTDS Govt of Kerala	CSIR - DST- State level collaboration	OADs - herbal formulations
CSIR-IICB	Vishwabharati University	Res Org - University	Insulin-gene expression - Translational research
CSIR-IICT	Kakatiya Univeristy PunjabUniveristy	Res Org - University	OADs
IIT - Guwahati, IIT-Patna	Tezpur University, Nagland University, Santiniketan	Res Org - University	Insulin Analogues
CSIR-NBRI	CSIR-IICT	Intra-institutional	Herbal formulations
CSIR-NBRI	CSIR-CIMAP	Intra-institutional	Herbal formulations
IISC	NII	Inter-institutional	OADS
CSIR-IICT	ICMR- NIN	Inter-institutional	NCE
UIPS- Chandigarh	Hamdard University	Inter-institutional	Herbal formulations
BHU	SRM University	Academia (Govt-Private)	Herbal formulations
Annamalai University	Loyala College	University - College	OADs
IMS- BHU	SASTRA University, ESCORT	*Clinical - Academia*	Herbal formulations
Jadavpur University	IPGMER	*Clinical – Academia*	OADs
Sentiss Pharma Pvt. Limited	DIPSAR	*Industry- academia*	Hebal formulation for Diabetic Retinopathy
Transgene BiotekLtd	Individual inventors	*Industry- academia (individual)*	Insulin Analogues
Tata Consultancy Services	Individual inventors	*Industry- academia (individual)*	POC Testing Device
Cadila Healthcare Limited	Sanzyme	Industrial (Firm- Firm) domestic	Insulin Analogues
Lupin Limited	Individual inventors	Domestic firm-foreign inventors	NCE
Impetis Biosciences Limited	Advinus therapeutic	Co- Patentee	new drug class - OADs
FTG Bio.	Vipragen Biosciences Pvt Limted,	Co- Patentee	NCE
Foreign firms			
Evolva SA	Individual inventors	Co- inventors	Drug delivery mechanism
Jenrin Discovery	Individual inventors	Co- inventors	Drug delivery mechanism
Sandoz AG	Individual inventors	Co- inventors	Drug delivery mechanism
GlaxoSmithKline	Individual inventors	Co- inventors	New drug class - OADs
Medivation Technologies	Individual inventors	Co- inventors	New drug class - OADs
Plant Lipids Private Limited	Individual inventors	Co- inventors	Plant based formulations

(Method: Patent analysis, Data Base: In PASS - IP, India)

Summary: Knowledge formation is core to the TIS function and influences all other functions. The knowledge in biomedical innovation system can be in many forms. As discussed in the previous chapters about scientific, technological and clinical knowledge in Diabetology, this section evaluates the role of different actors and organization contributes to the three major field of knowledge in Diabetology. This section analysis's the role of firms, research organisations, university and hospital in knowledge development in TIS in India. Understanding the global knowledge base also helps in evaluating the performance of actors and their contribution to the function of TIS. Apart from these core division of knowledge fields, there are clinical knowledge related to clinical trial, clinical practices, policy and programmers' also affects and contribute in this function. Their role has been evaluated in the next chapter.

5.4.2 F2: Influence on the direction of search:

This is a qualitative function of TIS that measures the intrinsic forces that influences the development of a particular TIS. For development of particular TIS, whole actors (Research organisations, Firms, medical research institutes, hospital and clinic in this TIS) and institutions at all the different stages of biomedical innovation must have sufficient incentive and/or pressures for the organization to be induced to do so. The focal point of current TIS is based on the problem sequences. Here, the major problem is Diabetes.

Diabetes as a global health problem:

Diabetes has become a global health hazard in both developed and developing countries. There is enormous pressure on/from global health organisations such as World Health Organisations, United Nation, American Diabetic Associations, NICE, International Diabetes Federations to effectively tackle the issues. MDG has focused on the communicable diseases where no mentioning of non- communicable disease in the millennium plan. However, with in a period of 15 years, global health priorities were changed. The SDGs focuses on Non-communicable Disease. The globalization process, the sedentary life-styles, sleep deprives, mental pressure all acumen to life-style related diseases.

Due to the association with the life-style, Diabetes earlier known to affect person in the higher echelon of the society, however, the disease prevalence rate changes over the time period. Diabetes became prevalent in both in developing and developed countries, affecting people across the socio-economic barriers, sex and race.

The situation also creates new opportunity for the firm (MNCs) to enter new market, emerging market, new geographical territories. As the Diabetes affects people across all the socio-economic groups, the issues of *availability, accessibility and affordability* became prominent. This trend has positive influence for the domestic Indian firms; those have capabilities in the process engineering and development of generic drugs. Overall, the conditions are favorable for both foreign and domestic firms in this segment.

Profitable sector for firms:

Diabetes is often terms as a life-style disease. Globally 80% of diabetes cases belong to Type 2 Diabetes Mellitus. Life style modification, long term intervention requires for effective management of type 2 diabetes. Long-term intervention (life time medication) is an added incentives for pharmaceutical and drug industry to enter this segment, compare to other tropical/ viral disease (e.g: An antibiotic medication last for few days or weeks, while diabetes and BP drugs requires lifelong medication. Hence the profit margin in this segment is higher.

Diabetes segment an opportunities for other related sectors:

Life-style segment is considers as a profitable segment in the market. With life-style modification is an key element here, that provides a window to growth of other sectors such as (nutrition, food industry, nutraceutical industry, alternate medicine, exercise equipments, over the counter (OTC) products, footwear industries (for diabetic foot), optic industries (products for diabetes neuropathy) along with the conventional drug, pharmaceutical, devices industries.

This function also talks about the mechanism that influences the direction of search with in TIS, not just factor that influence a sector.

Growth occurs in other TIS:

Apart from the vision, expectation and belief in growth potential in the life- style segments other factors also affect the TIS. Innovation does not occur in isolation, global TIS has a role in shaping domestic TIS through various means. The technological progression in the TIS in Diabetology shows, most of the new drug classes in the segment came after 1998. Out of major drug classes, three drug classes with novel drug delivery mechanism came to market in last 10 years (*DPP-4 Inhibitors – 1st drug in this class in 2006, GLP-1) agonist – 1st drug - 2005, SGLT2) inhibitors –1st drug -2013) , 15 new drug lunch occurs in the last 20 years.*[38]Similarly in device segment**,** the bionic pancreases, close- loop insulin drug delivery device came in 2012. The global technological growth in drugs (designer insulin, OADs), devices point-of-care (POC) devices, application of IT, health care management Aap, IT based solutions for data management, helps in growth of this segment. As the application are

[38] Detailed explained in chapters 4 global TIS, also see annexure on evolution of OADs

not just limited to the bio-pharma, biotech, device industries but also IT firms, functional food sectors. Besides technological progression, the global clinical knowledge base also increase many fold in the last 20 years.[39]

Change in the landscape:

India's demographic transitions, the urban-rural ratio, migrations, changing the status of health of the Nation-States, the transitions from the Communicable diseases to Non-communicable diseases, change in socio-economic status of its people, increase purchasing power of citizen that influences the out of pocket expenditure, have an influences on the market.

Actor's perceptions and assessment for future technological opportunities:

Biomedical innovation process is a multi-stage process, where actors have different functions. Final product is not the end of innovation process. A drug molecules travels from basic research to translational then clinical trial and at last in the market. Clinical trials and practices are important stages in the innovation process that offers solutions to the current problem as well as discover new problems. Through clinical practices, a drug molecule can be accessed, it efficacy and effectiveness be tested at the same time practice gives an indication to the future problems (side-effects). The knowledge created at the clinical stage again transfer to the basic research for the further improvement of products. Actor's assessments are also related to the specific product segment in the sectors. Actors can predict the future technological progress in a specific segment according to the trajectory of development process.

The direction of search in the insulin segment is to increase longevity (from daily dose, meal-time dose to weekly doses – ultra long Insulins), increase duration of the effects (from few hours to few days), to mimic the physiological cycle of insulin inside body cavity (smart insulin – that can changes amount of secretion at meal time and at the bed time, our body require more insulin at the time of food intake and less amount at bed-time, so error in manual insulin intake will leads to hyperglycemia or hypoglycemia conditions). The direction of search also indicates future alternate mode of drug delivery methods *Inhaled Insulins (Pulmonary Insulins), oral insulin, insulin pills or insulin tablet, Nasal insulin, Oral insulin, Insulin Patches* etc.

[39] Growth in global clinical trials for Diabetology in India is explained in the next chapter

The direction of search in the device segment is POC device, affordable test kits, diagnostic device, small- user friendly self monitoring glucose monitoring device. In the technological front the future progression are towards *Non- invasive lancet devices, alternate testing sites* (without needle pick in hand), *alternate mode of detection (wrist watch, sonar radiations) etc.* The *direction of search* also indicates IT based data management, integration of diagnostic devices with health Aap, cloud based management techniques of data.

Crisis in the current business:

Drug discovery process is high resource driven intense process. The process of drug discovery involves multiple phases. The rate of drug failure is very high. Only 5% of NCE can reach clinical stages. The objective of this study is to locate and investigate translational research process. The process involves long gestation period. *The crisis also creates opportunities.*

In biomedical innovation, collaboration is common at each stage of innovation process. The study identifies collaboration at co-patenting stages, intermediary stages and product development stages. The collaboration is not limited to the research and innovation process. It occurs at research financing stage, PPP mode of development, at different translational level between Research Organization/Knowledge institutes – CROs, CROs- Hospitals, Firm-hospital at clinical trials, Firm- clinician at clinical practice level. All these collaborations and linkages are mentioned at different stages of innovation process in this study.

The translational process in biomedical innovation is the conversion of proof of concept into a successful market product. But the innovation process does not end at the market stages. The Market failure of new technologies and product are part of crisis and learning opportunities. The first two rapid acting inhaled insulin lunched in the market (*Exubera* in 2006 and *Afrezza* in 2014) were market disasters (Oleck, 2016). The reason for failure includes competing existing technologies and products, trust deficits among clinical practitioners, patient's consents along with the effectiveness and efficacy of the new product.

5.4.3 F3: Entrepreneurial experimentation:

For any TIS*Uncertainty* is a fundamental. The uncertainty is not just limited to the early stage innovation, experimentation but also related to the product development and market stage (Rosenburg, 1996) However, from social perspectives, uncertainty reduction is done through the social learning process and acts of entrepreneurial experimentations. (Kemp,1998)

The biomedical innovation system, the multi-stage process involves challenges at every steps of innovation process. This system functions is characterized by the number of *new entrants*, *number and range of new technological applications*, *complementary technology in TIS.*

New Entrants:

The patent analysis of Indian firms shows encouraging trends as many new actors/players are emerged in this segment in last ten years. The detail firm level patent analysis has five categories,except for the big established firm all other categories of firms shows encouraging trend. As Diabetology is a knowledge field it consists of many technological applications. The new entrants are engaged in developing various technologies, products, processes and contribute to the overall development of TIS.

In the *biopharmaceutical category* of firms, out of 17 firms, 15 firms entered this segment in last 10 years. This category of firms is unique to the biomedical innovation system, are different from the well established big firms as it involves biotechnology companies, drug discovery services, contract research organisations, and clinical research organisations. The focus area of research of these firms is similar to the big firms in development of products related to *Insulin* and *Oral anti- diabetic drugs*. The difference is the focus on new drug classes *(DPP-IV, alpha glukosidaseinhibitor,SGLT-2 inhibitors, sitagliptin, empagliflozin, teneligliptin)* as compare to the big firms where the patenting activities are on the old drug classes.

Apart from the established products and processes, firms are also engaged in experimentation that helps in building the TIS. The *new technological application and alternate methods* such as the novel methods of drug delivery system by Reliance Life Science, new chewable solid OADs by BAFNA pharmaceuticals, Stem cell encapsulation methods by DiponEdBiointelligence, Chennai and Industry scale production of stem cells by Kasiak Research, Mumbai. The experimentation process further validates with collaborative work

with foreign MNCs, Aurigene with Novartis (International collaborations – DPP-IV molecules) and Impetis Biosciences with Advinus therapeutic (TATA group) for (NCE molecules) are some example of collaboration in this category.

In biomedical innovation, India has unique position in *herbal formulation* related experimentation and innovation due to its strong traditional base medicine AYUSH system. For the life-style segment, the applications of herbal formulation are more evident than other emergency or tropical medicine or technologies. In the knowledge field of Diabetology, there are more than15 firms, majorities are patents belongs to last 5 years. In these categories, the firms are not just limited to AYUSH but other functional foods, neutraceutical and FMCG companies. The industry academia collaboration in this categories helps in nurturing of experimentation and entrepreneurial experimentations.

Diagnostic and device is an important segment in Diabetology. The affordability is key issues to address in the developing countries. The entrepreneurial experimentations and technological development process of innovator show indicate the direction of research. There are 9 new firms in this category. The technological development includes Point-of Care (POC) device, Mobile aap, IT- based solutions.

The startup or incubators are also an indicator of the function entrepreneurial experimentations. The following list is startups in the area of Diabetology in India.

Table 16: List of Startup in the area of Diabetology in India

Startup Companies	**Year of establishment**	**Objective and Purpose**
BeatO,	2015	Diabetes monitoring app, Glucometer, and smart phone applications for management of diabetes
AADAR	2018	IIT, Bombay incubated Ayurveda based preventive healthcare startup aims to curb lifestyle ailments like protein deficiencies, blood sugar, indigestion, cholesterol, and obesity with herb-based products.
PathShodh	2015	This medical device startup was incubated at Centre for Nano Science and Engineering (CeNSE), IISc. The product includes multi analytic devices, POC devices, glucometer and kidney function test kits.
Diabport Health Care	2017	A startup focusing on need for awareness about diabetes and its complications.

(Source – DIPP: Startup list and secondary literatures)

Diversion of product portfolio:

This function is not limited to the new entrant, but also the existing actors or players erstwhile activity in other segment, now diversifying their product portfolio due to positive inducement. The big IT firms such as HCL, TCS has entered diabetes device segment, with affordable POC devices. The firms previously not active in this segment such as CadilaPhama, Sun Pharma diversify their product portfolio due the positive market. Diabetes also associated with the co-morbidities with kidney failure, high BP, cholesterol, obesity, hence firms active in other related research also contributes to the experimentation process.

5.4.4 F4: Market Formation:

Diabetes currently is major epidemic, engulfing both developing and developed country equally. The market size for the global diabetes drugs market was registered to be USD 67.5 billion in 2017 and the segment is expected to record a CAGR of 5.65% during the forecast period, 2019-2024. North America dominates the market, followed by Asia-Pacific region. (Mordor Intelligence) China and India are two potential emerging markets in this segment due to highest number of diabetic patient in this country. Approximately 10% of all diabetes cases are Type 1, and approximately 90% of all cases of diabetes worldwide are of Type 2. The growing prevalence of diabetes is the major driver for the global diabetes care drugs market. Additionally, rising awareness regarding diabetes care, growing prevalence of obesity, and technological advancements are further driving the market. The diabetes drug market has two major categories (Insulin and Oral- anti diabetic drugs) similarly; the global diabetes devices market is expected to reach USD 35.5 billion by 2024, with CAGR of 7.0% (Grandview research). The device segment can be categorized as Monitoring and Diagnostic Devices (Lancets, Analog Glucose Monitor, Continuous Glucose Monitor, Test Strips and Insulin Delivery Devices (Syringe, Pen, Pump, and injector). Test strips captured the largest share in the monitoring and diagnostics device segment while insulin pens accounted for the largest revenue share among insulin delivery devices in 2016. The market for diabetes segment or overall life-style segment will have a positive growth in near future.

Dominance of foreign firms

Novo Nordisk, Sanofi and Eli Lilly are three major actors dominates global insulin segment. Wockhardt Ltd. (India) is a potential emerging actor in the insulin segment. USV pharma (glycomet), MSD pharma (Janumet) are two generics drugs have highest market share among India firm in domestic market.(AIOCDPharma- BS)

The reason for the dominance of foreign firms in diabetes drug segment is that unavailability of generic formulations indicates that most of the new drug classes are patent protected. Except, two drug classes (Sulfonylurea (SU) & Biguanides) all other drug classes have their first drug presence in the market in last 15 years. For e;g DPP-4 inhibitors (Sitagliptin- 2006, Linagliptin- 2011) GLP-1 agonist -1st drug in 2005. In (SGLT2) inhibitors drug class all four new drugs (Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin) came to the market during 2013-2017.

The firms Novo Nordisk and Eli Lilly have first mover advantages in the insulin segment. Insulin was invented in the year 1921. *Eli Lilly* signed an agreement to pay royalties to the Toronto University to increase the production of insulin 1922. The following year *Nordisk Insulin Laboratorium (now Novo Nordisk*) was established. Novo Nordisk being first protamine insulin in early 1930s. Protomine insulin (NPH/intermediary insulin) is one of the earliest innovation to prolong the period of insulin reaction in human body with the addition of protamine to insulin These firms have legacy of 80 year in insulin segment give them added advantages to dominant this segment.

Tehnological development, acquisitions and market formation

There are few firms at global level both in drug and device segment has hegemony over global diabetic market. The historical evidence of show, besides R&D activites of the firms, major acquistions, mergers helps firms to consolidate patents and related product and artifacts. The acquistion patterns also an indicator of future technogical development and future market.

Case - Diagnostic Sector:

The history of technological development in diagnostic sector in diabetology shows, there are 3 major firms dominant the sector during 1950s to 1980s. *Ames Company, (a*division of Miles Laboratory) and Boehringer Mannheim are two firms pioneered in developing first dry reagent strip techniques in early 1950s and then Self monitoring blood glucose (SMBG) device in early 1970s. Their product portfolio includes:

Boehringer Mannheim -*Glucotest/ testap* (1954), *Combur-Test (*1964) – *first combo test strip, Reflomat (Stat Tek), Glucometer –(1974)*

Ames Company, *(a*division of Miles Laboratory) – *Clinitest (1941) -first conveninent tablet test, Clinistix (Diastix)*first*'dip and read'* urine reagent strip (1956) and *Dextrostixthe first blood glucose test strip* (1964), *Ames Reflectance Meter (ARM)*: The *first blood glucose meter (*1970)

Lifescan-*Glucochek - Glucometer* (1980)

During the period of mid 1990s major acquisition occurred in the diagnostic sectors. *Bayer, Abbott and Roche* acquired *Ames, MediSense and Boehringer Mannheim* respectively during the period of 1995-98 and *LifeScan became a part of* Johnson*& Johnson.* Currently all these firms have maximum number of patents in diagnostics and devices segment in Diabetology[40]. These firms have consolidates the techniques related to diagnostic and became market leaders in this segment with range of product portfolio acquired or developed based on foundational work of these firms.

Indicators of future of technological development:

Acquisition, collaborations are indictors of future market or technological progress. Bayer acquire OTC division of Roche (1995), sold its device segment to Panasonic Healthcare Holding in 2015. A new firm Ascensia Diabetes Care (2016) was established continuing the legacy of Ames &Bayers – glucometer products. The recent collaboration of Ascensia indicates the future of technological development and emerging market in this sector. From 2015- 2018, Ascensia's six collaboration are with different firms mostly IT support services. The nature of collaborations is related to IT based online data management, integration of insulin pump with wireless communiation devices, integration of diabetes measurement data with mobile aap based digital platform.

Contribution of domestic firms:

Interview -Firm 1: *(Senior sales –marketing in a reputed domestic firm)*

The three big pharmaceutical companies Sanofi, Novo, Eli Lilly dominates diabetes segment with combine market shares of more than eightly percentage globally. The situation is not different in India. but there is ample oppurtunity and profit for domesitc firm in life style segment. The future market seems extreme positive , as the disease burden show upward trend. New firms, products are entering in the market rapidly, even established firms, those never have product in this segment, now diversitying their product portfolio toward diabetes and lifestyle products.

In the top generics brand going by the moving annual turnover (MAT) values for diabetes, USV's Glycomet and MSD Pharma's Janumet are two generic products have significant market share in diabetes segment in India.

[40]Explained in chapter four - patenting of global firms in drug and device segment

The Indian firms have expertise in process engineering based generic drugs. As most of the new diabetes drugs class are still under patent protection that hinder firms to explore the opportunist for drug development in this segment. The new drug discovery process is difficult and resource intensive process. There are two successful translational product from India firms in diabetes are *Remogliflozin – Glenmark (successful drug lunch through in-licensing) and Saroglitazar (ZYH1), or LipaglynTM - Zydus cadila*

The translational process are difficult, many Indian firms opts for out-licensed of new molecules in return for revenue, royalties. The following list is NCE molecules out licensed by Indian firms in diabetes.

Table 17: Out- licensed novel molecules by Indian firm in Diabetology

Out license molecules	***Year***	***Indian firms***	***Foreign firms***	***Areas in Diabetology***
DRF 2593/ Balaglitazone	1997	Dr Reddy's Laboratories (DRL)	Novo Nordisk	PPARγ agonist
Ragaglitazar or DRF 2725	1998	Dr Reddy's Laboratories (DRL)	Novo Nordisk	dual-acting PPARα/γ agonist
DRF 4158	2000	Dr Reddy's Laboratories (DRL)	Novartis	PPARα/γ agonist
TRC-4186	2002	Torrent pharmacy	Novartis	AGE-breaker
Melogliptin or GRC 8200,	2006	Glenmark	Merck and Co.	DPPIV inhibitor
CNX-012-570	2014	Connexios Life Sciences	Boehringer Ingelheim	AMPK agonists

For life-style diseases, where preventions and management is optimal treatment method, traditional medicine (AYUSH) have larger role. The market for herbal medicine is good for diabetes. With the institutional support, there are several translational products are lunched in the market or in late- development stages of innovation. They are BGR- 34, *AYUSH – 82,* Right Sugar, Ayush – D for Diabetes (ayurveda), D-5 choornam.

5.4.5 F5: Legitimation:

Legitimacy is a matter of social acceptance and compliance with relevant institutions, In the knowledge field of diabetes, and biomedical innovation system in India, where number of technologies or methods use for treatment of disease, there are two issues that stand out to be in the ambit of this functions.

Issues with herbal formulations:

The aggressive advocacy and commercialization of ayurvedic and herbal product in recent times helps in booming of alternative therapies market in life-style segment, however, these drugs have been criticized for the lack of rigorous pharmacological data or meaningful clinical trials and efficacy. There are no concrete evidences of clinical trial data, toxicological data or animal trials and publication for herbal drugs. There are also methodological problems in conducting pharmacological and clinical trials of AYUSH products

Interview - AYUSH: *(AYUSH – practitioners, person associated with manufacuring ayush product and policy issues)*- Combined opinion

The issues lies with herbal based formulation is their toxicility profile are not fully explained. There are presence of heavy material in ingredient and final product. It is difficult to access the standards ingredients and quantifing the process of making herbal formulations. There is batch-to batch variation in sample products due to unreliable standards of practices in manufacturing. The issues are not just limited to manufacturing but also with raw ingredients such as indiscriminate, poor-post harvesting treatment practices of herbal medicine.

AYUSH and herbal based formulations are popular in India; however there is lack of cultural acceptability across the globe that hinders the market growth of herbal products at globally. To legitimize the products or increase social acceptance of herbal formulation, multiple intervention are required at various stages. Standardizing Pharmacovigilance, toxicological and clinical documentation, well-documented quality control procedure, process validation, standardizing manufacturing, along with focus on R&D high-yield varieties and domestication of herbal medicine, improving post harvesting treatment methods required. There is a need for modern infrastructure, human resources including well trained worker, medical taxonomist, herbalist and chiropractors.

Use of Insulin injections and other social stigma associated with diabetes:

In the conventional, allopathic medicine there are not many problematic issues lies with the manufacturing or product development that can address this function rather we found issues related to clinical practice, patient consent & perception about certain treatment procedure, clinician-patient interaction and attitude of society towards diabetic patient.

Interview - Clinical practitioner *(Clinician &Chairman, Delhi Diabetic Research Centre, also active in social awareness drives for type 1 diabetes)*

Needle phobia, exist among patients. Once, treatment procedure includes insulin in-take in procedure cannot be reversed. The patients with type-1 diabetes requires insulin intake on daily basis, multiple times. Taking daily injection is still a social stigma; however it also depends on the social, educational awareness of patient and society.

Women: *Some societies has discrimination attitude towards women with diabetes due to lack of awareness. People have preconceived notion that the offspring will be a diabetic kid, it affects their marriage prospect. If a married house-wife has diabetes, she faces unnecessary harassment of being lazy or leading a sedentary life style in side house. The ignorance leads to confrontations, separation, divorces and depression.*

Kids: *Excessive urination and thirst are part of diabetes symptoms, a diabetic kid faces harassment in school from teacher or fellow those unaware of the conditions. All these issues can tackle through public awareness about the disease, its clinical symptom and measures.*

There is also a case study where a two women patient with similar clinical conditions belongs to two different socio- economic group had different fate in life. A woman belong to poor family with T1 diabetes condition died at the age of 18, due to family ignorance and social boycott while other patient belongs to middle class- educated family is happily married with two non-diabetic kids. The DDRC also runs a Diabetic matrimonial site exclusively for diabetic patients. **(Figure 16)**

Figure 16: Diabetic Matrimonial web-site of DRCC

Source: Delhi Diabetes and Research Centre (DDRC)

5.4.6 F6: Resource Mobilization

As the TIS evolve, a range of different resources requires mobilization for the functioning of TIS. The TIS requires different competence and the instrument that helps in capacity building. The mobilization requires building *human capital, financial capital and complementary assets (products, services and infrastructures)*

In biomedical innovation, where the study focuses on Diabetology as a knowledge field, the competence building in human resources occurs at different stages through scientific knowledge at basic stage, translational knowledge at applied stage, clinical knowledge at clinical stages and finally at clinical practice level. As the biomedical innovation system is multi-stage process where all different knowledge fields are controlled and regulated by different organisations and institutions.

Promoting Translational research:

During the 1990s and early 2000s, the translational research in India was not the foray of public research. The private sectors has limited or no access to existing technologies and professional diverse skill-sets to consolidate technologies for later-stage product-oriented development. ***Department of Biotechnology (DBT),*** Govt. of India, took initiatives on translational research around 2005. The initial focus of DBT' was confined to couple of disease. However, in the past few years, DBT has created sustainable framework for various biomedical fields that focuses exclusively on translational research through National Biotechnology Development Strategy (NBDS) in 2007. Under NBDS initial focus is to *develop specialized human resources* and *specialized centre for promoting translational research* and networking opportunities in the area of biomedical healthcare technologies.

Human resource Development:

DBT- Regional Centre for Biotechnology (RCB) was established in partnership with UNESCO in 2006 to create human resources for translational research in India. RCB offers specialized doctoral and master program, domain specific training and aimed at producing highly specialized cadre capable of translating research in to practice for societal benefits. RCB, in overall term, is contributing to the system building activities for human resources through education, training, and research in biotechnology with contribution from other countries and academic institutions of the regions and provides a meeting place where innovation, enterprise and industry is expected to foster and develop.

DBT-Translational Health Science and Technology Institute (THSTI) was established in 2009, an autonomous institution promoting multi-disciplinary research to translate technological advancement into medical innovation for affordable healthcare solutions. THSTI is modeled on the Harvard- MIT Health Science and Technology (HM-HST) programme for multi-disciplinary research founded in 1970, integrating science, medical and engineering. Apart from the institutions, DBT promotes biomedical innovation and translational research through various policy and programmes.

Promoting basic research: The scientific knowledge base is important for the translational and clinical knowledge. The study analyses broader scientific environment that helps in nurturing innovation capacity building in India. There are various organization and institutions promotes scientific and biomedical research in India such as MST, DST, DSIR, DBT, MHRD, UGC, AICTE, ICMR, DHR etc.

The **Table 18** identifies important programmes helps building human capital for biomedical innovation in India. The human resources support programmes are meant for financial support to individual and organization as well as skill development and capacity building.

Encouraging scientific temper, and early stage science promotion is key to build science base of a country. Different ministries and department through various programmes such as Kishore VaigyanikProtsahan Yojana (KVPY), INSPIRE- SEATS (for school going student) INSPIRE- SHE (for higher education) and INSPIRE- AORC for PhD and Post doctoralprogrammes support human resource development. Govt. organisations also make effort though popularizations of science through Science Olympiad, National Children's Science Congress, National Teachers' Science Congress (NTSC) etc. There are programmes supports basic and biomedical scientists in their mid-carrier act as incentives, encouragement and validation of their contribution to the scientific progress. DSIR's J.C. Bose National fellowship is meant for senior scientist, *Distinguished fellowship* for eminent senior scientist and Science Chair for outstanding scientists in scientific research. Similarly, CSIR's *Bhatnagar Award one of the highest multi-disciplinary science award in India. DHR and ICMR promote biomedical research through* Basanti Devi Amir Chand Prize (Biomedical Sciences), ICMR Kshanika Oration Award (Biomedical Sciences for women scientists), ICMR Prize for Biomedical Research for scientists belonging to Underprivileged communities and ICMR Prize for Biomedical Research conducted underdeveloped areas - Biomedical Sciences.

Human Resources Mobilization programmes:

In biomedical research the knowledge formation is global; the knowledge involves complex knowledge of biotechnology, stem cell research, nano technology etc where India is a technological follower country. Science co-operation with developed country are important for development of human capital and capacities. There are specific programme helps in mobilizations of human capital, formation of network and knowledge exchanges at national and international level. *Teachers Associateship for Research Excellence (TARE)* helps research and scientist working in private, state university to utilize biomedical facilities in central R&D institutes. *VAJRA (Visiting Advanced Joint Research) Faculty scheme* and *Ramanujan Fellowship* are specific programmes meant for capturing oversea talents scientist, academician who wish to work in Indian R&D organization work for specific period of time. *Overseas Postdoctoral fellowship* gives international exposure to India students. *DBT-Heidelberg Graduate programme* a Joint doctoral degree, *Khorana Program for Scholar* in the fields of biomedical and biotechnology , *Indo- US Genome Engineering/ Editing Initiative (GETin) program* specially crafted Skill Development helps in building biomedical capacity through international exposure.*Skill Vigyan Program, Biotechnology Skill Enhancement Programme (BiSEP) and* Biotech Industrial Training program are intended to bridge the gap between industry- academia skill that will help in developing translational research skills in India.

Promoting Medical Education: Clinical innovation and clinical practices are core to biomedical innovation process, as the study focuses on the knowledge field of Diabetology, the clinical management of the disease is the main functional goal of TIS. In India, clinical care is an umbrella term, where human resources are from diverse field and institutions that regulates them also distinct. Medical education regulates through Medical Council of India, Pharmacy education through Pharmacy Council of India and Nursing education through Indian Nursing Council. Further, the PG and Fellow programs in medicine are regulated through National Board Examination. NBE's offers Diplomat of National Board (DNB) and Fellow of National Board (FNB) in various Broad Specialties, Super specialties and Sub Specialties area. Endocrinology is the sub-specialties area that addresses challenges in Diabetes management. The specialist course are limited in number, the limited human capital in the clinical area possess a biggest challenges to address current growing epidemic of diabetes in India. Human resource capacity in clinician management are not limited to doctor or nurses but various intermediary actors, para-medico, PHCs, rural ASHA workers etc.

Table 18: Programme for Human Resource Development in Biomedical Research

Human Resources Development	***Purpose***
DST	
INSPIRE - Scheme for Early Attraction of Talents for Science (SEATS)	Class 6^{th} 10^{th} - for promoting scientific temper attract young talent towards science education
INSPIRE - Scholarship for Higher Education (SHE)	For encouraging bachelor and master programme in natural science
INSPIRE - Assured Opportunity for Research Careers (AORC).	Support PhD and Post doctoral research in basic and applied science.
Swarnajayanti Fellowships	Promote young scientist for doing basic research in frontier area
DST- SERB	
Year of Science Chair professorship	Grant support outstanding scientists in science, technology, enginnering and mathematics (STEM)
Distinguished Fellowship	Grant support for eminent senior scientist
JC Bose National Fellowship	Grant support for Senior scientist
Ramanujan Fellowship ***HR mobilization***	For researcher or scientist wish to return to India for working in Indian R&D organization
Distinguished Investigator Award (DIA)	Grant support for basic research in frontier areas
Teachers Associateship for Research Excellence (TARE) ***HR mobilization***	Facilitate permanent faculties of State and private universities, colleges to carryout research in public funded institutions.
Start-up Research Grant (SRG)	For young researchers Post Doc support Start-up grant for Young Scientists (YSS)
Overseas Postdoctoral fellowship ***HR mobilization***	To build National capacity in frontier areas of Science and Engineering through oversea training
National Post Doctoral Fellowship	For young researchers Post Doc support
VAJRA (Visiting Advanced Joint Research) Faculty scheme ***HR mobilization***	For oversea scientist,academician NRI/PIO/OCI for working in Indian R&D organization work for specific period of time.
DBT	
Biotechnology Skill Enhancement Programme (BiSEP) ***Translational Skill Development***	To bridge the gap between industry- academia skill
Skill Vigyan Program ***Translational Skill Development***	Skill development for students, technician, faculty and entrepreneur in the area of Biotechnology
Biotech Industrial Training program ***Translational Skill Development***	Industry specific programme for students
DBT- Heidelberg Graduate programme ***HR- internatonal co-operation***	Joint doctoral degree on big data research
Indo- US Genome Engineering/ Editing Initiative (GETin) program ***HR mobilization – Int. co-operation***	For capacity building in the frontline area, HR training, R&D linkages and collaboration
Khorana Program for Scholar ***HR mobilization – Int. co-operation***	For promote biomedical and biotech research through Indo-USA co-operation
Ramalingaswami Re-entry Fellowship	For researcher or scientist wish to return to India for working in biotechnology area.
DBT- Welcome Trust Fellowship	For basic biomedical researcher
Support for Human resources Academic and Research Programmes (SHARP)	ICMR-DHR all kind of fellowship

(Sources- Compiled from Institutional databases)

Research Infrastructure:

Research infrastructure is critical for development of biomedical innovation and capacity building. India possess a sound research infrastructure through is vast research networks, organization and laboratories of CSIR, ICMR, DBT, IISCs, IITs, Central Universities, State Universities etc. Besides that there are various programmes that helps in infrastructure development such as FIST–DST programmes are meant for improvement of basic research facilities at PG colleges, PURSE-DST is a R&D incentive grant for infrastructure development.

Resource sharing

Biomedical research required high-tech technologies, for a developing country like India, affordability is a measure concern. To address this problem, different ministries and departments invested in building critical infrastructures for biomedical research at various premier research organisations in India, however, those facilities are open of other smaller organization, SME, MSME, Start-up, individual innovators. SAIFs–DST, CRTDH – DSIR, and SAHAJ–DBT programs promotes resource sharing among research Institutes, universities, Colleges, start -ups and entrepreneurs. CSIR- IHBT, and CSIR- CCMB are two primer organization through DSIR-CRTDH are building Industrial R&D and Common Research Facilities (BIRD-crf) in the area of 'Affordable health' to address healthcare challenges for diagnostics and biopharmaceuticals in India.

Table 19: Programme for R&D infrastructure and Finance in Biomedical Research

R&D Infrastructure	***Purpose***
DST	
Fund for Improvement of S&T Infrastructure in Universities and other Higher Educational Institutions (FIST) - DST	Basic equipment and facilities for advance research at PG colleges, centers and Universities
Sophisticated Analytical Instrument Facilities (SAIFs) – SRISTI - DST ***Resource sharing***	18 SAIFs facilities at premier research organization in India
Promotion of University Research and Scientific Excellence (PURSE) - DST	R&D Incentive Grant for infrastructure– based on publication output
DSIR	
Common Research and Technology Development Hubs (CRTDH) Building Industrial R&D and Common Research Facilities (BIRD-CRF) ***Resource sharing***	Facility where Startups & MSMEs in life- sciences can utilize sophisticated testing facilities, equipment & infrastructure, intellectual support necessary industry-institution interactions
Scientific Infrastructure Access for Harnessing Academia University Research Joint Collaboration, (SAHAJ)'. –DBT ***Resource sharing***	Share its equipment and infrastructure to Research Institutes, Universities, Colleges and Start -ups / Entrepreneurs.
Research Finance	
SERB - Core Research Grant (CRG)	Extramural Research funding
High Risk - High Reward Research (HRHR)	conceptually new and risky research
Scheme for Funding Industry Relevant R&D (IRRD)	To academic institution and national lab for solving industry relevant research
Intensification of Research in High Priority Area (IRHPA)	high priority, multidisciplinary / multi-institutional
DHR - Model Rural Health Research Units (MRHRUs)	Capacity building research translation to rural population and health services delivery
DHR - Grant-in-aid (GIA) Scheme	Public health, Translational research

(Sources- Compiled from Institutional databases)

Research finance:

In biomedical innovation process, different organization and institutions supports different activities at different stages. At basic and translational research stage, DBT, DSIR, ICMR, DHR helps and promotes research, different firms and private organization, hospital invest in research at clinical stage, at disease management stage organization like WHO, ADA, MOHFW, DGHS along with NGOs, philanthropy organization contribution in research and

innovation activities. Biomedical innovation is intense- resource driven innovation process. The various departmental support for biomedical research leads to duplication of work. To avoid duplication and consolidation of funds for bigger investment on high priority programmes there are various unique biomedical financing progrmmes are recently lunch suitable for resource constrain country like India.

DST -Biomedical Device and Technology Development Programme (BDTD)

BDTD is a three- tier support programmes in the core area of medical devices (diagnostic, life-support and surgical instruments) initiated in 2016. The programme support projects from concept development stage to pilot testing of product through financial support in early stage prototype development (concept, testing, lab experiment), late stage prototype development (testing and validation product) and finally Pilot stage (complete technological design with industrial applications). Multi-disciplinarity is core to biomedical research. The progrmme support multi-diciplinary as involvement of *Clinician* is mandatory in the technological development programmes.

MHRD - IMPacting Research INnovation and Technology (IMPRINT)

The philosophical basis of IMPRINT programme is translation of knowledge to a useful product. IMPRINT is a joint initiative of MHRD and DST involves pan-India collaboration of IITs and IISC to address enginnering problems in the country in ten core domain area of national importance. There are 4 projects sanctioned under this programmes supports some of the most advance areas of biomedical research in Diabetology such as development of artificial pancrease – close loop insulin delivery system, micro encapsulation device for islet transplantations, POC device for diagnostic and functional food.

Both these programme are initiated in last 3-4 years, shows the policy inclination towards translational research in India. As the programmes are comparatively new, evaluations of projects are not possible. The characteristic feature of these programmes is supporting trans-disciplinarity, diverse expertise in projects (combination of engineers, clinician, scientist, basic and applied researcher).

DSIR - Patent Acquisition and Collaborative Research and Technology Development (PACE)

PACE programmes was lunched in 2017 to address the problem of fewer patents in India. All though this programme is not directly related to biomedical innovation, the scheme supports translational research process with two main objectives of technology & IP acquisition and co-development projects with R&D institutions. The scheme supports the complete project from patent acquisitions to co-development through proof of concept/ laboratory stage to pilot stage, and commercialization of product.

DSIR - Promoting Innovations in Individuals, Start-ups and MSMEs (PRISM)

PRISM is similar to the BDTD programme with a three- tier support system. It supports the whole translational process from proof of concept to product development. Affordable Healthcare is one of the core focus area in this scheme. The program was initated during 12th plan in 2013.

Grant Challenge India- This is a unique initiative in the biomedical financing programmes, which includes different department (DBT, BIRAC) and International foundations, donor and societies (Bill & Melinda Gates Foundation, Wellcome Trust, US AID) to fostering innovation to solve key global health problems. These projects are mission-directed research programmes support context specific challenges to health research and innovation system in India. Consolidation of funds and mission- oriented research helps in finding the objectives.

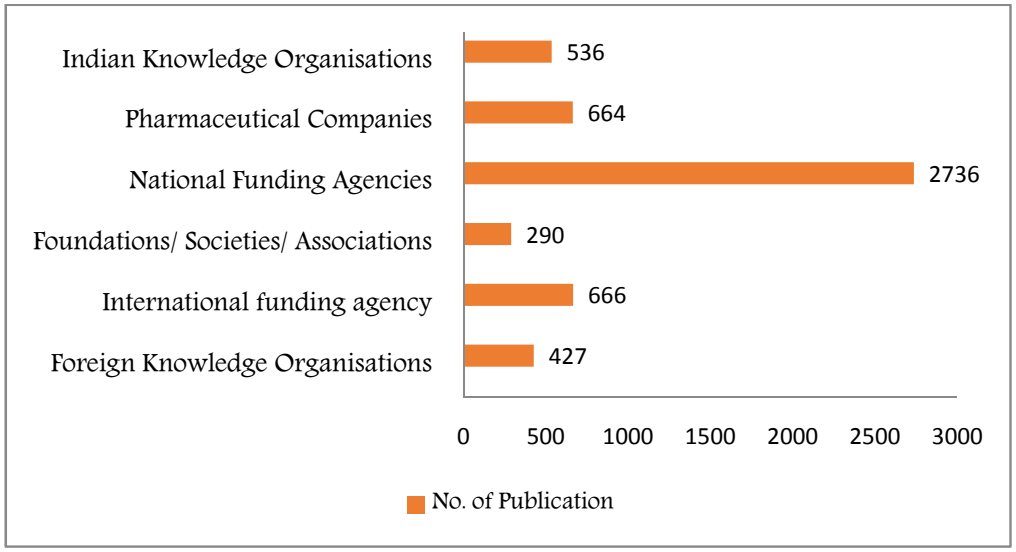
The **Table 20** below shows different programmes and project supporting Diabetology research and innovation in India.

Table 20: Translational Project under various Programmes in Diabetology

Programmes	***No. of Projects***	***Research Areas in Diabetology***	***Organisations/ Firms/ PPP- mode***
BIRAC- BIPP	10	TRC150094 – novel molecule IN-105 tablets (oral insulin) Drug diabetic foot ulcer High Fibre rice POC diagnostics,	Torrent Pharma, Biocon, NovaLead Pharma, (VLife Sciences), Dr Mohans Healthcare PathShodh Healthcare
BIRAC- SIBRI	8	Stem cell research Plant based formulations (AYUSH) Novel drug delivery Diabetic retinopathy Diabetic footwear ulcer (DFU)	Shantani Proteome Analytics, Advanced Neuroscience Allies, Arjuna Natural, PhytoMyco Research, AdvenioTecnoSys ,Weinnovate Biosolutions , Yostra Labs
BIRAC- PACE	2	Herbal medicine for DFU, Cloud based diabetes data management	IIT-BHU Amrita School of Biotech
BIRAC- SPARSH	1	Affordable diagnostic- Diabetes Peripheral Neuropathy	Yostra Labs
BIRAC- BIG	5	Gene expression, DFU, NCE, Sensor based Insole (Footwear for diabetes)	Yostra Labs, Novo Informatics, Crystalin Research Pvt, PetaVista Healthcare
BIRAC- IIPME	1	Glucometer, mobile Aap	Individual inventor
MHRD- IMPRINT	4	Macro-encapsulation device for islet cell transplantation, Artificial Pancreas for T1 diabetes, POC Device , Designer food formulation (Neutraceutical)	IIT, Hyderabad with Asian Institute of Gastroenterology, Centre for Bio-Systems Sciences and Engineering, IISC ,IISC with PathShodh Healthcare , IIT, Kharagpur
TePP (DSIR+ TIFAC)	3	Herbal formulation (AYUSH)	Individual inventors

(Sources- Compiled from institutional databases)

Figure 17: Research sponsored by funding agencies in Diabetology in India[41]



(Source: analysis through Scopus advance search tool, Elsevier)

Diabetes research in India is being supported by different financial agencies for various different purposes. The **Figure 17** indicates the financial supported received by the authors for the research or clinical work. The maximum numbers of research sponsors in Diabetology is by national funding agencies like UGC (485), ICMR (455), CSIR (448), DST (390) &DBT (179). Diabetes research in India also receives ample foreign funds from various sources such as international funding agencies, knowledge organization, foundation and societies and pharma companies. International funding agencies like National Institute of Health, USA, WHO, Medical Research Council, UK etc. The foundations include Bill and Melinda Gates Foundations, research societies, trust (Wellcome Trust) medical associations (ADA). The publication sponsored by pharmacompanies shows the collaboration and linkages between firm-hospital, firm-clinician as drug trials results, results of Post Marketing Studies (PMS), clinical efficacy of drugs are published by clinician.

[41]The innovation indicator 'Funding Sponsor' is a recent advance in the Scopus analytics. The database calculates this indicator through the funding acknowledgment text in an article. This method has limitation as the declaration of funding sources is subjected to author's declaration. The categories 1&6 Knowledge Organisations (both Indian and foreign) includes universities, hospitals, research institutes and private institutes

5.4.7 F7: Development of positive externalities:

The system nature of innovation, diffusion and performance indicates the positive externalities that help in formation and growth of TIS. This function measure the overall system performance, the positive externalities draws mainly from four functions resource mobilization, influence on the direction of search, market formation and entrepreneurial experimentations. Entry of new firms and diversity of activities helps in growth of TIS. Information flow and knowledge spill over contributes to the dynamics of knowledge development and diffusion. Biomedical innovation is a complex system of knowledge development and diffusion process. International collaborations in specific knowledge domain or Institutional co-operation for capacity building are important indicators of dynamism in the TIS.

Table 21: International collaborative projects in Diabetology

Collaborative Programmes	***No. of projects***	***Research Areas in Diabetology***
DST - IFCPAR / CEFIPRA Indo-France	2	New Chemical Entities
DST –USISTEF Indo- USA	2	Formulation, device
DST – IGSTC Indo-German	2	Nanotech, Diabetic Foot ulcer
DST- Sweden	1	Biomedical
DST-UKIER	1	Biomedical
DST- International Division* (2004-2018)	15	Biomedical /Clinical
MOHFW – HMSC [42](2000- 2017)	34	Clinical research

(Sources – HMSC volumes I-IV, Institutional repositories)

The international research collaboration shows a shift in research priority in the country over disease burden. The maximum numbers of HMSC research proposal were from Communicable Disease (TB & HIV/AIDS) during 2000-07, however trend shifts in favour of Non- communicable disease by 2013-15. There are 34 proposals on diabetes research during this period. The proposal also includes studying the co- morbidity of diabetes with TB, CVD, Hypertensions and Chronic kidney diseases. The limitation of the international collaborative

[42]Health Ministry's Screening Committee (HMSC), is a high level committee that evaluates international biomedical research proposal that requires foreign collaboration or assistance from foreign funding. It also monitors the progress of bilateral agreements between India and other collaborating countries. HMSC has the final authority over approval for transfer of biological materials

project is the duration of sanctioned projects is not more than two years. For biomedical innovation the time-period is not fruitful. International collaboration at institutional or govt. level helps building innovation system and contributes in developing positive externalities. **(Table 21 & 22)**

Table 22: International Memorandum of Understanding (MoU) for Scientific Co-operation in Diabetology

Host institute	***Collaborative partners***	***Areas of collaboration in Diabetology***
MOHFW 2012	Department of Health and Human Services (HHS), USA	Capacity building, training, developing tools of disease control and prevention molecular, genetics, social and environmental determinant of diabetes
ICMR 2018	French National Institute of Health and Medical Research (INSERM)	Research collaboration in diabetes and metabolic disorders
ICMR 2009	London School of Hygiene and Tropical Medicine, London (LSHTM)	Priority areas of public health, support to NRHM
ICMR 2011	Global Alliance for Chronic Diseases (GACD)	Prevention of CVD, diabetes and Obesity
ICMR 2006	University of Minnesota, USA 2006	Research collaboration, medical educations
ICMR 2007	Boston University, 2007	Research collaboration, medical educations
ICMR 2007	University of California Los Angeles (UCLA -2007	Clinical translational research
ICMR 2009	Karolinska Institute, Sweden -2009	Clinical translational research
ICMR 2012	Academy of Finland (AF), 2012	Clinical translational research
DBT	Department of Health & Human Services, USA	Indo-US collaboration on Vision Research

(Sources – Institutional repositories)

5.4.8 Summary: This chapter conceptualizes Diabetology as knowledge field to understand biomedical innovation system in India through systematic evaluation of structure and functions in a TIS framework. The attempt was to draw the structure of biomedical innovation system at both vertically and horizontal level to canvass all the innovation actors in the different stages of biomedical innovation. The chapter identifies the structural elements of TIS: actors, organisations, institution, network and all technological factors that influence TIS.

Once the structure of BIS was identified, the next objective was to indentify functions of TIS. The function are not mutually exclusive, there is no clear distinction between actors and their performances. One actor can contribute to multiple functions and a single function can be performed by many actors. This chapter provides detailed analysis of seven TIS functions.

In the biomedical innovation process, clinical trials, clinical knowledge and practices have lot to contribute in post- improvement of product sequences. The clinical trials and practices also contribute to the various functions like knowledge development and diffusion, legitimacy, and other related functions. The next chapter focuses on these issues in detail.

CHAPTER SIX

BIOMEDICAL INNOVATION SYSTEM IN INDIA – II

(CLINICAL TRIALS, CLINICAL PRACTICES, POLICIES & PROGRAMMES)

6.1 Introduction

The innovation process travels through many stages from the conceptual stages to final product. In a biomedical innovation process different artifacts or products travels from basic or laboratory stages to final product in the market. Clinical Trial is fulcrum to any biomedical research holds a critical position in between the laboratory research and final product that can be useful for the mankind. This chapter covers how knowledge formation occurs at this stages, clinical research, clinical practices, public policy and health management stage. This chapter also focuses on evidence based research, clinical trials and evidence-based public policy formulation. The chapter discuss in details role of clinical trials beyond new drug trials, towards contribution to evidence based research and policy formulation. The other focus are of the chapter is to identify and access the roles of policy, programmes and institution to address the translational problems related to clinical practices and management issues. Innovation and translational focuses have least attention in this are rather more focuses on translation of new product formation rather utilization of existing services. This chapter will make an attempt to address some of these issues.

6.2 Contribution of clinical trials in the knowledge field

Clinical trials are essential for the development of new drug or treatments procedure. In the Technological Innovation Process, this stage draws an analogy to the lab validation or technological demonstration in TIS but the role of clinical trials goes beyond validations of a product or process. (Metcalfe, 2004) A clinical study is preceded by pre-clinical study that examines the safety and efficacy of drug or device at laboratory stage. The process varies depending upon the product or artifacts such as a new drug molecule, a medical device, gene therapy, diagnostic tool. The pre-clinical study of a new drug candidate involves assessment steps of pharmacodyamics (PD), Pharmacokinetics (PK), ADME (absorption, distribution, metabolism and excretion), toxicological assessment and many in-vitro and in-vivo test

before entering the clinical stage. The drug candidates also undergo different animal studies (murine, canine, primates, porcine). A product or device does not require these tests. Some medical devices undergoes biocompatible testing that test their sustainability in a living environment.

There are various phases of clinical trials such as: Phase Zero, I, II, III and IV. The Initial phases Zero, I and II operates over a small controlled group of patients to find the best dose formulation and its side effects. Phase III trials are involves maximum human subjects. The approval of drug candidates depends on the phase III results. Phase IV also known as Post Marketing Studies (PMS) to assess the long-term effect of drug.

The knowledge formation in this stage is not limited to drug development process only. Clinical trials have a bigger contribution to the domain of clinical practices. In addition to testing new drugs and devices, clinical trials provide a scientific basis for advising and treating patients. Clinical trials helps in standardizing practices, International clinical trial results helps in harmonization of treatment process hence contributes to evidence based research, trials, practices and policy formulation.

6.2.1 Global clinical trials in Diabetology:

The **Table 23** gives information about some landmark clinical studies in the area of Diabetology. The impact of these studies are not just helped in drug trials, but also helped in taking policy decision based on evidences, formulating clinical guidelines, methodology and best practices.

The University Group Diabetes Program (UGDP), 1st randomized controlled trial (RCT) of treatments for Type 2 diabetes, initiated in 1961 became a standard protocol in chronic disease trials. The trial demonstrated the effective use of common protocol with multiple site and investigators and use of statistician apparently became standard in the RCT. The use of statistics for investigation rather observation became first contribution towards evidence

based research and policy over perception based outcome. For UGDP enrollment starts in 1961 continued till 1978. The purpose of the study is to evaluate effectiveness of anti - diabetic drugs formulation *(Tolbutamide, Phenormin and Insulin)* in the preventing or delaying cardiovascular complication. The outcome of this study has a larger effect beyond the clinical level. Negative result for SU class drugs (*Tolbutamide and Phenormin*) lead to the collapse of Upjohn Company in the market. 1970s is also the period where most of the 1st generation SU class drugs became obsolete. (Blackburn, 2017)

Besides drug trials, a clinical trial also establishes universal clinical practices, norms, management techniques and helps in formulation standard care procedure in health policy and management. Diabetes Control and Complications Trial (DCCT) is another trial for type 1 diabetes patients in early 1980s to test the glucose hypothesis and determine whether the complications of type 1 diabetes (T1DM) could be prevented or delayed. The outcome of this study leads to establishes universal clinical practices of intensive therapy (INT) (a practice of multiple doses of insulin per day) and continuous monitoring of blood glucose. (Nathan, 2014)

The NIDDK-sponsored Diabetes Prevention Program (DPP) and DPP Outcomes Study (DPPOS) are important life-style modification programmers' shows diabetes can be prevent or delay by losing a modest amount of weight through lifestyle changes (dietary changes and increased physical activity) taking minimal medication at a cost effective way. UK Prospective Diabetes Study (UKPDS) is the largest and longest study ever conducted on T2 Diabetes patients' focuses on established cardiovascular complication associated with diabetes. Most recent clinical trials, ADVANCE, ACCORD and LEADER are also studies related to diabetes and BP co morbidity.

Table 23: Landmark Global Clinical Trials studies in Diabetology

Name of Trial	Years of Enrollment	Enrollment Sample size	Purpose	Method	Outcome
UGDP (1970)	1961-1978	823 Type 2 diabetic patients	To evaluate effectiveness of anti -diabetic drugs in preventing or delaying cardiovascular complication	Tolbutamide, Phenormin (a sulfonylurea)- and Insulins	Negative result for Tolbutamide Collapse of Upjohn in the market
DCCT EDIC (follow-up study of DCCT)	1982-1993 1994 to present	1,441 Type 1 diabetic patients	To test the glucose hypothesis and determine whether the complications of type 1 diabetes (T1DM) could be prevented or delayed	INT (Intensive therapy) - 3 time Insulin pre day/ Insulin pump guided by SMBG	INT effectiveness improving healthy life span
DPP DPP-OC Outcome studies	1996- 2001 2002- present	3234 Type 2 diabetic patients	Life style changes or metformin delay or prevent T2DM	DPP life style change programme with metformin	Effective for all participating racial and ethnic groups and both men and women specially elderly
UKPDS 1998	1977-1997	5102 Type 2 diabetic patients	To compare the advantages and disadvantages of different anti diabetic medications and benefits of different blood pressure (BP) targets.	Multiple OADs drug therapy compared	Treatment with several drugs is beneficial. cost-effectiveness Screening programme necessary
ADVANCE 2009 Built on UKPDS	2001-03	11,140 Type 2 diabetic patients 215 centers in 20 countries	Benefits of different blood pressure (BP) in diabetes management	Multiple drug therapy	Intensive glycemic control targeting HbA1C ≤6.5% improved micro vascular outcomes
ACCORD (2008)	2008	10,251 Type 2 diabetic patients	To determine whether therapeutic targeting HbA1C <6% would reduce the rate of CV risk factors.	Multiple drug therapy	Significant reductions in CV events
LEADER (2016)	2010-12	9000 adults 410 sites in 32 countries	Cardio vascular complications with diabetes	Liraglutide	Liraglutide had significant reductions in CV events

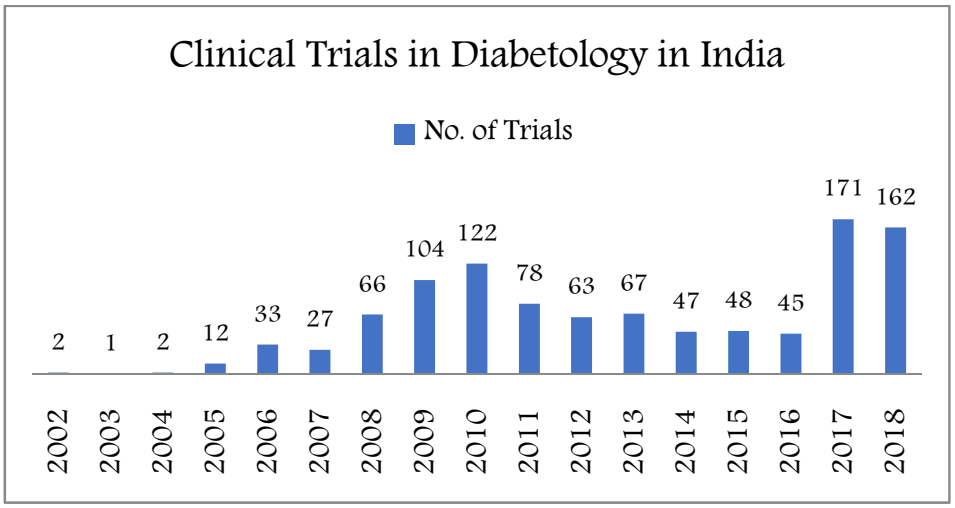
Source: Author's compilation

6.2.2 Clinical Trials in India

Globally, 21031 international clinical trials[43] registered at WHO-ICTRP shows the enormous activities in clinical trials and research occurring in the area of Diabetology. These trials also involves 2279 clinical trials in children indicates diabetes is breaking age barriers even affecting people at the young age. The clinical trial registry- India (CTRI) has more than 1050 registered clinical trials in diabetes. The **Table 24** shows the year-wise clinical trials registered in the area of diabetes.

There are also structural and institutional changes affected the registration process during the period of 2009 to 2016. The CTRI- India was launched in the year 2007, but for the initial period the registration was on the voluntary basis. The trial registration in India through CTRI became mandatory from 2009 onwards by CDSCO. Again from 2018 retrospective registration of trials stopped, only prospective trials allowed. Both these periods shows growing number of clinical trials. The period in between 2011-2016 shows decline in registration of trials due to number of initiatives to standardize the regulatory guidelines and enforced rules to maintain a balance between ethical issues and business.

Figure: Registered Clinical Trials in the area of Diabetology in India

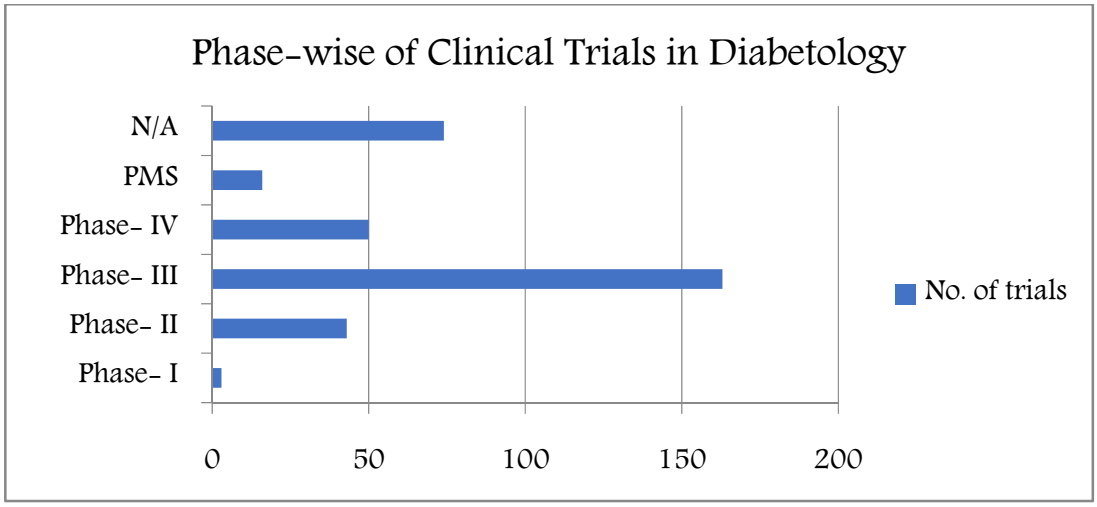


(Source – Clinical Trial Registry- India)

[43] Clinical Trials are important innovation indicators give an idea about current research, drug trials, NCE under investigations and standard clinical practices and norms. In this study ICTRP-WHO database is as an indicator for International clinical trials and CTRI- India for Clinical Trials registered in India. Except global trend, for most of the analysis CTRI- India is being used. The number of trials varies from database to database depending on the coverage. The data were last accessed in February 2019

The phase wise clinical trial data reveals that maximum number of trial belongs to phase III trials (**Figure 19)** and most of these drug candidates in this category belong to foreign firms. India became a favorable destination for global clinical trials due to number of reasons. India constitutes 18% of world population and one-fifth of global health burden of diseases. In diabetes, India's position is second to China. Apart from availability of subjects, skilled healthcare professionals, cost effectiveness and timeliness of prerequisites drug application process favors foreign firms conducting clinical trials in India.

Figure 19: Phase-wise Clinical Trials in the area of Diabetology in India



(Source – Clinical Trial Registry- India)

The **Table 24** reveals the list of novel drug molecule of foreign firms registered for clinical trial in India. Most of the novel molecules by foreign firms entered for phase III trials in India now became successful product in the global market. Multicentre, international randomize clinical trials have added advantages. The pre-clinical studies, or early phases of clinical trials addresses the bioavailability, safety and stability of the drugs. However, how a human body reacts to the drug is very subjective. The response may differ with races, sex, climatic condition, geographical region and food habit. In this regards, a clinical trials of the drugs of foreign firms in India is useful. The **Table 25** shows the list of novel drug molecule of Indian firms in the area of Diabetology. Only two successful products Cadila – Lipaglyn (Saraglitazar) and Glenmark's Remogliflozin are at post marketing stages. Glenmark's drug candidate is an out-licensed molecule. *Except two drug candidates by Cadila and Glenmark mentioned above, most of these drug molecules by Indian firms have failed to cross the phase II barrier.*

Table 24: Research in pipeline: Foreign firms

Foreign Firms in India	Novel Molecules	Characteristics	Phase Of Development
Novo Nordisk	Tresiba® (insulin degludec) (NN1250)	Long-acting basal insulin *Type 1 and 2 diabetes*	Completed
	Ryzodeg® (insulin degludec and insulin aspart) (NN5401)	Mixed insulin *Type 1 and 2 diabetes*	Completed
	Semaglutide (NN9535)	Glucagon-like peptide-1(GLP-1) analogue(once-weekly)	Completed
Sanofi	Lixisenatide (AVE0010)	Glucagon-like peptide-1(GLP-1) agonist (once-daily)	Completed
Eli Lilly	[1]LY2963016 (insulin glargine)	Long-acting basal insulin	Completed
	LY2189265 (dulaglutide)	Glucagon-like peptide-1(GLP-1) analogue(once-weekly)	Completed
	GLP1-PEG (LY2428757)	Pegylated glucagon-like peptide-1 (GLP-1)PEGanalogue	Phase II
Merck & Co.	MK-0941	Glucokinase activator (GKA)	Phase II
AstraZeneca	AZD 1656	Antihyperglycaemics	Discontinued
Boehringer Ingelheim	[1]Linagliptin (BI-1356)	Dipeptidyl peptidase (DPP)-4 inhibitor	Completed
	[1]Empagliflozin (BI 10773)	Sodium glucose co-transporter 2 (SGLT2) inhibitor	Completed
Johnson & Johnson	Canagliflozin (JNJ-28431754)	Sodium glucose co-transporter 2 (SGLT2) inhibitor	Completed
Pfizer	[2]PF-04523655 (RTP801I- 14)	19-nucleotide methylated double-stranded siRNA targeting the RTP801 gene, for the treatment of diabetic macular edema (DME) *Diabetic Retinopathy*	Phase II
	[3]Ertugliflozin (MK-8835/PF-04971729)	Sodium-glucose co-transporter 2 (SGLT2) inhibitor	Phase III
	PF-00489791	Long-acting Phosphodiesterase 5 (PDE5) Inhibitor *Diabetic Nephropathy*	Phase II
	PF-04937319	Partial glucokinase activator	Phase II
Takeda	Alogliptin (SYR-322)	Dipeptidyl peptidase (DPP)-IV inhibitor	Completed
BristolMyers Squibb	*Dapagliflozin (BMS 512148)	Sodium glucose co-transporter type 2 (SGLT2) inhibitor	Completed

(Source: CTRI Database and institutional repositories)

Table 25: Research in pipeline: Indian firms

Domestic Firms	Novel Molecules	Characteristics	Phase Of Development
Biocon	IN-105	Oral insulin	phase III
Panecea	PBL-1427	Dipeptidyl peptidase (DPP)-4 inhibitor	phase I
Piramal	P1736-05	Non PPAR gamma insulin sensitizing Compound	phase II
	P2202	Diabetes-metabolic syndrome	phase I
	PDM011011	Bitter Melon capsules	phase II
	P7435	Diglyceride-acyltransferase(DGAT1) Inhibitor	preclinical
	P11187	GPR40 agonist	preclinical
Torrent	TRC 4186	Advanced glycation end products (AGEs)	Phase II
	TRC 150094	Functional analog of iodothyronines	Phase II
Cadila	ZYH1	PPAR alpha-gamma -*Dyslipidemia*	Phase III
	Lipaglyn (Saraglitazar)	Dual PPAR agonist *Diabetesdyslipidemia*	Post Marketing Stage
	ZYD1	Glucagon-like peptide-1(GLP-1) agonist	Phase I
	ZYO1	Cannabinoid receptor(CB-1) antagonist *Obesity*	Phase II
	ZYH7	Dyslipidemia and metabolic diseases	Phase II
	ZYH2	PPAR alpha-gamma: *diabetes*	Phase I
	ZYOG1	Glucagon-like peptide-1(GLP-1) agonist	phase I
	ZYDPLA 1	Long acting DPP-IV (once weakly)	Phase I
Glenmark	GRC 17536	Transient Receptor Potential Ankyrin 1 TRPA1 Inhibitor *(Diabetic neuropathy)*	Phase II
Glenmark	Remogliflozin	SGLT2 Inhibitor	Post Marketing Stage

(Source: CTRI Database and institutional repositories)

The following section address the research question on evidence based practices, challenges in clinical practices and challenges in public policy management for Diabetes. This section also describes the existing policy programmers' that addresses T2 challenges of translational research (clinical practices)

6.3 Clinical Trial: Evidence based knowledge and Practices

New drug trials:

A clinical study involves multiple phases of trials in Phase Zero, I, II, III and IV contribute to unique knowledge generation at each stage that helps in finding best dose formulation besides addressing the efficacy of the new drugs. Phase III trials are involves maximum patient involvement that indirectly helps in generating knowledge related to clinical practices for new drugs. The knowledge formation in this stage is not limited to drug development process only. Clinical trials have a bigger contribution to the domain of clinical practices. In addition to testing new drugs and devices, clinical trials provide a scientific basis for advising and treating patients. Clinical trials helps in standardizing practices, International clinical trial results helps in harmonization of treatment process hence contributes to evidence based research, trials, practices and policy formulation. The RCT demonstrates effectiveness of a common protocol among multiple investigators and collaborators with different points of coordinating at different geographical locations. Besides drug trials, a clinical trial also establishes universal clinical practices, norms, management techniques and helps in formulation standard care procedure in health policy and management. UGDP was the first RCT in the area of Diabetology establishes universal clinical practices norms.

Drug trial is a complex process. Comparisons of drug are not easy as every new drug response differently to different body types. There are many complication associated with diabetes make drug comparison ever more difficult. However, the knowledge formation, during practices, even negative results contributes to the post-improvement of the products.

Observation studies

Clinical trials knowledge are not restricted to the new drug development, it also established various existing standard practices, contribute in developing method, and clinical diagnostics. Observation of glycemic control in pregnant women (CTRI/2008/091/000179), behavioral changes and impact of physical activities on controlling diabetes (CTRI/2009/091/000068) does not require new interventions, rather new methodological, innovation in procedure to

prevent or control of disease. An observational study also involves long term drug study known at post marketing trial.

Combining method of treatment

After clinical trials of new drug become mandatory in India, numbers of clinical trials on traditional medicines were registered at CTRI database. The clinical trials data revealed that a number of studies are under trial to find out the effectiveness of traditional or poly herbal formulation in the patients of Diabetes Mellitus. These trials are studying activity and safety of ayurvedic formulation such *as Ashwagadha* and *Haridra*in patients freshly diagnosed with Type 2 Diabetes mellitus in collaboration with leading hospital & research center in India.

Some of the multi-centered randomized control trial aims to evaluate how lifestyle modification through yoga & complementary medicine can effectively manage diabetes and other clinical conditions like depression and quality of life in patients. Although AYUSH and Conventional medicine are two entirely different scheme of practices, there are clinical evidence of combining treatment methods, insulin and OADs along with yoga, music therapy for glycemic control.

Life-style modification programmes:

Life- style modification is an integral part of clinical practices for diabetes management. The NIDDK-sponsored Diabetes Prevention Program (DPP) and DPP Outcomes Study (DPPOS) are important global life-style modification programme shows diabetes can be prevent or delay by losing a modest amount of weight through lifestyle changes (dietary changes and increased physical activity) taking minimal medication at a cost effective way. In India, MDRF- (D-CLIP), an RCT is cost-effectiveness, sustainable, culturally appropriate, lifestyle intervention program that helped in diabetes management in rural *Tamil Nadu*.

Similar successful clinical trials K-DPP, AIIMS- ROLIDM, RSSDI WB-SELIP are specific evidence based for life-style management/ community development programmes help in understanding India specific issues and challenges in diabetic management through effective practices.

Prevalence Studies - Registries

Population based prevalence studies such as INdiaDIABetes (INDIAB study), Registry of Youth Onset Diabetes in India (YDR), PURSE-HIS (Population Study of Urban, Rural and

Semi-urban Regions for the Detection of Endovascular Disease and Prevalence of Risk Factors and Holistic Intervention Study) helps in identifying the country, region specific prevalence and incident rate, that helps in taking policy measures for disease management.

Advance medical procedures: Clinical trials indicate advances in surgical treatment methods related to islet transplantation, other advance medical procedure such as stem cell research for type 1 diabetes (CTRI/2017/12/010878), Nano medicine. The **table** below is an indication of different type of CTs other then drug trial that contribute in evidence based clinical practices.

Table 26: Contribution of CTs in knowledge development for clinical practices

Clinical Trials	Title	Contributions
CTRI/2013/02/003412	Health care delivery model for the management of hypertension and diabetes at CHCs and District Hospitals of Himachal Pradesh.	Model health care delivery
CTRI/2008/091/000179	Evidence of Good Glycemic control in Conceptions through Assisted Reproduction Technology [EGG CART Study]	Observational studies
CTRI/2013/02/003417	Population based study and intervention through diet, exercise conversion of Pre-Diabetes to Diabetes	DPRP-DST sponsor Life-style program
CTRI/2013/07/003835	A study of impact of tele-counselling on life style parameters in diabetes	Observations studies
CTRI/2018/05/013957	Diabetic Retinopathy in Udupi district	Population based observations
NCT01283308	Diabetes Community Lifestyle Improvement Program (D-CLIP) cost-effect, Sustainable, culturally appropriate Randomize Clinical Trial	Lifestyle intervention programmes
CTRI/2016/05/006933	National Bariatric Registry of India	Registry to study prevalence
CTRI/2013/01/003316	Yoga and Fenugreek in the prevention of type 2 diabetes mellitus (traditional and modern methods)	Clinical practices combination

(Sources – CTRI- India and ICTRP- WHO)

6.4 Challenges in Clinical Practices: (*Based on the interviews*)

Clinical practice is a complex issue; the determinants are not limited at the clinical level, rather combination of various socio-economic, societal factors that influence clinical practices. The following section is a comparative analysis of two clinical practitioners' perception on treatment procedure and how a socio- economic factor influences the clinical decision.

Clinical practices – **Clinician 1 & 2** (Comparisons)

Both the practitioners belong to the same tier III city but have different patient population.

C1- He is a practitioner with DNB endocrinology degree, experience in CTs, experiences as a consultant in big private hospital in tier-I city. The clinical setup is medium in size, located in prime location with good number of supporting staff. The consultant fee is higher than C2; the patients mostly belong to middle, upper- middle and higher class population.

C2- He is a consultant endocrinologist, with DNB degree from top reputed national medical college in India. The clinical setup is small (one room set), with one support staff. The consultant fee is lower than C1. The patients mostly belong to low, lower-middle class population.

(In type- 1 diabetes, the intake of insulin is mandatory, while in type -2 the requirement depending on the condition of patient. The opinions below are for type-2 diabetes.)

C1: If treatment process requires use of insulin why not! There is no harm in using insulin at early age.

C2: No doubt, insulin is gold standard treatment procedure; titration of insulin is easy that helps in formulation or recommending appropriate dose for treatment. However, I avoid prescribing insulin, until diabetes cannot be regulated through OADs.

Recommending branded drugs: new drug classes

> *C1: New anti-diabetic drug classes, which are recently introduced in the market, is better than older one in regulating the disease but comes with an exorbitant price tag. I recommend the drugs to the patient who can afford it for better clinical outcome.*
>
> *C2: The cost-benefit analysis of the treatment is important while recommending drugs. No doubt, new drug classes are better at clinical efficacy and effectiveness, but at what cost? One of my patient (a farmer) taking OADs for last 20 years (the cost is 1Rs/per tablet), and his sugar level is effectively managed by that treatment procedure.*

Both the consultant agrees that socio- economic condition of patients, their purchasing power and out-of pocket expenditure are important factor that helps in decision making while recommending a medicine.

The following interview is pondered into clinical treatment procedure in Ayurveda and how it is different from conventional methods of treatment.

Clinical practices - AYUSH-1 *(Head, Kayachikitsa in a govt. ayurvedic medical college)*

> *The principle of treatment method in the Ayurveda is different from conventional allopathic medicine. The principles of pharmacology in ayurveda are based on five major element; Rasa(taste), Guna (Properties), Virya (active principle), Vipak (biotransformation) and Prabhav (Specific action). Panchabhutas (Akasha, Vayu, Agni, Jal, Prithivi) are physio-chemical basis of life. When life evolved, out of these five, three came forward to control and regulate the biological functions. These three (Vata, Pitta, Kapha) are known as tridhatu (tridosha) are pathological conditions have specific functions of Vikshepa (movement), Adana (assimilation) and Visarga (growth) respectively. The system take whole body as a system in treating diseases rather focuses on a single organ or cells.*

Policy Issues:

Clinician-3: *(Leading endocrinologist in India, former president of International Diabetes Federation having extensive knowledge and clinical contribution in clinical research, practices and policy formulation in diabetes both national and global level)*

Educating general practitioner about mode of treatment

The first screening of disease occurs at Primary Health Center, where diagnosis and treatment process are done by general physician. Eighty percent of population, visit PHC or district hospital, does not consult specialist. There is less number of endocrine specialists in the country mostly restricted to urban areas. In that case, if proper diagnostic or treatment occurs at the PHC rural or semi-urban area, the prevention of diabetes can be done. A multi-lingual diagnostic manual, with detailed treatment methodology for multiple complications related to diabetes and its complications should be provided to the PHC, Rural general practitioner.

Awareness through educations

Diabetes was predominantly associated with the older ages. But the changing scenario indicates diabetes has no age bar. Now, the incident rates among younger peoples and kids are increasing. Due to excessive urination and thirst associated with this disease, diabetic kids undergo frequent mental harassment during school time. Teachers and fellows are unaware of the clinical conditions

The school curriculum should include the prevention, treatment method and awareness manual how to treat diabetic patient. Recently, MHRD provides guideline how to treat diabetic patient during exam by relaxing some norm to take food, medication and use lavatory during exam. Role of women in the family is important is managing life-style intervention; hence it is important to education women about healthy dietary habit.

Preventive care policy

Mass screening can averts larger scale NCD problems in India. The out-of pocket expenditure is more in NCD due to life-time expenditure. Current programs, Ayushman Bharat, other insurance based support are limited to hospital based recurrence, does not includes preventive treatment

Need for diabetic educators

Researcher: *(A post doctoral fellow, run an NGO Diabetes Pathsala, works at grassroots level screening and awareness drive)*

> *Role of women is important in managing life-style related problems. The NGO creates awareness drive in rural India, with diet-chat, quiz, and prizes. Women are responsible for dietary management of entire family.*
>
> *There is social stigma associated with type -1 disease. There is need of Diabetic educator, those who can create awareness, and also solves basis diagnostic problems.*

Clinical Practices challenges (Complied responses from number of Clinicians)

> *There are different guidelines for diabetes management. In India practitioner mostly followed American Diabetes Associations (ADA) guidelines. However, there is variation in the practice, especially regarding test limits and methods*

Dilemma in practices

> *Diabetes is associated with various multiple diseases that make the situation complicated in term of diagnosis and practices. There are many new OADs with better efficacy are present in the market, but choices depends on number of factors and determinants.*

Patients' responses

> *Doctor- patient trust is important in clinical management. In some cases doctors are not fully aware of clinical condition of the patient. Patient takes multiple treatments without doctors' consent.*

6.5 Addressing Translational Challenges through policy and programmes:

Transitional research is an important policy instrument to effectively counter any public health crisis. The empirical literature on translation research discussed two major translational gaps 'basic research-clinical studies' (T1) and 'clinical studies-clinical practices' (T2).

Woolf (2008) identifies global policy, organization are more incline toward addressing T1 challenges rather T2 challenge. T2 translational is important especially for the resource- poor setting countries like India as effective management of diseases with existing setting requires innovative clinical practice and implementation strategy.

The analysis shows a number of institutions, government, ministries, and department such as DST, MST, DSIR, DBT, DHR, ICMR, CDSCO, DIPP, Dept of Pharma are instrumental in promoting and shaping translational research, basic research and clinical research in India, hence effectively addressing T1 challenges. *(For detail see function-resource mobilization)*

T2 challenges require an entire different setup as implementation requires contribution from health services. Directorate General of Health Services (DGHS), under Ministry of Health and Family Welfare is the nodal agency in India for health services. National Health Mission (combination of Rural- NRHM & Urban - NUHM), is a flagship programme of Govt. of India, is instrumental in implementation of various health services in India. In the study we focus on the policy and instrument that help in management of Diabetes. National Health Programmes is an important programmes as it covers entire health care services eco-system in India from Rural Medical Dispensary (RMD), Primary Health Centre (PHC), Community Health Centre (CHC), Urban Health Centre (UHC); district, Sub-divisional and Rural hospitals along with large tertiary care and teaching hospitals and other public hospitals including Railways, ESIS, CGHS, Armed Forces etc.

The primary focus of health services in India was on communicable disease till early 2000. Mission oriented disease specific programmes on TB, HIV, Vector- bone diseases, Leprosy, Integrated Disease Management Programme (IDSP) were the focal point of health services. Only two national programmes on National Cancer Control Program (NCCP) and National Programme for Control of Blindness & Visual Impairment (NPCBVI) were dealing with NCD issues at that time.

6.5.1 National Programme on Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS)

The flagship programme was launched as a pilot program in 2008, in 10 State (1 district each) with main objective to reduce burden of NCD (Diabetes, CVD and Stroke) through three major forms of interventions: *Early diagnosis and management of NCD, Special focus on high risk disease prevalence population and focus on awareness and health promotion in general public.* The programmes became full- fledged programme in 2010 with focus on strengthening infrastructure, human resource, health promotion, management and referral. The programmes finance is maintained through contribution of centre and state (60:40).

Early diagnosis:

For chronic diseases, early diagnosis is important for clinical management. The programme envisioned to address the issues through population based screening[44] and opportunistic screening however, the implementation is yet to be started. The pilot program, under school health programme completed screening of school children in four districts due to increase incident rate in young diabetic population.

Infrastructures development:

The program initiate setting up NCD clinic/ NCD cell at national, state and district levels for early diagnosis, treatment and follow-up for common NCDs. The infrastructural development includes availability of *Glucometers, Glucostips* at the NCD centre and timely maintenance and calibration through *Biomedical Equipment Maintenance Programme.*

Human resource capabilities:

For NCD screening, 3-5 days training programs for ASHA and ANM workers in village and primary healthcare centre, about the history, sign, symptoms basic pathology, awareness and operating glucometer and BP instruments.

The NCD cells provide free diagnostic facilities and drugs for patients for the maximum limit are 3 month, which is not sufficient and suitable for chronic diseases management.

[44]Population screenings are meant for all individuals in a target group of populations (sorted by age), in an organized program. This screening creates awareness in the community that leads to opportunistic screening (patient became self-motivated for the screening/test)

Awareness and health promotion

NPCDCS promotes healthy life style at level of workplace, school and community level through behavior change with involvement of community, civil society, community based organisations, media, outreach Camps. Overall, the objective of the programmes is better health outcome through preventive measures.

Recent initiatives:

Due to the co-morbidities associated with diabetes the recent guideline includes prevention and management of Chronic Obstructive Pulmonary Disease (COPD) and Chronic Kidney Disease (CKD), integration of RNTCP with NPCDCS, wherein the "National Framework for Joint Tuberculosis-Diabetes collaborative activities. The guideline is unique joint disease management for diabetes and TB.

Role of AYUSH:

For chronic disease managements, where prevention and management of disease are the ultimate treatment methodology, herbal formulations, traditional medicine and practices has bigger role. The NPCDCS programmes has initiated a pilot projects in six districts on ***'Integration of AYUSH'*** with integration of facilities, human resources and methodologies (integration of Yoga) in the conventional services for prevention and management of common NCDs.

Limitations: The programme is in the initial phase of implementation; hence effective evaluation is not possible at this stage. The resources and financial allocation shows Cancer receives maximum funds. For cancer programmes there is provision for one time financial supports. The problem with chronic disease like TB, Diabetes is that, although the recurring cost, out of pocket expenditure is high, the government financial assistance scheme in NPCDCS or other flagship programmes like AYUSHMAN BHARAT does not covers the cost. The policy should move from treatment based, hospitalized insurance to prevention measurement and supporting preventive care.

National Programme for Health Care of the Elderly (NPHCE) is another new NCD programmes focuses on elderly population in the countries. The resources and facilities for this programme are integrated with NPCDCS, as NCD cell is common platform for providing services related to NCD.

Other programmes such as *Free Diagnostics Services Initiative*, *Pradhanmantri National Dialysis programme* lunched in 2017 are interlinked services related to kidney related complication, diabetes and hypertensions. *Health GIS* is a programmes from MOHFW to map the diseases using spatial pattern. e-health and telemedicine programmes such as *mDiabetes is an awareness drive, No more tension Aap is a stress management applications*

6.6 Summary:

For communicable disease managements, role of NGOs have been fully utilized for management of immunization, TB, AIDS programmes, similar efforts requires for management of disease not just for services but also form health literacy. WHO-EM globally and NPPA- DPCO at national level tackles the issues of affordability through list of essential medicine for management of disease. The problem in diabetes is no new patented drugs are included in the list. Most of the diabetic new formulations are in the market in the recent decade. The WHO- Diabetes country profile shows lack of equipments and infrastructure for management of diabetes in primary health care centers. (Jena, 2018)

Overall this chapter describes the important of clinical trials, the contribution of clinical trial knowledge in the knowledge formation, diffusion process, the CTs in India and the NCEs under investigation. This chapter describes CT knowledge beyond the NCEs and contribution in clinical practices, further challenges in clinical practices and addressing T2 challenges.

CHAPTER SEVEN

ISSUES AND CHALLLEGES IN TRANSLATIONAL RESEARCH

7.1 Introduction:

The major challenges in structure and functions of biomedical research and innovation is that the actors, organisations and institutions have different objectives at each stages and works in different environments and innovation- ecosystems. Hence, the problems lay not only in their own eco-system but also when it translates from one stage to other. So, the entire process from idea/ concept stage to market stage in a product or process development or at clinical practice level has its own challenges. TIS framework has methods for identifying inducement and blocking mechanism that will help to improve the focal TIS and helps in policy formulation or interventions. However, the inducement and blockage mechanism in TIS identifies system problems with in the focal structures of TIS but not beyond that. What is being achieved in the TIS is therefore only in part a result of the internal dynamics of the TIS. Exogenous factors also come into play, influencing the internal dynamics. From a policy perspective, it is particularly important to understand the blocking mechanisms that shape the nature of the dynamics. It is empirically possible, and very useful, to map the relationship between inducement/ blocking mechanisms and functional patterns. The larger context includes the sector in which the TIS operates, e:g basic research (the overall research environment. university- Research organization) , translations (pharmaceutical/ biopharmaceutical structure), practices (clinical setup). The system problem or failure mechanism addresses these sectoral problems that arise beyond the focal structure or functional component of TIS.

This chapter identifies issues and challenges at basic research, applied research, clinical research and translational research, problems in market, clinical practices and public policy level. This chapter also identifying challenges related to key innovation indicators such as research financing, research infrastructures, human resources, policy, guidance problems. The central concept of the focal TIS is to identify solutions to prevent and treatment of problem related to diabetes. Sometimes, solutions do not exist in development of new product or artifact, but how effectively use the existing resources at clinical level. The chapter covers the issues related to clinical practices at grass root level, the socio-economic & ethical complications.

The chapters identifying successful translational products and artifacts that developed in the Indian biomedical innovation eco-system, also the product at various stages of development. The chapter attempts to find out the issues related to translational process, the success or failure behind translation, the products that lost in translational process.

7.2 Problems in defining Translational Research:

As the primary data involves addressing the problems and challenges pertinent to the sector and institutes. Many participants were not comfortable in discussing the issues. Prior consent was taken from the participant before taking the interviews. We intentionally do not disclose any name and address of the participant as per their wish.*

Scientist 1: (Molecular Scientist):

> *'Basic research is important and key to the success of translational research. Some of the emerging areas such as 'gut microbes' has wider ranges of applications in cancer, diabetes, CVD and 'genome editing' is molecular technique You cannot predict translational capabilities at the basic stage but basic research can have lots of translational function, hence strong basic research is important."*

Scientist 2: (Sr. Principle Scientist)

> *"There is no distinct boundary between basic and translational research. The potential outcomes of a research whether contribute to basic research or translational research sometimes difficult to analyze. There are diseases (mostly neurocongitive diseases) till date does not have potential drug candidates, diagnostic method or mode of treatment. Basic research investigating diseases profile, comparing abnormal brain with normal brain, finding new target sites does not directly contribute to product development or treatment method. However, the seminal contributions to the knowledge field by the basic research is stepping stone towards translational process. This knowledge contributes to the development of drug and treatment method. Hence robust basic research is important but everything needs to be envisioned as translational research."*

The current policy regime needs to understand these nuances of scientific research and innovation process. All the scientific research is not envisioned for a product or process. Many basic inventions and their poteintial of translational to a product/process only discovered decade after the invention. Indirectly, laboratory research help in creating skilled labour forces, human capitals in the highly specialized areas of biomedical innovation.They contributes to knowledge production, travel for career advancement leads to knowledge diffusion at that knowledge being used for societal benefit. Don't you think that is a form of translation? The end results of translational process should have some societal benefit.

Measuring translational research – an analytical problem

In **(figure X*Y),** analysis of the knowledge distribution in various field in Diabetology. The categories are clinical knowledge, basic & applied knowledge, translational knowledge. The most difficult part of categorization of knowledge field is differentiating basic and translational knowledge field. Similarly, it is also difficult to identifying the research journals (knowledge field), relevant actors, organisations and institutions from translational research perspectives. From TIS perspectives, when unit of analysis is a knowledge field, every innovation in the field of studies (artifacts, devices, drug, and insulin) belongs to different core discipline. These analytical problems raise a pertinent question. Does translational research is part of core discipline or a separate knowledge field?

Measuring research output - an analytical problem

The use of TIS framework has certain advantages over, sectoral system in this study, as it allows both vertically as well as horizontally connection of actors, organisations and institutions in the development of specific technologies. Biomedical innovation system is a multifaceted, multi-directional innovation process where actors, organisations and institutions works and interacts at different innovation eco-system. The respondents have different point of views on my question on research output.

Q. What is your preference mode of research output/ clinical output? (Patents, Publications, Clinical Trial Protocol & Management, Policy & regulations, Clinical Practices, Product development, others…..)

The actors at research stage, translational stage and clinical stage have different objectives and hence their research output varies. Clinician prefers publications along with clinical practices, basic and translational researchers prefer patents and publications. Within a homogeneous systems (e;g basic research stage – University/ research organization) there is variation in preferable mode of research output.

Scientist 3: (Principle Scientist)

> *The choice of preference between patents, publication and product development is not an individual choice but an organization preference. The organization preference is not static; it also changes over the time period. In CSIR different Director Generals have different opinion. During the period of Dr. R.A. Mashelkar as DG CSIR (1995-2006) the preference was given to the patents. Publication was given priority by next DGs. The current priority is translational research (product development)*

Translational Gaps in biomedical innovation system in India:

(Problems in transferring knowledge from basic research to clinical research)

The primary data analysis based on the field work indicates that major problem in translation of product development from basic research stage to clinical research stage is weak academia-industrial collaboration in product development related to biomedical innovation process.

Problems associated with new drug molecules

Scientist 2: (Sr. Principle Scientist):

> *The drug development is complex, high risk, resource intensive process. A new drug molecule (new chemical entities or new biological entities) when developed in our laboratories, it requires pre-clinical testing of that molecule. The drugs under goes through various process of validation such as Pharmacokinetics (PK),Pharmcodynamics(PD), ADME, toxicological tests then followed by animal*

testing with either murine (rat or mice) or canine (dog). All the parameters of GLP-guidelines followed during the process.

With existing infrastructures, we are capable of doing pre-clinical testing and animal testing on small laboratory animals. Drug test on primates (monkeys) or higher animal requires larger setup, infrastructures and finance, which is not possible in the scientific laboratory. There is an also ethical issue involved on bigger experimental animal, scientist does not want to confront animal activists group like (PETA).

Credibility issues: *The drug molecule requires further validation. At this stage, we approach Contact Research Organisations (CROs) with our samples. However, there is lack of interest from firms for collaborations with Indian partners. CROs are more incline to collaborate with foreign firms.(larger financial gain from MNCs then govt. funds is also a reason). They take interest in further development of drug, only if it validates by a foreign partner. We have to share our sample with foreign colleague, for further validations of our drug molecules.*

Problems associated while dealing with experimental animals

In translational research role of experimental animal are very important. Animal model[45] have been used to address a variety of scientific questions, from basic science to the development and assessment of novel vaccines, or therapies. The remarkable anatomical and physiological similarities between humans and animals, particularly mammals, have prompted researchers to investigate a large range of mechanisms and assess novel therapies in animal models before applying their discoveries to humans. Animal testing of drug is pre-requisite before being translated to humans. (Sinoussi, 2015)

[45] Animal model is an animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. E.g. Animals with transplanted human cancers or other tissues are called xenograft models.(NIH-National Cancer Institute)

Scientist 3: (Principle Scientist) & Scientist 4: (Principle Scientist)

Supply-chain problems

In India, all animal models are not available. Researchers have to import them from the foreign countries (mostly USA). The import cost is an additional burden. Even the food for those animals has to be imported.

Research priority

Animal models are important to understanding the physiology of disease condition. Animal models for all different types of cancers are available; hence most of the translational work occurs in Oncology. Same is the case for diabetes research. However, does animal models also depends on priority of diseases? Type-I diseases (cancer and diabetes) mostly prevalent in developed countries have animal models but a disease specific to developing countries or under-developed countries might not have an animal model. This condition certainly affects the translational ability and deciding research priorities.

Missing eco-system:

In USA, there is a dense network and collaboration between top universities, laboratories, firms, animal breeding centers building a strong translational base to develop new animal models for disease. In India, that eco-system is missing, hence adversely affect translational capabilities.

Q. What are the major reasons for failure in reproducibility and translational ability of non-clinical studies for further development? (Knowledge/ Guidance/ Finance/ Human Resources/ Infrastructures/ Others…..)

Scientist 5: (Translational scientist- toxicologist)

Improper study design has an impact on the results. The problems may arise due to lack of knowledge in Pharmacovigilance, toxicity assessment, lack of skilled manpower (including investigators and quality data assessors for better prediction/outcome). Proper infrastructures are not available for some of the translational work. OECD Guidelines are followed for toxicity assessment. Good Laboratory Practices (GLP) guidelines are important for the laboratory works.

National GLP Compliance Monitoring Authority (NGCMA) is the nodal agency under DST implements and monitor GLP in India. However, the GLP certification is voluntary in nature.

Regulatory delay and lack of inter-ministerial co-ordinations

Committee for the Purpose of Supervision and Control of Experiments on Animals (CPCSEA), under Department of Animal Husbandry and Dairying, Ministry of Agriculture and Farmer Welfare, Govt. of India is the nodal agency regulates and approves experimentation on animals in India. The committee was established under the Prevention of Cruelty to Animals Act 1960. The Committee formulated the 'Breeding of and Experiments on Animals (Control and Supervision) Rules, 1998' to regulate the experimentation on animals. The main functions of CPCSEA includes Registration of establishments conducting animal experimentation or breeding of animals, Selection and assignment of nominees for the Institutional Animal Ethics Committees, Approval of Animal House Facilities*, permission for conducting experiments involving use of animals, recommendation for import of animals for use in experiments.*

National Institute of Animal Welfare (NIAW), Ministry of Environment, Forest and Climate Change, GOI is the nodal organization fulfills the statutory requirements that laid down the Prevention of Cruelty to Animals Act, 1960.

Scientist 3: (Principle Scientist)

The regulatory clearance for the conducting experiments, or import of animal got unnecessary delayed; even the food required for the experimental animal requires regulatory clearance. NIAW and CPCSEA come under different ministries. The lack of co-ordination hampers the research and translational activities.

Missing innovation eco-system in India:

Scientist 2: (Sr. Principle Scientist), Scientist 4: (Principle Scientist) and

Scientist 5: (Translational scientist- toxicologist)

> *The establishment of CSIR institutions was to cater the local advantages. India's premier research organization, firms and CROs are located in Hyderabad. There is a lack of co-ordination among them. There is no major breakthrough, indigenous product or new molecule came in last decade. All the scientist and researcher have strong opinion about building innovation ecosystem, which is missing in the current scenario.*

Problems in Research Financing:

Scientist 3: (Principle Scientist), Scientist 2: (Sr. Principle Scientist):

> *Scientific funding is politically driven in India. Priorities changes with every government. Earlier, during election year we receive fewer funds, but the amount was compensated next year. After 12th Plan (2012-17) the scientific research funding has decreased. There is no-plan fund now, so it is difficult for us to set up our prior agenda. Government encourages to generation funds through product or translational work, however, in science based setup translation is difficult and time consuming process. The research scientist voluntarily teaches at school level to enhance scientific temper among the students, that contribution is like an translational work, ultimately benefitting the society.*

Extra-mural research funding / research projects:

Organisations and institutions like ICMR, CSIR, DBT, DST, DSIR and DHR supports biomedical innovation through extramural funding or specific prograrmmes.

> *In USA, most of the biomedical research is funded by National Institutes of Health (NIH). The research grants are highly competitive and process of project approval is transparent (grading system- point based evaluations). The applicant those unable to receive funds, at least have a clear idea of their weakness, lacuna in their proposal that helps them for the future grants. Once the research proposal got approved, there*

is a clear time-bound disbursement of funds that helps scientist prioritizing their work schedule.

You can predict who will receive the fund in India. The selection or review processes of financial agencies' project review committees (PRCs) are opaque and unpredictable. There is no clear guideline or time-line for approval process. Even for approved projects the grant release got delayed, faces many administrative hurdles leads to delay in the procurements of reagent, instruments that ultimately hampers the research work

Research infrastructure:

Scientist 3: (Principle Scientist), Scientist 2: (Sr. Principle Scientist):

In the current India academic setup, with all existing resources, infrastructure and skill level, the system is competent enough to do research only up to the small animal model (mice) to some extent rabbit not beyond that. The current infrastructure is sufficient for laboratory research. For other translational work requires larger capital, enormous funds (Animal testing (higher order) are very expensive), different level of expertise, regulatory knowledge requires, which is not possible in a research organization. Hence, there is a weak collaboration among CROs and research organisations.

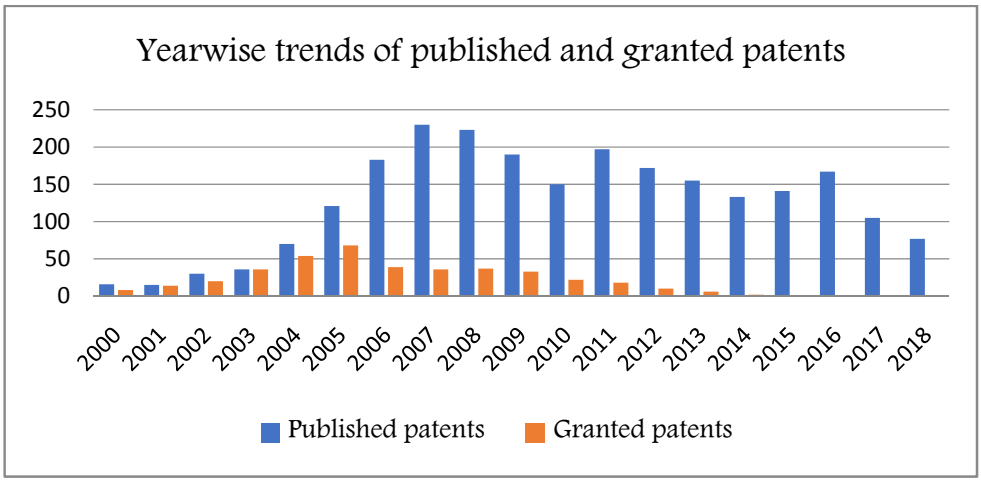
7.3 Problems at basic research:

Patent related problems:

The Chapter five shows us the patenting trends in Diabetology in India. Patenting from Indian firms and actors are very less. Most of the patent applications are from foreign firms through PCT routes. The maximum number of patent application in Indian categories are from big firms but last 10 year trend shows the patent application are minimum from this category which is a significant point to ponder with respect to the biomedical innovation capacity building in India.

On contrary, the patent application from smaller laboratories (science-based and translational base research organisations), start-up firms, AYUSH, Dignostic firms have increased in last 5 years shown the tremendous growth potential in this sectors. The cause of concern in this sector is most of these application seeks domestic patents not international patent. The PCT applications are less in these categories. There are also sectors issues related to AYUSH products, herbal formulation where patenting is not applicable. There are number of single or independent assignees have patent applications but translating patent to a product is a difficult task without institutional supports.

Figure 20: Comparing Published and Granted patent in Diabetology in India



(Source: Patent analysis of published patents through IP-India database)

There are 2411 published patents and 404 granted patents through the period from 2000-2018. The percentage of granted patents is 16.7% (404 granted out of 2411) of total application. **(Figure 20)** Out of these granted patent shows PCT applications have greater success rate both in term of approval and time of processing. Mostly of the PCT applications are foreign patents. The reason for higher approval rate of PCT application as it's validates by other global patent office, even one patent granted at any offices increase the acceptability of those patents. Another reason, these applications are already being supported by prior act search results, that reduces the time of process of examination, hence decision making requires lesser time than other. Domestic application have lesser number of approved patents, however these is no particular trend is being observed here.

Delay in patent process:

Delay in patenting process, can have multiple reasons. We observed some reasons for delaying or rejection of patents application in India.

From applicant perspectives:

The table mentioned some of the reasons for delay, abandoned or rejection of patents. In India, the deadline to file an RFE is 48 months from the filing/priority date. Most applicants prefer to file the RFE closer to the deadline rather than along with or close to the filing date of the application. There are delay from the applicant side in from request for exam, not filling complete specification in time, non payment of fees in the stipulated time period, delay in fulfilling non-technical and technical formalities (drawing in right orientation).There is also an institutional delay on grant of patent in herbal or traditional based formulations in India due to the additional process of NBA approval.[46]

[46] Patents on biological resources and traditional knowledge based formulations require to resolves the Access and Benefit Sharing (ABS) issues as per the Biodiversity Act (BDA-2002). National Biodiversity Authority under Ministry of Environment and forest is the nodal agency in India to grant ABS approval. The underlying principles of ABS (Section 6 of BD Act) is to ensure that access to biological resources and/or associated traditional knowledge is based on a set of principles, terms and conditions that include securing prior informed consent (PIC), finalizing mutually agreed terms (MATs) and ensuring fair and equitable benefit sharing. While granting the approval under this section, NBA impose benefit sharing fee or royalty or both or impose conditions including the sharing of financial benefits arising out of the commercial utilization of such rights.

From institutional perspectives:

Capabilities issues: The burden of applications, infrastructures, administrative delay, processing of patent application, capabilities of dealing with non-technical and technical formalities, the strength of patent examiners and quality of examiner, capabilities of appellate authorities, capabilities national and regional offices affects decision overall system. These issues are being discussed in the next chapter.

Problems in Patenting – IPR issues: Role of PFC (Patent facilitating centre)

Patent Facilitating Centre is an in-house institutional setup to facilitate patent application (both domestic and international applications), helps in capturing, filing, prosecution, maintenance of patent applications. In India, most of the premier biomedical research institutes or concern regulatory department such as DST, DBT, CSIR and ICMR have their own facilitation centers.

Scientist 3: (Principle Scientist)

> *All the research or innovations are not patentable. Filling of patents and maintenances of patent is a complicated and expensive process. As CSIR, take the burden of finance and maintenances fees of the patent, there is no financial difficulties to maintain the institutional patent, however, the case is different for an individual innovators/ grass root innovators.*

Lack of co-ordination & Lack of expertise

> *The filling of patents, maintenances and facilitation comes under the Business Development Wing in our organization. Scientific work and patenting work belongs to two different domains. We are unable to communicate our requirements they do not understand our language. Ultimately, the burden of writing specification and other technical requirements come to the scientist; those already are being over burden with scientific and administrative work. *(Other-side of the story is not been captured and verified in this research)*

In USA, the PFC teams are composed of battery of lawyers, professional expertise (those having knowledge of patent drafting, prior art search). In India what PFC requires is dynamism in approach; diversity in human resources management in a PFC. The multi-disciplinary team composition will help scientific community not only for filling a patent or maintenance but also helps them in prosecution and defend their patents.

Publication issues:

India has 2nd largest pools of diabetic patients globally, however, she stood at 7th position in terms of total number of research publications from 2000-2018, distinctly lags behinds many developed and developing countries in terms of publications. Diabetology is the clinical science of diabetes mellitus, its diagnosis, treatment and follow-up. The core subject area is medicine and endocrinology amount to 64% total literatures, however for an innovation system to develop a strong science and translational base is required.

Credibility issues:

Major share of the research publications from India are published in low impact journals below 5 impact factors.

7.4 Problems in Conducting Clinical Trials:

Practitioner 1: *(Consultant endocrinologist with years of experience in conducting clinical trials)*

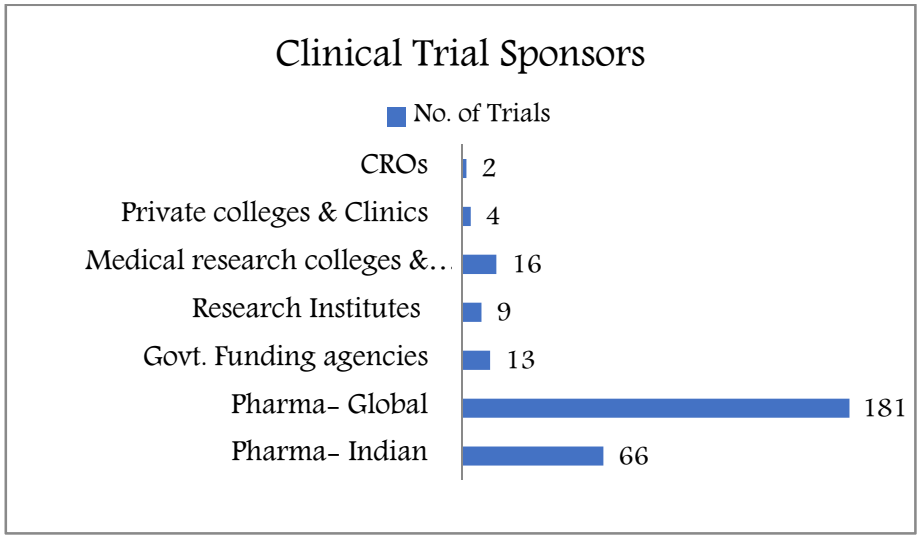
> *Designing clinical trials are problematic. The number of clinical trials has decreased in last few years due to regulatory challenges. Maximum number of diabetes patients' lives in Asia. However, not enough patients are recruited in the clinical trials from this region. In global Clinical Trials for drug, sample size is very less from India. But India is one of the emerging markets for life-style diseases. Drug*
>
> *Drug comparisons are not easy task. As each patient can have unique complications and clinical conditions. India as a region also has lots of diverse populations. The nature of disease 'diabetes' have lots of co-morbidity and complications related to hypertension, kidney failure, liver, foot, eyes*

Practitioner 2: *(Consultant endocrinologist with years of experience in conducting clinical trials*)

> *There is lack of reliable, accurate and adequate source of information of clinical Trials in India. There are no proper documentations on clinical trials works. The negative results should encourage for publications. For last 4-5 year international trial has decreased due to regulatory hurdles. The sample size from Indian population in global CTs are very less compare to the disease burden or market size.*

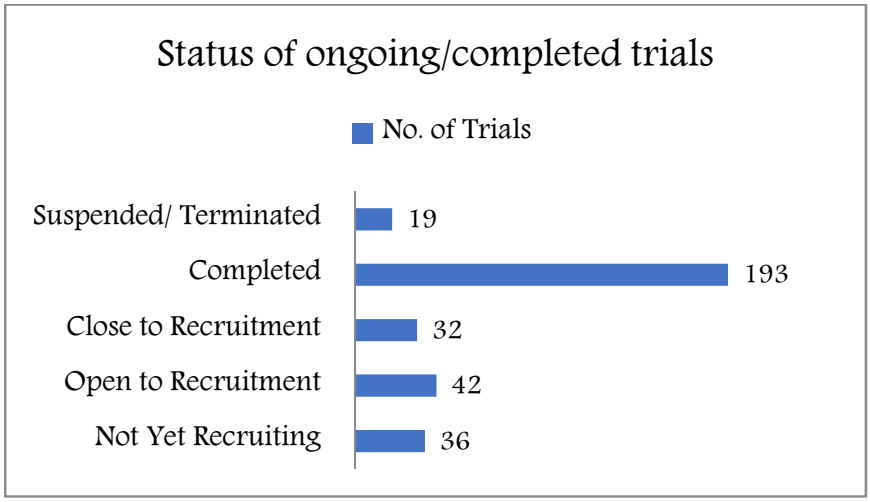
Figure 21 shows maximum number of CTs are sponsor by global firms (181) compare to Indian firms (66) indicate lack of research on new NCE/NBE by domestic firms. Every TIS is unique in its structure and function. Diabetes is a type -1 disease receives maximum research priorities in both developed and developing country. If we compare this clinical trial sponsor to any type-II or type-III diseases the scenario changes complete. For TB, malaria the total number of CTs are very less, also the larger amount of CTs sponsor through Govt. funding agencies, followed by Indian firm rather by a foreign firms.

Figure 21: Clinical Trials Sponsors in Diabetology in India



(Source – Clinical Trial Registry- India)

Figure 22: Status of Clinical Trials in Diabetology in India



(Source – Clinical Trial Registry- India)

Figure 22 indicate the status of ongoing and completed clinical trials on Diabetology. The most of the completed registered clinical trials belongs to foreign firms. Some of the trials face recruitment issues. The clinical trial data reveals that there are more than 36 trials where recruiting not yet started. For new prospective trials, or trial registered for last 2-3 years it is

not an issues however, there are more than 6 registered CTs trials shows recruitment status not recruiting are registered before 2015.

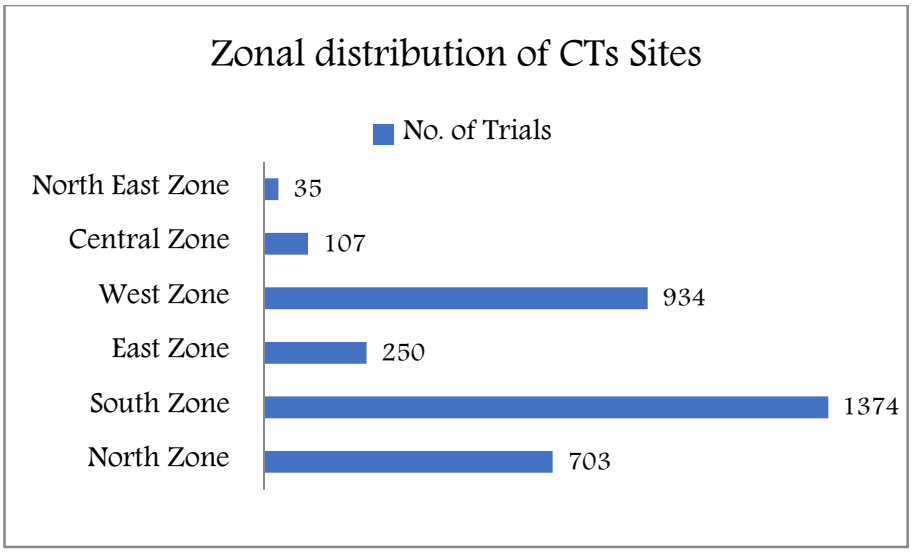
Practitioner 2: *(Consultant endocrinologist with years of experience in conducting clinical trials*)

> *Patient recruitment is not a big problem in diabetes due to larger patient pool but retention of patient in clinical trials is an issues. Patient does not turn up for the follow-up programmers'. Not meeting the desired target, drop-out rates are some key challenges for conducting clinical trials in India.*

Contract Research Organization (CRO) 1: *(Associate Director of international CROs based in India)*

> *Clinical trials requires co-operation among diverse group of stakeholders. The cost of conducting clinical trials has increased. Increase trial cost, lack of local infrastructures, disorganized study programs, paucity of time, research naïve sites, shortage of qualified staff, complexity of trial and study designs are major challenges in conducting CTs in India. Patient recruitment, retention and follow-up issues also affect trial time, management and results.*

Figure 23: Zonal distribution of Clinical Trials in Diabetology in India



(Source – Clinical Trial Registry- India)

There is great diversity among CTs site in India with maximum trial occurs in south zone followed by west zone. The issues and challenges related to clinical practice and public policy are already discussed in *chapter five and six*.

7.5 Inducement mechanism in TIS:

Technological innovation system has two major elements structure and functions of innovations. Functions of an innovation system are context specific. Measuring innovation function is considered as big breakthrough in innovation system research. In the TIS framework functional pattern are shaped by certain inducement and blockage mechanisms. These indicators does not always resides with in a system, but also affected by the external factors and influences by other sectoral issues. Bergek, 2007 identified two inducement mechanisms as *belief in growth potential* and *Government R&D Policy*. Both the indicators have positive influence on the functions of innovation system.

In biomedical innovation system positive inducement factors for growth of the knowledge field Diabetology is due to various functions of innovations that *influences direction of search.* Diabetes became global health problem recently leads to increase attention at both global and local level. Growth occurs in other TIS, changing global landscape and India's demographic transitions are inducement factor of growth of this segment. Diabetes is a profitable segment and its co-morbidities helps diversification of products of existing firms. There are many new entrants and entrepreneurial experimentation has grown recently of this segment. (Explained in detail *function-influence of direction of search, positive externalities in Chapter five*)

Government policy and programmes also have a positive influence in development of this sector. The *function resource mobilization* describes in details about the instrument, programmes that initiative by the government that helps in growth of this sector. DBT is instrumental in promoting translational research and biomedical innovation system in India. The resource mobilization includes nurturing human resources, investing in infrastructure, financing innovation and other support system. DST-BDTD, IMPRINT, DSIR- PRISM are the programmes that promotes biomedical research India. (Explained in detail *function-resource mobilization in Chapter five*)

7.6 Summary of System Problems in TIS:

The 'blocking mechanism' in the TIS framework receives large attention from innovation scholars due to its positive implication on improvement of system. The blocking mechanisms are the barrier to the development of functions in a TIS framework. The blockage mechanism further conceptualized as system problem, system weakness and system failure mechanisms that hinder the development process. Klein-Woolthuis (2005) identifies system problems related to both structural and functional dimension of TIS. The system problems were related to the *presence* and *capabilities problems* in the structural elements of TIS such as *actors, institutions, interaction, and infrastructure.*

Biomedical innovation system is a multi stage innovation process; consist of three major knowledge bases basic, applied and clinical research. There are inherent problems associated with in each stages of development also in intermediary translational phases. In the basic research stages there are actors and institution present and contribute to the system however, less number of patents filled from Indian actors' shows lack of capabilities in patenting. In terms of number of publication, there is growth in the number of publications among Indian actors however; most of the publication are in the low impact journals.

Our primary data through interview reveals that the research group or team compositions in the basic or applied research level are homogeneous in nature. For biomedical innovation a combination of expertise requires at one place from the discipline of medicine, engineering, biomedical research, toxicologist etc. These are weak interaction among different sets of actor and institution at different stages of innovation in India. In the clinical and management stage, there is need of diabetic educators.

The chapter issues and challenges in translational research have systematically evaluated the problems at various stages including the problems associated with the translational stages from one stage to other.

7.7 Successful translational products in Diabetology in India

Translational research is a complex, difficult, challenges, time-consuming resource driven innovation process. The previous section highlight all the system problems associated with the biomedical innovation process in India at each stage of innovation. Every basic research should envision for translational research and application but only few became successful product that can be use for human health and society. The study was able to find out some of the successful translational products in Diabetology in India. As we take Diabetology as a knowledge field, where group of product includes drug and device segment, the translational products includes both drugs and devices. We not only identified the products, also examine the trajectory of development process through different innovation indicators taken for analysis in this study.

Category A: *Herbal Formulation*

Case Study 1:BGR- 34 (Herbal – affordable health)

- Anti- diabetic herbal drug (NBRMAP-DB) is jointly developed by CSIR-NBRI and CSIR-CIMAP an anti-diabetic herbal formulation from a combination of natural extracts derived from six plant species mentioned in ancient Ayurveda texts. (2015) The six plant species are Daruharidra (Berberis aristata), giloy (Tinospora cordifolia), vijaysar (Pterocarpus marsupium), gudmar (Gymnemasylvestre), manjeestha (Rubia cordifolia) and methi (Fenugreek). The formulation purportedly releases 34 active phytoconstituents, which work as DPP-4 Inhibitors to regulate blood glucose levels.
- The drug has approval of Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), India and supported by Govt. of India at various platform.
- Clinical trials: 18 month Clinical trials across the states of Delhi, Himachal Pradesh, Haryana, Punjab and Karnataka - {CTRI/2016/11/007476 and CTRI/2017/09/009709}
- Development and commercialistion: The drug has been licensed to Delhi-based Aimil Pharamaceuticals Pvt. Ltd. for commercialization. (2017)
- The product is rebranded as BGR-34
- Market: The herbal drug costs Rs. 5 per pill, and has been launched in parts of North India.
- Patent application No. 1591/DEL/2014, Applicant- CSIR(Inventors scientists from CIMAP and NBRI), Title: A synergistic herbal composition useful for the management of

diabetes

- Date of filing: 12/06/2014, publication date: 31.08.2016, Request for examination: 25.01. 2017, patent status – application awaiting examination

Figure 24: Herbal formulation (BGR -34)

Final product: BGR- 34 (AIMIL Pharmaceuticals)

Case Study 2: AYUSH – 82 (Herbal Formulation)

- Anti- diabetic herbal drug is developed by CCRAS, from a combination of four herbal ingredients; karela (Momordica charantia), jamun (Syzygiumcumini), amra (Spondiasmombin) and gudmar (Gymnemasylvestre) along with shilajit
- The drug has approval of Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), India.
- Patent: Not found
- Clinical Trials: Not registered with CTRI
- Clinical trials: Double blind clinical human trial studies of more than 800 patients.
- The formulation is transferred by National Research Development Corporation (NRDC-DSIR with signed License Agreement with Kudos Laboratories India for commercialization.
- The product is rebranded as IME9

Figure 25: Herbal formulation (AYUSH 82, IME-9, RIGHT SUGAR)

Final product: IME-9 (Kudos Ayurveda) & Right Sugar (Chaturbhuj Pharmaceutical)

Issues:

Besides above two products Right Sugar^{TM} a CCRAS herbal formulation is being developed and commercialised by Chaturbhuj Pharmaceutical through technology transfer from NRDC platform. Under AYUSH Scheme, many new similar drugs are in pipeline for diabetes and life style diseases at different developmental stages. Ayush – D for Diabetes (ayurveda), D-5 choornam by Central Council for Research in Siddha (CCRS) (Pat application No. 2578/CHE/2015) and other Unani formulations by Central Council for Research in Unani Medicine (CCRUM) and homeopathy formulation by Central Council of Homoeopathy (CCRH)

Although the aggressive advocacy and commercialization of a product in recent times helps in booming of alternative therapies market in life-style segment, however, these drugs have been criticized for the lack of rigorous pharmacological data or meaningful clinical trials and efficacy. There are no concrete evidences of clinical trial data, toxicological data or animal trials and publication for BGR-34 and AYUSH-82 in CTRI registry. The publication of results in low impact, predatory journals also hampers the credibility. The Advertising Standards Council of India banned an advertisement for BGR-34 in 2016 for spurious claim of "curing Type 2 Diabetes Mellitus without any side effects". It held the advertisement to violate the Drugs & Magic Remedies Act by offering to cure an incurable disease and under the purview of disseminating unsubstantiated claims without any corresponding data. There are also several methodological problems in conducting pharmacological and clinical trials of AYUSH products The ICMR guidelines for waived or relaxed rules for rigorous pharmacological and toxicology studies for Ayurvedic products provided they were

"prepared in same way as mentioned in ancient Ayurvedic treatises" is being criticized. The lack of enforcement of CAM practices is also its limitations.

Category B: ***Oral Anti Diabetic drug (OADs)***

Case 3: Saroglitazar (ZYH1), or LipaglynTM - Zydus Cadila

- The drug originates from a research program initiated at Zydus Cadila in 2000 and an IND submission in 2004 after extensive structure-activity relationship studies and preclinical characterization.
- The compound belongs to the class of 'glitazars', dual peroxisome proliferator-activated receptor (PPAR) agonists with affinity towards both PPARα and PPARγ

Evidence from Patents analysis:

- Patent application WO 03/009841 A1, with a priority date of July 26, 2001
- Indian patent application (711/MUM/2001) - Date of filling– 26.7.2001 Patent Title: "Novel heterocyclic compounds, their preparation, pharmaceutical compositions containing them and their use in medicine"
- Granted patent Number: 220639 - Date of Grant- 30.05.2008, Patent Grant period- 2006-2020

Evidence from Clinical Trial analysis: (Phase- I trials to Post Marketing Stages)

- CTRI/2009/091/000527 - Safety and efficacy of 2 mg and 4 mg of ZYH1 compound:
- Prospective Randomised Efficacy and Safety of Saroglitazar (PRESS V)
- CTRI/2009/091/000533 - PRESS VI) – compare molecule
- CTRI/2010/091/000164 - PRESS I
- CTRI/2010/091/000165 - PRESS II
- CTRI/2010/091/000166 - PRESS III
- CTRI/2013/06/003754 – Post marketing studies
- CTRI/2015/06/005845 - Saroglitazar (LipaglynTM) on Postprandial Lipemia in T2DM (PRESS XIII)
- CTRI/2015/10/006236 - drug's effect in non-alcoholic steatohepatitis (NASH)

- CTRI/2014/08/004885 – drug's effect in HIV-associated lipodystrophy
- CTRI/2016/03/006778
- CTRI/2017/10/010306 - Effect of saroglitazar in patients with type 2 diabetes mellitus
- Saroglitazar has been approved and marketed in India since September, 2013
- Cadila Healthcare has initated two major initiatives: the saroglitazar Patients Registry Programme (PRP) and the Periodic Safety Update Reporting after approval of saroglitazar for marketing..

Evidence of commercialization of product:

- From Section 146(2), patent documents working of patents, declaration regarding the working of the patented invention on commercial scale in India. A total sale of mentioned product is Rs. 2156.29 Lakhs for the financial year 2017 and Rs. 74 Crores for this financial year 2018.

Figure 26: Oral Anti Diabetic Drug (Saroglitazar)

Final product: Saroglitazar (Lipaglyn) by Zydus Cadila

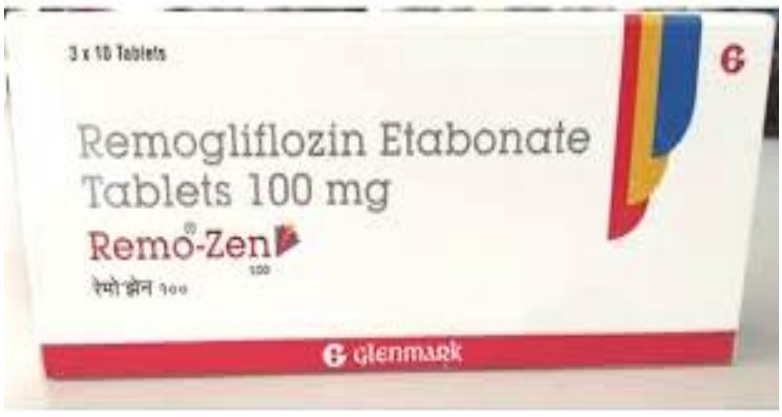
Case 4: Remogliflozin – Glenmark (successful drug lunch through in-licensing)

- Remogliflozin is drug for the treatment of non-alcoholic steatohepatitis (NASH) and type 2 diabetes.
- Remogliflozin was discovered and developed by the Japanese company Kissei Pharmaceutical, and later developed by GlaxoSmithKline and Glenmark collaborator BHV Pharma

Evidence from Clinical Trial analysis:

- CTRI/2017/07/009121: Title "A clinical trial to study effect of a remogliflozin etabonate in the treatment of diabetes mellitus" - Phase III clinical trials with 57 sites
- Glenmark has only one patent application on Remogliflozin in 2018.
  Patent application- 201827022067: Title-'Oral pharmaceutical formulations of Remogliflozin'
- Remogliflozin was commercially launched first in India by Glenmark in May 2019
- As the drug lunched in the year 2019, there is no evidence of commercial success is available.

Figure 27: Oral Anti Diabetic Drug (Remogliflozin)



Final product: Remogliflozin (RemoZen) by Glenmark

Category C : ***(Diabetic footwear for DFU)***

Case 5: DIASTEP™: Therapeutic open footwear for the diabetic patients with risk of mild to moderate foot problems.

- The footwear is designed for people with diabetes to prevent diabetic foot ulcers (DFU) and other undesirable foot problems. The product ia a collaborative research efforts of Central Leather Research Institute, Chennai and MV Hospital for Diabetes and Diabetes Research Centre, Royapuram, Chennai.
- The present invention is to provide therapeutic open footwear for the diabetic patients with foot injury due to neuropathy but without deformity in the feet adapted such that the footwear reduces the abnormal distribution of plantar foot pressure. Also the present invention is to provide the patients with diabetic foot injury, complete open footwear prescribed according to risk perception for a particular patient, comprising selective topsole, insole and bottom sole made of appropriately selected material. The therapeutic footwear a unit molded sole made from polyurethane (PU) with extra depth to provide larger area for more effective pressure distribution and outsole having special tread for better grip and traction
- Indian Patent Application No. 624/CHE/2007, Title "Preventive Footwear for People with Risk of Mild to Moderate Foot Problems" jointly by: CSIR-CLRI, Diabetes Research Centre, Chennai (a unit under the MV Hospital for Diabetes and Diabetes Research Centre) and Novo Nordisk Educational Foundation, Bengaluru (2006).
- The Trade Mark "DIASTEP" was awarded in 2008.
- The technology transfer knowhow was transferred to M/s MV Diabetes Health Care, Chennai
- The DIASTEP Diabetic Footwear was formally launched on 2nd November 2009
- The PATENT was finally GRANTED in 2018 with the PATENT No. 302551

Figure 28: Diabetic Footwear (DIASTEP)

Final product: Diastep (CSIR-CLRI & MV Diabetes Health care)

Category D – *(Device & Diagnostics)*

Case 6: PathShodh (Healthcare startup from CeNSE, IISc Bangalore)

- PathShodh Healthcare Pvt. Ltd. is a medical device research and development company incubated at the Indian Institute of Science (IISc), Bangalore. The major research and capabilities includes affordable Point-of-care medical devices to measure multiple bio-markers targeting diabetes and its complications.
- IP portfolio includes one US patent and 5 international patents applications as mentioned in the company profile. The patent information could not trace through patent analysis.
- A diagnostics or medical device follows a different path of development process then the drug development. The process includes proof of concept, prototype, lab validation, technology development, technology validation, integration and market lunch (as explained in literature review). Hence could be traced through patent analysis or clinical trial data.
- The company received startup grants for scale up from Government agencies. Two major translational Programmes IMPRINT and BIPP have funded the research and innovation activities of this company.
- **IMPRINT** : Under the domain area of supporting agencies MOH&FW, GOI
  Project ID -4550
  Title:*Efficient Glycemic Control for the Management of Diabetes Complications: Intervention with Novel Point of Care Device for Community Healthcare POC & Surveillance system :*Applicants: IISc, PathShodh Healthcare, Samatvam Diabetes Centre, Anand Diagnostic Laboratory, Cost:- 326.40 (in lakhs)
- **BIPP** –BIRAC, DBT
  Title: *Diabetes Management Device and Test Strips: Scale up, Quality Control and Deployment :* Applicant: PathShodh Healthcare Private Limited

Figure 29: Point-of-care devices for diabetes management

1 **2** **3**

Final product: 1.Multi-analyte device, 2. Glycemic index device,3. Glucometer device

In the biomedical innovation system in India, Due to growth in the non-communicable diseases, there is increasing focus towards affordable, lost cost, point of care device and diagnostics. Many new start-ups have emerged in this segment recently.

There is an increase support from government programmes and agencies for validation and scale up of affordable medical device innovation in India. Some of the BIRAC supported projects includes "Innovation in mHealth" – Amrita Vishawa Vidyapeetham and WIPRO joint developed cost effective device in diabetes management., LSYNC – Smart, all in one compact Glucometer by Biosense technology private limited, A telemedicine platform 'Chiron Eye' for diabetic retinopathy developed by AdvenioTechnoSys Pvt Limited.

7.8 Summary:

This chapter has successfully identified different translational products in both drug and device segment in Diabetology in India. Translational process is difficult and challenging. Every innovation has its own development path way and its unique sets of challenges. In the drug development both herbal medicine and allopathic medicine have different sets of challenges and development process. The translation process shows multiple indicators are not sufficient to trace and measure the development pathway. The developments in different segment also indicate there is more support for herbal formulation and devices segment through government supported programmes and policies.

CHAPTER SEVEN

CONCLUSIONS

The study is an attempt to understand the biomedical innovation system in India, the process of biomedical innovation through the lenses of translational research from bench to bed. A biomedical innovation system is a complex multi-stage innovation process, where actors, organisation and institution are placed in three core domain knowledge field such as *basic, translational* and *clinical* research. The three different domains have different objectives, working environment and institutional set-up. However, the ultimate purpose of all the three stages is to solve a common problem, i.e. disease or betterment of human health and environment.

The biomedical innovation field has many facets; the analysis can be done in multiple ways. The analyst may focus on a product or artefact, the process of drug development, new devices & diagnosis, and surgical or medical procedures. Another way of doing the analysis is to focus on a knowledge fieldan of an emerging area of biomedical sectors such as biotechnology, molecular biology, nanotech, system biology, rDNA technology etc. *The focal point of the current study is a knowledge field (Diabetology). Focusing on the knowledge field where disease is the core problem the study attempts to understand both drug development process and diagnostic & device development as drug and devices both are important for solving the core problem of diabetes.*

From a theoretical perspective, the study tthe ook the innovation system approach to understand the complex process. Among all other innovation system framework, we found Technological Innovation System (TIS) was most suitable framework for this study due to the flexibility it provides during analysis such as focusing on *context* and *purpose* of study rather on *system boundaries*, or emphasizes on *functions* of innovation (how well a system perform, how well co-ordinate the actions of actors or institutions) rather *structure* of innovation. The functions help in evaluating the systemthe as the translational process; identification of translational process are also an important objective of this study. The framework also provides a systemic approach to analysis *(see analytical framework chapter). Due to all the above benefits of TIS, Biomedical innovation system fits into this system approach; however the operationalising TIS framework for the study is quite challenging.*

Major finding of the study:

The study maps the biomedical innovation system in India using a disease as a focal point of analysis. The study identifies structural elements in an innovation system the actors, organisations, institutions and network. Biomedical innovation is a multi-stage innovation process, so the structure elements and their interaction vary at each stage basic research, pre-clinical, clinical trials and clinical practice. The structure categorizes actor, institutions and its interaction at each stage of development.

The structure identifies the network and collaboration that contributes in the formation, development and diffusion of knowledge. This includes formal network, associations, societies in the field of medicines at clinical stages, such as diabetes associations, endocrinological societies, at basic stages different scientific associations, technologist associations, at pre-clinical stages toxicology associations etc. The other network, collaboration or linkages are identified through interaction between domain experts, co-patenting, co- publishing, co- authorship, research sponsor- project investigators, firm-hospital, industry- academia, funding agencies – research or clinical organisations, public-private partnership (PPP) programmes, firm- firm interaction, NGOs- public institutions, policy making agencies with policy implementing agencies, international regulatory bodies with national regulators at various stages. From translational perspective, interactions among three stages of BIS are important for translating ideas from basic research to clinical practices. The study gave prime importance to identify *industry-academia linkages, clinical-academia or clinical-industry linkage* along with collaboration at each stages.

The study identifies the role of actors, organization and institutions in development of functions of innovation and analysis their contributions. In TIS, the knowledge field is global, Chapter Four gives a global perspective of technological knowledge, it's evolution and progression in drug development, diagnostic & device segment through methods combination of clinical literature and patent analysis of selected global firms in Diabetology.

In Chapter five, the study analyses the contemporary knowledge field in India, the contribution of research organization, universities, firms, institutes, hospital and medical research institutes in shaping biomedical innovation system in India. The patent analysis also identifies the contribution of big pharma companies, biopharmaceutical firms, herbal based industries, diagnostic-devices based industries and actors in India.

Entrepreneurial experimentation is a key component for the growth of TIS. In the life-style segment, many new start-ups have emerged in last five year. IIT-B incubated AADAR (2017), an ayurvedic based healthcare preventive startup, IISc incubated PathShodh (2015), a cost effective POC devices startup, *BeatO(*2015), smart phone application based diabetes management startup are few to mention here. Along with startups established firms such as TCS, HCL entered diabetes device segment and many pharmaceuticals companies restructured their product portfolio to capture the growing life-style market segment.

The study analyses the role of institutions, govt. Agencies, policy, programmes that are instrumental in shaping biomedical innovation system in India. The study scrutinized the programmes related to human resource development, research financing and infrastructure development. Biomedical innovation is a highly sophisticated complex specialized field of innovation where knowledge diffuses from developed countries. In that case, international co-operation, skill exchanges programmes became prominent, Indo- US Genome Engineering/ Editing Initiative (GETin) program, Khorana Program for Scholar, DBT-Heidelberg Graduate programme, Ramanujan Fellowship are some of the govt programmes helps in building human resource capabilities in biomedical research through knowledge exchange and skill development.

In the developing countries, where resources are limited, programmes, the policy requia res fine balance between promoting scientific innovation and effective utilizationthe of the resource. On one hand programme like High Risk - High Reward Research (HRHR), Intensification of Research in High Priority Area (IRHPA) promotes conceptually new and risky research and innovation, on the other hand programmes like DST- SRISTI, DST-Sophisticated Analytical Instrument Facilities (SAIFs), Common Research and Technology Development Hubs (CRTDH), DSIR - Building Industrial R&D and Common Research Facilities (BIRD-CRF), DBT - Scientific Infrastructure Access for Harnessing Academia University Research Joint Collaboration, (SAHAJ)' promote resource sharing , sharing of infrastructures for biomedical innovation among university, SMEs, entrepreneurs.

Research financing is critical for biomedical innovation and development. As a basic, translational and clinical research activity belongs to three different innovation eco-systems, most of the institutions promote activities within their domain area. From translational perspective, it is important to promote the whole translation process from bench to bed. Innovative funding mechanism such as Grant Challenge India, MHRD - Impacting Research

Innovation and Technology (IMPRINT), DST -BDTD, BIRAC- BIPP, SIBRI, PACE, SPARSH, BIG address key financial challenges related to biomedical and translational research in India.

Clinical Trials, clinical practices, policies and programmers':

Clinical Trial the is the fulcrum to any biomedical research holds a critical position in between the laboratory research and final product. Innovation literature gives least attentions towards clinical trials, practices or health services based activities. The study is a novel attempt on this direction to cover the entire biomedical innovation process, including role of clinical trials, practices and health services programmes for management of disease.

The study identifies major global clinical trials in Diabetology, where the scope of the trials are beyond drug development or drug comparison, rather on formulating policy decision based on evidences, formulating clinical guidelines, methodology and best practices.

The study identifies the new NCE/NBE under investigation at various stages of CTs by both foreign and Indian firms in India. What we found in our study is, most of the novel molecules by foreign firm entered at Phase III trial have successfully completed trials now in the market as a successful product, while most of the novel molecules by Indian firms have never reached phase- III trials. *(Exception two successful translational products by Indian firms)*

The study also identifies the evidence based practices, observational studies, innovative treatment methodology (combining traditional AYUSH with conventional medicine), yoga-music with OADs, insulin for diabetes management etc. The prevalence studies (INDIAB, YDR) community based life-style modification programmers' (D-CLIP,K-DPP) that helps in overall health improvement in a definite population or community.

The chapter six also critically examines the challenges in clinical practices through interview based responses from clinician and health policy experts and analyses the policy and programmers' related to health services for effective management of diabetes in India. National Programme on Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS) and National Programme for Health Care of the Elderly (NPHCE) are two major programmes in India that tackle the issues of diabetes in India. The study examines these programs on various parameters including access, infrastructure, human resources, finances, policy and guidance.

Innovation and translational research challenges:

The chapter seven identifies systemic challenges, issues at basic research, applied translational research and clinical research stages. The system issues includes problems in market, clinical practices and public policy issues related to clinical practices at grass root level, the socio-economic & ethical complications in diabetes management.

As the focus of the study is on translation, the study also gives impetus to analysis the role of intermediary and support organisations in biomedical innovation process. The study covers two such categories (role of patent facilitation centers and role of experimental animal facilities and issues and challenge in translation processes).

One of the major contributions of this study is identification of successful translational products (drug. device and artifacts) in Diabetology in the Indian biomedical innovation eco-system. We identifies four categories of developments:- herbal formulation, conventional OADs, footwear and diagnostic and devices segment. Our concluding observation on this translational product is Translational process is difficult and challenging. Every innovation has its own development path way and its unique sets of challenges even in same categories drug development herbal and conventional medicine have different path of development. The current government policy and institutions promotes herbal based formulation and drug and device segment.

Limitation and challenges:

TIS is most suitable framework for this study. Bergek (2008) and other innovation scholar have studies innovation system using multiple indicators in the energy sector, sustainable energy, solar, wind energy etc. In the biomedical research where innovation is a multi-stage process, the implementation is challenging. The biomedical innovation process involves horizontal development within the phases (science base, translational base or clinical base) and also vertical development (how a product or a device translates from basic laboratory stage to the final product stages). The vertical process is a complex process in a knowledge field, as both drug and device development process involves multiple phase and different trajectory of development process. *(See figure –stages of innovation in BIS in literature review).* Drug development process involves stages from NCE to preclinical, toxicology, animal studies, five phases of clinicanaimil trials, then market lunch, post marketing studies

and clinical practices. Similarly, the device undergoes through prototype development, proof of concept, technology demonstration, validation, integration and market lunch stages.

Methodological challenges:

There was no referral model available to map biomedical research and innovation process; hence we attempt to create our own methodology to identifying the actors, organization and institutions at different stages. For emerging innovation system, where standard models are not available, the methodology has its limitation. Mixed methodology is the most suitable method for this study, but the choices of methods are critical as the study demands analysis of both structure and function of innovation. Hence, the methods should helps in identification of actors, organization and institutions as well as assess their functions.

Measuring innovation and problems of innovation indicators:

The study uses different methods for identification of actors, organisations, institutions at different stages of innovation. *Patent analysis, Publication data, Citation analysis, Clinical trial data analysis* were used in this study not only for the identification of actors but also to access the performance of the actors and institutions. The rationale being taking all these methods was to maps entire innovation process from basic research stage to market stages.

Even with multiple methods, the study found its inability to found all the actors and assess their performance using above methods. The identification of innovation indicator is difficult in biomedical innovation process as different actors and institutions have different objectives and functions. In the Indian context, especially the actors in *Traditional medicine, AYUSH, grass root innovators those contribute to the knowledge fields of Diabetology cannot be identified or their performance can be measured through above indicators. The study also identifying that although patent is an important innovation indicator for assessing the performance of a firm due to its commercial aspect and industrial application, Patent analysis cannot fully assess the performance of Indian firms as their capabilities lies in process engineering and generic drugs. The present study use institutional repositories and secondary data for identification and accessing the above actors in the Indian context.*

The problems also lies with the limitation related to database scope and coverage, The study covers multi –actors, and tries to identifying issues through multiple questioners suitable for the specific actors. However, as the knowledge field is so vast and various sub-actor, intermediary presents at different stages, it is difficult to cover the entire horizon of

biomedical innovation through primary data. There are limitation regarding time, access and resources.

Contribution to the knowledge field:

The present study contributes to the innovation system literature. Technological Innovation Systems are context specific. Every TIS has different structure and function. Two TIS may have same structure and different function or vice-versa. The present study is an attempt to understand TIS with a focal point of 'Diabetology as knowledge field'. The TIS gives a schematic representation of the structure and functions of biomedical innovation in India. This study may contribute as a reference model for future study. Even if the focal point shifts e;g instead of diabetes for cancer or a tropical disease like malaria, the function or structure might be different but the actors, organization and identification methodology and innovation indicators will be similar.

The study identifies successful translational product, process and also their path of trajectory of development process and institutional challenges involving at various stages innovation and development in India.

Global literatures and India specific innovation studies focuses on specific sectors mostly at firm level, pharmaceutical innovation or science- based innovation studies to some extent. The innovation studies literatures have least attention towards contribution of hospitals, clinician or clinical practices. The study is a novel attempt to cover the entire horizon of innovation process from basic- laboratory stage to clinical- practice or post-improvement process.

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ANNEXURE – I

TABLE: IPC (INTERNATIONAL PATENT CLASSIFICATION) CLASSES IN THE AREA OF DIABETOLOGY

IPC	Descriptions of Main Class and Subclasses related to Diabetology patents
	A: Human Necessities (Health; Life saving ;amusement) A61: Medical or Veterinary Sciences; Hygiene
A61K	**A61K : PREPARATIONS FOR MEDICAL, DENTAL, OR TOILET PURPOSES** ***Subclasses:*** Dental preparations – 6/00, Cosmetics, perfumes – 8/00, Pharmaceutical preparation – 9/00 Characterized by active ingredients :- Organic active ingredients – 31/00, **35**/00, 36/00, 38/00 Materials from animals, protozoa, bacteria or viruses – **35**/00 Materials from algae, fungi, lichens or Plants – 36/00 Inorganic active ingredients – 33/00, **35**/00 Obtained by treating material with wave energy or particle radiation 41/00 For testing in vivo – 49/00. **45**/00 Radioactive ingredients – 51/00 Vaccines – 39/00, **45**/00 Carriers – 47/00 Medicinal preparation with genetic material, gene therapy – 48/00
	C: Chemistry; Metallurgy C07: Organic Chemistry
C07K	**C07K : PEPTIDES** ***Subclasses:*** Preparation – 1/00 Undefined numbers of amino acids – 2/00 Having up to 20 amino acids in an undefined or only partially defined sequences 4/00 Having up to 20 amino acids in a fully defined sequences 5/00 – 9/00 Depsipeptides having up to 20 amino acids in a fully defined sequences – 11/00 Having more than 20 amino acids – 14/00 Immunoglobulins - - 16/00 Carrier bound/immobolised peptides – 17/00 Hybrid peptides – 19/00
	A: Human Necessities (Health; Life saving ;amusement) A61: Medical or Veterinary Sciences; Hygiene
A61P	**A61P : SPECIFIC THERAPEUTIC ACTIVITY OF CHEMICAL COMPOUNDS OR MEDICINAL PREPARATIONS** ***Relevant subclasses related to Diabetology:*** A61P 1/00 : Drugs for disorders of the alimentary tract or the digestive system A61P 1/18 : for pancreatic disorders, e.g. : pancreatic enzymes A61P 3/00 : Drugs for disorders of the metabolism A61P 3/02 : Nutrients (vitamins/minerals) A61P 3/04 : Anorexiants (anti obesity agents) A61P 3/06 : Antihyperlipidemics A61P 3/08 : for glucose homeostasis (pancreatic hormones) A61P 3/10 : **for hyperglycemia (anti diabetics)**

	A61P 5/00 : Drugs for disorders of the endocrine system A61P 5/48 : of the pancreatic hormone A61P 5/50 : for increasing or potentiating the activity of insulin A61P 7/00 : Drugs for disorders of the blood or the extracellular fluid A61P 7/12 : Antidiuretics e.g. drugs for diabetes insipidus A61P 9/00 : Drugs for disorders of the Cardiovascular Disorder *(indirect/co-morbidity)* A61P 9/04 : Inotropic agents (Drugs for heart failures) A61P 9/10 : for treating ischemic or arthrosclerosis diseases (Retinopathy) A61P 9/04 : anti- hypertensive drugs (Blood Pressure) A61P 13/00 : Drugs for disorders of the urinary system *(indirect/co-morbidity)* A61P 13/02 : for urine/ urinary tract A61P 13/12 : of the kidneys A61P 25/00 : Drugs for disorders of the nervous system *(indirect/co-morbidity)* A61P 25/02 : for peripheral neuropathies (Diabetic Foot Ulcer/ DFU) A61P 27/00 : Drugs for disorders of the senses *(indirect/co-morbidity)* A61P 27/02 : Ophthalmic agents (Diabetic retinopathy) A61P 31/00 : Anti-infectives (antibiotics, antiseptics, chemotherapeutics) A61P 31/06 : For tuberculosis *(indirect/co-morbidity)* A61P 37/00 : Drugs for immunological/allergic disorders A61P 37/06 : Immunosuppressants (drugs for graft rejections (Pancreatic transplantations) ***problematic***
C07D	C: Chemistry; Metallurgy C07: Organic Chemistry C07D: HETEROCYCLIC COMPOUNDS (MACROMOLECULAR COMPOUNDS ***Further sub-classification requires understanding the structure of bio molecules***
A61B	A: Human Necessities (Health; Life saving ;amusement) A61: Medical or Veterinary Sciences; Hygiene **A61B : Diagnosis; surgery; identification (analysing biological materials)** A61B 5/145 : Drugs for immunological/allergic disorders
G01N	G: Physics G01: Measuring or Testing G01N: Investigating or analyzing materials by determining their chemical or physical properties
G06F	G: Physics G06: Computing; Calculating; Counting G06F: Electric digital data processing
C12Q	C : Chemistry; Metallurgy C12: Biochemistry; Microbiology; Enzymology; Mutation Or Genetic Engineering C12Q: Measuring or testing processes involving enzymes or microorganisms
A61M	A: Human Necessities (Health; Life saving ;amusement) A61: Medical or Veterinary Sciences; Hygiene A61M : Devices for introducing media into, or onto, the body

ANNEXURE – II

EVOLUTION OF MODERN DAY INSULIN

Timeline	***Significance***
1869	Paul Langerhans, found a cluster of unknown cells within pancreases that produces digestive juices. These insulin-producing beta cells later named after him as *"Islets of Langerhans"*
1889	Oskar Minkowski and Joseph von Mering strengthen the arguments of decisive role of pancreases in regulating diabetes
1901	Eugene Opie discovers that the Islets of Langerhans produce insulin and that the destruction of these cells resulted in diabetes.
1916	Prof.Nicolae Paulescu develops an extract of the pancreas and shows that it lowers blood sugar in diabetic dogs.
1921	*Frederick Banting and Charles H. Best* from University of Toronto successfully extract insulin. They received nobel prize in medicine for discovery of insulin in 1923.
1922	**First Human Trial:** Insulin administrated to a 14 year boy Leonard Thompson with type 1 diabetes symptoms.
1922	*Eli Lilly* signed an agreement to pay royalties to the Toronto University to increase the production of insulin
1923	*Nordisk Insulin Laboratorium (now Novo Nordisk*) was established
Period of slow- acting insulin development (Mid 1920s to mid 1930s)	
1936	Hans Christian Hagedorn discovered that the action of insulin can be prolonged by addition of protamine. Novo Nordisk being first protamine insulin
Period of Intermediate-acting Neutral Protamine Hagedorn (NPH) insulin development(Mid 1930s onwards)	
Period of Long-acting Protamine Zinc Insulin (PZI) insulin development (Mid 1940s onwards)	
1949	Becton Dickinson and Company begins production of a standardized insulin syringe
Decade of Lente insulin development (1950s- 60s)	
1955	Frederick Sanger characterized the amino acid sequence of human insulin, making it the first protein to be sequenced Sanger receives the Nobel Prize in Chemistry for this research on determining structure of protein in 1958.
1963	Insulin becomes the first human protein to be chemically synthesized
1960s	Decade of Purified insulin development: Purified versions of animal insulin were developed by chromatographic techniques known as "monocomponent MC" "single peak" insulin in order to reduce the allergic reactions.
1971	Insulin receptors are discovered on cell membranes, This discovery contributes to the knowledge development related to insulin resistance or type 2 diabetes.
1976	The first insulin pump is invented but it was impractical to carry due to its larger size
1978	Biotechnology firm Genentech uses recombinant DNA techniques to produce synthetic "human" insulin. Insulin is the first human protein by to be manufactured through biotechnology.
1980s:Decade of Recombinant human insulin development	
1982	The FDA approves human insulin produced by genetically altered bacteria.
	Synthetic insulin is renamed as 'human insulin' marking it as distinct from insulin derived from animals. Humulin, manufactured by Eli Lilly, becomes widely available Human insulin has the advantage of being less likely to allergic reactions than animal insulin.
1985	Novo Nordisk introduces the Insulin Pen delivery system.
1990s	Decade of Insulin analogs / Modern insulin/ Designer insulin: The structure of human insulin was modified by altering the amino acid sequence (addition, deletion, or exchange of amino acids) to produce insulin with better pharmacokinetic properties, which came to be known as a "modern insulin" or "designer insulin."
2000s onwards	Alternate mode of insulin delivery: Nasal insulin, Oral insulin, Insulin Patches and various newer ways of delivery methods and devices were discovered.

(Source: Compiled from Das & Saha, 2011, American Diabetic Associations, DiabetesUK)

ANNEXURE – III

EVOLUTION IN DIAGNOSTIC TECHNOLOGY

Timeline	***Significance***
Medieval period	Uroscopy/ Urine Flavour Wheels – urine sample based on appearance, colour, sedimentation and taste
1841	*Karl Trommer*: The ***first clinical test*** for sugar in urine by subjecting a urine sample to acid hydrolysis.
1848	*Von Fehling*: Qualitative testing of urine using the reducing properties of glucose with alkaline cupric sulphate reagents to produce coloured cuprous oxide
1850	*Jules Maumene*: First to develop a simple ***'reagent strip'***
1883	*George Oliver*: Published *Bedside Urine Testing* in 1883 and marketed a range of reagent papers for testing urine, and used the reduction of alkaline indigo-carmine to detect sugar.
1908	Quantitative blood sugar method: with copper reduction and gravimetric measurement. Stanley Benedict devised an improved copper reagent for measuring urine sugar in 1908
Period of development in Dry-Reagent Chemistry	
	The first ever dryreagent test strip developed in the 19th century was the litmus paper
Urinary dry reagent testing	
1928	The development of a dry-reagent test strip for urinary glucose measurements by the use of the key enzyme glucose oxidase, first identified by Muller in 1928 and characterized by Keilin and Hartree in 1948
1954	*Glucotest/ testap* roll licensed by Eli Lilly to Boehringer Mannheim
1956	Keston and Teller independently used glucose oxidase in linked reactions to measure glucose. This method was adapted later to measure plasma glucose in the clinical chemistry laboratory
1941	*Clinitest* (a modified copper reagent tablet) introduced by *Ames Company, (a* division of Miles Laboratory) - *the* ***first conveninent tablet test*** *for measurement.*
1956	*Clinistix (Diastix)* a'***dip and read'*** urine reagent strip introduced by Miles-Ames Laboratory
Blood glucose dry-reagent test strips *(visually monitored blood glucose test strips)*	
1964	*Dextrostix the* ***first blood glucose test strip*** introduced by Ames research team under Ernest C Adams .It is a paper reagent strip which used the glucose oxidase/peroxidise reaction but with an outer semipermeable membrane which trapped red blood cells but allowed soluble glucose to pass through to react with the dry reagents *(US Patent No 3092465/1963)*
1964	*Combur-Test* developed by Boehringer Mannheim for glucose, protein and pH of Urine. Later range extened to Ketones – *Ketostix/Ketodiastix, Now – Roche- Multistix Urine strips*
1965	*Chemstrip bG (*blood glucose strip) was developed by Boehringer Mannheim. A user friendly product with better visualization of colour then *dextrostix*.
1970s	***Period of Self-Monitoring of Blood Glucose (SMBG)***
1970	*Ames Reflectance Meter (ARM)*: The ***first blood glucose meter*** is an instrument (Photometric/ Colourimetric) to produce quantitative blood glucose results developed by *Anton Clemens* at Ames- Miles Laboratory
1972	*Eyetone Blood Glucose Meter* by Japanese company Kyoto-Daiichi (later Arkray) produced and had a marketing agreement with Ames to launch the product in the USA.
1974	*Reflomat (Stat Tek),* a reflectance meter using a modified reagent strip produced by *Boehringer Mannheim*. requiring a much smaller volume of blood (20–30 μL).
1980	*Dextrometer* was the first meter with a digital display and could be operated by battery/power
1980	*Glucochek* introduced by Lifescan. The instrument, later known as *Glucoscan*, was a batterydriven, digital reflectance meter manufactured by Medistron, with the reagent strip produced in Japan by Eiken. *Glucoscan II* (1983) and *Glucoscan 2000 (1986)* – followup products
1981	*Glucometer-I* developed by Ames is the first personal blood glucose meter.

1982	*Reflocheck* lunched by *Boehringer Mannheim (BM)*, a small portable reflectance meter using *Reflotest strips* which were wiped with a cotton ball and had a *barcode for calibration*.
1984	*AccuChek* (*Reflolux* in Europe) by *Boehringer Mannheim* with improved reagent strips that required smaller volumes of blood, with *BM Test-Glycemie 20-800R* that could also be read visually with a more stable colour.
1985	*Glucometer II- first glucosemeter to provide memory for results* having additional features like push-button programming for a preset calibration than the predecessor.
1986	*Glucostix,* developed by Ames is an improved two-pad reagent strip, which was used with the
1986	1986- *Glucometer M – first with event markers and computer interface* *1987- Glucofacts- first PC software applications (data management system*) which could be linked with *Glucometer M*. 1989- *GlucofactsDataLink- the first telephone modem to allow data from home blood glucose to be sent electronically to a doctor.*
1986	*Accu-Chek II* / *Reflolux II* lunched by *Boehringer Mannheim.*
1987	*Accu-Chek II M*/ *Reflolux II M* lunched by *Boehringer Mannheim.(*Memory & PC interface*)*
1987	*OneTouch* Meter was introduced by *Lifescan*.This innovation has regarded as beginning of '**second generation'** blood glucose monitoring system (BGMS)- Automated Digital read out meter with photometric test strips
	Biosensor blood glucose meters
1950s	Leland Clarke, developed 'oxygen electrode' later known as "Clarke electrode" that measures ambient oxygen concentration in a liquid using catalytic platinum was the foremost central concept that leads to the development of the first biosensor electrode.
1962	The Clark oxygen electrode laid the basis for the first glucose biosensor (also the first biosensor of any type) invented by Clark and Lyon
1987	*The ExacTech System,* the **first blood glucose biosensor system** was launched by *MediSense.* The enzyme electrode strip was developed by Genetic International in conjuction with Cranford and Oxford universities. The meter was available in two highly original forms, a slim pen or a thin card. The satisfactory evaluation of device interms of accuracy, precision and error grid analysis and successful use of electrode technology leads to the birth of the **third-generation BGMS**.
1987-*policy*	American Diabetic Association (ADA) lowered the referred glucose meter deviation compared to laboratory reference methods to 15%.
	Period of Smaller Glucose Meters (1991- 2000)
1991	*Reflolux S/ Accu-Chek III* introduced by *Boehringer Mannheim*
1992	*OneTouch II* by Lifescan (Johnson & Johnson), was a reflectance blood glucose system that eliminated the need to time accurately the application of blood to the test strip and its removal prior to the measurement of the colour.
1992	*Accutrend* range: *Accutrend Mini* (1994), *Accutrend Alpha* (1996) by Boehringer Mannheim has barcoded reagent test strips that prevented the misuse, precalibrated meter, simple use etc..
1993	*Ascensia Glucometer Elite* introduced by Ames (Bayer) – *the first meter with capillary gap,* ***'SIP-IN' technology*** *and first low volume 3 microliters(3* μL*) BGMS*.
1994-98	Lunch of Biosensors based products: *MediSense Companion II* (1994) by MediSense (Abbott) *AccuChek Advantage* (1996) by Roche (Boehringer Mannheim) *Medisense Precision QID* (1998) by MediSense (Abbott)
1995-98 *market*	*Bayer, Abbott and Roche* acquired *Ames, MediSense and Boehringer Mannheim* respectively. *LifeScan (now with platinum equity)* was acquired by *Johnson & Johnson* in 1986
1997-*policy*	Two major CTs on diabetes the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complication Trial (DCCT) were completed and concluded that blood glucose monitoring is an integral part of intensive diabetic treatment and management.

1996-*policy*	ADA lowered the target variation to 5% between meters and the laboratory method.
1994-*policy*	Public awareness Campaign, *Four is the Floor* (4 mmol/L), raised the importance of self awareness and the clinical risks of hypoglycaemia.
1997	*Glucometer Dex & Glucometer Esprit* introduced by Bayer the *first consumer* ***cartridge-based multi-strip systems*** for BGM with a biosensor instrument, and offered a 100-test memory that could be downloaded to a personal computer via the Bayer WinGlucofacts data management system. *Ascensia Microlet Vaculance – the first lancing device for* ***AST- Alternate Site Testing*** *designed to enhance blood collections from site other than the fingertips*
2001 onwards	*OneTouch* by Johnson and Johnson (Lifescan) produced at least five variations. This used Ultra reagent strips (glucose oxidase), a 1 μL blood sample and was one of the earliest meters to be plasma calibrated met ISO 15197 with 99% of clinical precision and accuracy *OneTouch UltraSmart* collects and organises test results as an electronic 'logbook' *OneTouch Ultravue* (2009) had a colour display, a reagent strip ejector for used strips, and a simple interface without push buttons; features that can help the less-able diabetic.
2002	*SoftSense blood glucose meter* by MediSense (Abbott) offered fully automated sensor using an integral lancing device and electrode capable of collecting a sample and performing glucose measurements on a blood sample obtained from the forearm, upper arm or the base of the thumb. (AST)
2003	*Freestyle* launched by TheraSense (Abbott) is one of the smallest meters then available (just 38 g), which used (GDH-PQQ) glucose test strip and coulometry
2003	*Ascensia Breeze* by Bayer. used **autodiscs (10 Strips)** rather than one strips, and less blood sample (2–3 μL) with autocalibration
2004	*Ascensia Contour,* most popular product of Bayer requires only 0.6 μL of sample and offering results in 15 seconds. The device evaluation met ISO 15197 strandard and found suitable for patient for self-monitoring.
2007	*Ascensia Breeze II* minimizes the blood requirement to 1 μL of sample with a rapid response and a more advanced data management system.
2010	*Contour USB* is a plug-and-play facility to connect to *Glucofacts Deluxe software* for enhanced display features for type 1 childern, especially.
Alternative BGMS	
1999	*Glucowatch Biographer* by Cyngnus Inc. is a '**wristwatch**' automatic and non- invasive glucose monitoring system an alternate to conventional blood glucose monitors.
2008	*SensoCard plus* by BBI Healthcare **Talking** blood glucose meter is a audio blood glucose test kit targeting visually impaired, elderly and children

(Source: Ascensia Diabetes Care, Clarke 2012)

ANNEXURE – IV

EVOLUTION IN ORAL ANTI-DIABETIC DRUG

Timeline	*Significance*
	Drug Classes- Sulfonylureas (SU)& Biguanides
1920s	*Guanidine* compounds were discovered in *Galega extracts*, the animal studies indicates lowering of blood sugar level. Less toxic derivatives such as *Synthalin A* and *Synthalin B* were used for treatment, however their uses decline after discovery of insulin.
1922	*Biguanides -Metformin* was first described in the scientific literature in 1922, by Emil Werner and James Bell. Slotta and Tschesche discovered its sugar-lowering action in rabbits in 1929. However, other guanidine analogs, such as *Synthalins*, grab more attention but soon all OADs were overshadowed by insulin until its revival at mid 1950s. It was introduced as a medication in France in 1957 and the United States in 1995. *Metformin* is listed on the *WHO-List of Essential Medicines**
1955	*Sulfonylureas (SU)* oral medications that stimulate the pancreas to release more insulin became available for human use.
1956	*SU- Carbutamide* patented in the year 1953 and approved for medical use 1956. Marketed as *Glucidoral* by Servier Laboratory- France/ Eli Lilly.
1956	*SU- Tolbutamide* was discovered, *Orinase* was developed by Upjohn Co
1957	*Biguanides -Buformin* was synthesized as an oral antidiabetic agent *(US Pat No:2961377)*
1957	*Biguanides -Phenformin* was discovered by Ungar, Freedman and Seymour Shapiro while working for the US Vitamin Corporation. Clinical trials begun in 1958 showed it to be effective.
1958	*SU- Chlorpropamide - Diabinese* introduced by Pfizer
1964	*SU- Acetohexamide*- Lilly Industry Limited received USFDA approval
1965	*SU- Glyclopyramide*; Deamelin-S was lunched in Japan
1966	*SU- Tolazamide* received USFDA approval
1969	*SU- Glibornuride* by Meda AB was lunched in the market
1972	*SU- Gliclazide* was patented in 1966 and approved for medical use in 1972, Diamicron developed by Servier Laboratory- France. *Gliclazide* is listed on the *WHO-List of Essential Medicines*.*
1983	***Second-generation Sulfonylureas*** enter the market allowing patients to take smaller doses and with reduced side effects
1984	*SU- Glibenclamide* was discovered in 1969 and approved for medical by USFDA in 1984. It was developed in 1966 in a cooperative study between Boehringer Mannheim (now part of Roche) and Hoechst (now part of Sanofi-Aventis
1984	*SU- Glipizide* was patented in 1969 and approved for medical use in 1971; however, it received USFDA approval in 1984. It was developed by Andrx Pharmaceuticals, Inc
1995	*SU- Glimepiride* was patented in 1979 and approved for medical use in 1995 Amaryl by Sanofi Aventis is the first *Third-generation Sulfonylureas.*
	Important scienfic inventions
1980	*Captoril* (Capoten) is an angiotensin-converting enzyme (ACE) inhibitor patented in 1976 and

	approved for medical use in 1980. It received USFDA approval in 1981 to treat end-stage renal disease. Captoril became a generic medicine in US in 1996 after the expire of exclusive right to Bristol-Myers Squibb.It's main use are in hypertension, congestive heart failure/ myocardial infarction and preservation of kidney function in *diabetic nephropathy*. The development of Captorial was among the earliest success of **ligand-based drug design**.
1988	The first evidence of distinct **glucose- transport protein** is provided by David James in 1988. Glucose is discovered to be distributed into muscle and fat cells via a transporter known as ***GLUT-4 an insulin-regulated glucose transporter.*** Understanding how glucose is transported from the bloodstream into cells to be used as fuel is important to locating different drug targets that can improve insulin sensitivity.
1990	The 64K autoantibody associated with type 1 diabetes is identified. This protein ***Glutamate decarboxylase (GAD)*** is an important enzyme involved in cellular communication in the brain and pancreas. The immune system's attack on GAD triggers a progressive autoimmune response that leads to diabetes. These important discoveries leads to new classes of drugs.
Mid 1990s	The incretin hormone ***Glucagon-like peptide (GLP-1)*** is discovered. Incretin hormones are secreted from the gut in response to food, and encourage the body to produce insulin. Discovery of GLP-1 later lead to a new class of diabetes drugs that can increase insulin secretion in response to glucose, and even increase the amount of beta cells in the pancreas.
	Drug Class - Alpha-Glucosidase Inhibitors
1996	*Acarbose* (Glucobay/ Precose/ Prandase) an alpha-glucosidase inhibitor that slows digestion of some carbohydrates by Bayer Pharmaceutical is approved by USFDA. It is the first in the class of drug known as alpha-glucosidase inhibitor.
1994/97	*Voglibose* (Voglib) an alpha-glucosidase inhibitor by Takeda Pharma introduced as BASEN in Japan
1999	*Miglitol* (Glycet) another alpha-glucosidase inhibitor by Pharmacia & Upjohn Inc approved by USFDA. The generic version was introduced by Sun Pharma/Orient Pharma during 2015-16.
	Drug Class - Thiazolidinediones (TZD)
1997	*Troglitazone* (Rezulin) is approved by the USFDA for medical use in 1997. It was patented in 1983. It is the first in a class of drugs known as thiazolidinediones, and it improves insulin sensitivity in muscle cells. It is eventually removed from the market due to liver toxicity.
1999	*Pioglitazone* (Actos) was patented in 1985 and came into medical use in 1999. The generic version is now available.
1999	*Rosiglitazone* (Avandia) was introduced by GlaxoSmithKline (GSK). It was patented in 1987 and approved for medical use in 1999. The drug's patent expired in 2012
	Drug Class – Meglitinide
1997	*Repaglinide* (Prandin/ GlucoNorm/ Surepost/ NovoNorm) was developed by Novo Nordisk. Precursor drugs to repaglinide were invented in late 1983 by scientists at Dr Karl Thomae GmbH, a German drug manufacturer later the molecule was acquired by Boehringer Ingelheim in 1990. The drug was later licensed by Boehringer to Novo Nordisk, which filed an Investigational New Drug (IND) application for the compound with the USFDA 1992. Novo Nordisk filed its New Drug

	Application (NDA) for Prandin in 1997 which subsequently received USFDA approval.
2000	*Nateglinide* (Starlix) was developed by Japanese company Ajinomoto and sold by the Novartis
	Drug Class - Glucagon-like peptide-1 (GLP-1) agonist (Injectible Drugs)
2005	*Exenatide* (Byetta) approved by USFDA as a first-in-class incretin mimetic (GLP-1) drug to treat Type 2 Diabetes. Exenatide was first isolated by John Eng in 1992 at the Veterans Administration Medical Center, New York. It was developed by Amylin Pharmaceuticals and commercialized by AstraZeneca.
2009	*Liraglutide* (Victoza) by Novo Nordisk was approved for medical use in Europe in 2009 and in the United States in 2010
2013	*Lixisenatide* (Lyxumia/Adlyxin) by Sanofi was approved by the European Commission in 2013 and subsequently accepted by USFDA in the same year.
2014	*Dulaglutide* (Trulicity) by Eil Lilly was approved for medical use by USFDA in 2014
2017	*Semaglutide* (Ozempic) by Novo Nordisk was approved by the USFDA in 2017 and by the European Commission, the Health Canada and the Japanese Ministry of Health, Labour and Welfare in 2018.
	Drug Class - Dipeptidyl-peptidase-4 (DPP-4) inhibitors / gliptins
2006	*Sitagliptin* (Januvia) developed by Merck & Co the first in a new class of drugs known as DPP-4 inhibitors that enhance the body's ability to lower elevated blood sugar was approved by USFDA. DPP-4 is an enzyme that naturally blocks GLP-1 from working, so by inhibiting this enzyme, GLP-1 works in the gut to promote insulin secretion.
2008	*Vildagliptin* (LAF237/Galvus/Zomelis) by Novartis Europharm Limited was approved for medical use by European Medicines Agency in 2008 and at Australian PBS with certain restrictions, however this drug has not yet been approved by USFDA
2009	*Saxagliptin* (Onglyza) by Bristol-Myers Squibb approved for medical use by USFDA and European Medicine Agency in 2009. Initially solely developed by BMS later AstraZeneca joined in 2007 to co-develop the molecule and market it with BMS.
2010	*Alogliptin* (Nesina/ Vipidia) was developed by Syrrx (company acquired by Takeda Pharmaceutical Company) got approval in Japan in 2010 but failed its first USFDA NDA, finally received USFDA approval in 2013 for three formulations
2011	*Linagliptin* (Tradjenta) by Boehringer Ingelheim was approved for medical use in the USFDAin 2011
	Drug Class - Sodium glucose cotransporter 2 (SGLT2) inhibitors
2013	*Canagliflozin* (Invokana) is developed by Mitsubishi Tanabe Pharma and is marketed under license by Janssen, a division of Johnson & Johnson was approved for medical use by USFDA in 2013. It is the first in a new class of drugs know as the SGLT-2 inhibitors, for lowering elevated blood sugar in patients with T2DM. SGLT-2 inhibitors block the activity of sodium glucose transport proteins in the kidney, reducing glucose re-uptake and increasing secretion of glucose in the urine.
2014	*Dapagliflozin* (Farxiga/Forxiga) was developed by Bristol-Myers Squibb in partnership with AstraZeneca was approved for medical use by USFDA in 2014.

2014	*Empagliflozin* (Jardiance) was approved for medical use by European Medicines Agency and USFDA in 2014. It was developed by Boehringer Ingelheim and Eli Lilly and Company.
2017	*Ertugliflozin* (Steglatro) is developed by Merck Sharp & Dohme Corp was approved by USFDA in 2017 and in Europe in 2018.
	Drug Class – Others
2005	*Pramlintide* (Symlin) an injectable amylin analogue developed by Amylin Pharmaceuticals was approved for medicinal use by USFDA.

(Source: compiled from various sources)

ANNEXURE –V

INTERVIEW MANUALS

(Semi-structured questioners)

Format - 1

Questions for – Researcher, Scientist, Innovators, Patent assignees

1. What is/are your area/s of expertise? *(Basic/ Translational/ Applied/ Other...)*
2. What is the basic aim and functions of your organisation?
3. Who are your major stakeholders and how do you interact with them?
4. What is your major form of research output?
   (Patents/ Publications/NCE/NBE/Protocol/Method/Manual/Policy& Guideline)
5. What are your major sources of fund for research, innovation & translational activities?
6. What types of collaboration (formal & informal linkages) do you have and the nature of those collaborations?
7. What are the major obstacles and difficulties in academic research in your area?
   (Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others...)
8. **Do you have any experience about commercialization of academic research?**
9. How your organization assists in research commercialization activities?
10. How is your relationship with Technology Transfer Offices/Unit and University Incubator?
11. What are the major obstacles and difficulties in commercialization of academic research?
    (Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others...)
12. **Which areas of research grab maximum attentions for translational research?**
    (Lifestyle/NCD- Cancer, Diabetes, CVD/ Others……..…..)
    (CD/ Neglected diseases- TBs/ HIV/Malaria/ Vector-born Disease/ Others .....)
13. Which areas require maximum priorities in translational in terms of clinical importance, public health prospective?
    (Basic res/ Advance res (Mol Bio/Nano/Stem)/ Drug discovery/ Diagnostics/AYUSH)
14. Do you think too much attention on translational research kills basic research?
15. How easy/difficult it is for knowledge formation, consolidation, dissemination in TRs?
16. What are the major obstacles and difficulties in translational research?
    (Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others..)

Questions on Pre-clinical studies: applicable to specific domain experts

Format – 1A

1. What types of approaches uses in pre-clinical studies?
    a. *(Phenotypic screening/physiology approach/forward pharmacology/ classical pharmacology)*
    b. *or (Target based approach/ reverse pharmacology/reverse chemical biology)*
2. How identification or validations of therapeutic target occurs?
3. How to assess clinical translatability in phase 1/2 and early stages of innovation?
4. What are the methods/processes used for initial therapeutic validations of targets?
    a. *(in vitro, in vivo, in silico, other ...)*
5. How smooth/ difficult is the translational ability of results from animal models to humans?
6. Do you think animal models are still clinically most relevant for TRs? Is there any alternate model you can suggest?
7. How much diversity you find between the animal model and the human individual in terms of pathogenesis and how that will affects translational research?
8. Comment on the reproducibility, quality and reliability of non-clinical studies in drug development.
9. What is the accuracy of data relates to reproducibility of data from studies in the same model performed at different institutions? What percentage? If diverse, what are the reasons for that diversity?
10. Do different cohorts' studies from the same strains (nude mice/any animal) possess different results? Yes/No – if diverse, what are the reason for that diversity?
11. What are the ethical or regulatory issues you face while dealing with experimental animals?
12. What are the major reasons of failure for reproducibility and translational ability of non-clinical studies for further development?
    a. *(Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others...)*

	Least Impact	Moderate Impact	Most Impact	Please specify
Improper study design				
Cost compatibility				
Time line of the study				
Lack of knowledge of Pharmacovigilance				
Skilled manpower *(includes investigators & accessors for better a outcome)*				
Funding agencies/ conflict of interest				
Lack of proper infrastructures				
Lack of standard and protocols				
Regulatory gaps				

Advance Research:

1. Do you have any ideas about use of islet transplantation procedure for treatment of type 1 diabetes in India?
2. What are the different issues involves in the process of treatment?
   (Graft issues/availability/accessibility/affodibility/expertise/ethics/regulations)
3. What are the different applications of nanotech/ stem cell research in Diabetology research & Clinical Practices?
4. What are the different issues and challenges involves in the advance research?

Format - 2

Questions for- Doctors, Clinician, Practitioner, Clinical Investigators

1. What is/are your area/s of expertise?
2. What is the basic aim and functions of your organisation?
3. Who are your major stakeholders and how do you interact with them?
4. What types of collaboration (formal & informal linkages) do you have and the nature of those collaborations?
5. **Do you have any experience in conducting clinical trials of new drugs/device?**
6. Do you have any opinion, experience or obstacles/huddles in conducting observational/ interventional studies/BA-BE/PMS trials?
7. What are the major obstacles and difficulties you face while conducting and implementing clinical trials? (Ethical/Moral/Patients/Sponsor/Finance/ Human Resources/Infrastructures/Policy& Guidelines/Regulations/ Others...)
8. What are the major obstacles and difficulties for translating clinical research into clinical practices? (Patient prognosis/ attitude/physiological responses/ financial condition/ Human Resources/Infrastructures/ Policy/ Guidelines/Regulations/Knowledge/Skills/Others...)
9. Does outcome of clinical research/ trial/ policy affects clinical practices? How?
10. **According to you what is the major reasons for growing diabetic epidemic in India?**
11. What are the basic (or specialised) diagnostic/ clinical tests/drugs prescribes to combat diabetes?
12. What is your opinion about the affordability, accessibility & availability of the above for patients?
13. What is the role of diagnostic lab/industries/device on evidence based practices in life-style diseases (Diabetes)?
14. What is the role of patient in decision making? How informed /ill-informed patients have a role in your decision making?
15. What are the major obstacles and difficulties in management of diabetes in India? (Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others...)
16. **Do you have any experience/contribution in public health management/ public policy formulation?**
17. According to you, which is better? Perception-based/ evidence based practices and policy making?
18. What is your opinion about evidence-based research/practice/clinical implementation/ public policy formulations?
19. What are the clinical guidelines/policy/standard/ protocol available nationally or internationally to compact diabetes & how these guidelines being implemented at the ground level?
20. How guidelines are developed nationally or internationally? Perception based/ evidence based?
21. How often systemic review of guidelines/policy occurs at national/ international level?
22. Is there any community based lifestyle improvement programs in Diabetes? (observational/interventional/ awareness/registry/trials/ educational)
23. Can you give examples of best practices/ standard available for all patients and practitioner?

Format - 4

Questions for- Policy Institutes, Financial Agencies

1. What is the basic aim and functions of your organisation?
2. What is/are your area/s of expertise?
3. Who are your major stakeholders and how do you interact with them?
4. What are the major activities of your organisations?
   (Funding/ policy formulation /implementation/guidelines/ health evaluations/ consultancy/ co-ordination/ Others)
5. What types of collaboration (formal & informal linkages) do you have and their nature?
6. **What is the status of academic/health research funding in India?**
   (Academic/ Clinical/ Translational/ Health services/ S&T, others ...)
7. Do you have any priority areas in terms of research funding?
8. Which area of research attract maximum fund? (both applicant/demand and grant)
   (Basic/ Clinical/ Translational/ Diagnostic/ Drugs/ others.....)
9. What are the different types of funds available?
   (Long- term/ short-term/ ad-hoc/ intramural/ extramural/ taskforce/ Cohort/ Others.....)
10. What is the average duration of a project?
11. What are the criteria of evaluation for extramural funds/ grants?
12. Does evidence based research financing occurs or through any other method? (perception)
13. Is there any follow up/feedback/review mechanism exist to increase scalability of project?
    (During the period and after-completion)
14. Does health/academic research funding aliened with the disease burden/public health priorities?
    (Disease wise, mode of delivery: drug/diagnostic/device/process) management/policy/Other .)
15. Could you give a glance of grant in proportional to the specific areas of health research?
    (Lifestyle/NCD - Cancer/ Diabetes/ CVD/.. others)/ (Communicable-HIV/TB/hepatitis .....oth ers) (Neglected and rare diseases)/ Others.....
16. Do you think, there is disproportional fund allocation for Translational Research? *(T1& T2 stage)*
17. What is the status of research funding in the area of lifestyle/diabetes for last 5 years?
    (Both demand-supply; Negative/Stagnant/ Positive)
18. What are the issues and problems in research funding? *(Your opinion in general)*

	Not Exist	If Exist			Please specify
		Least Impact	Moderate Impact	Most Impact	
Insufficient grant/fund					
Disproportionate allocation of funds					
Duplication of grants *(diff agency same fun)*					
Bias towards established org/influence *(few reputed org. receives more funds)*					
Political influence/Change in govt. policy					
Lack of standard transparent protocols for allocation of grant/fund					
Wastage/ Under utilization of funds					
Structural and technical delay in implementation of projects					
Conflict of interest (personal/ institutional/ reviewer/political/others.....)					
Lack of proper evaluation & follow-up					
Regulatory gaps					
Others:					

Questions for- Policy institutes- in addition to above: (Guidelines)

1. What are the important policy guidelines (National/International/State/Local level) for management of research, innovation, translational activities in India?
2. Do you have any programmes/mechanism for promoting TRs activities in R&D and Innovation?
3. Do you have any programmes/mechanism for promoting TRs activities in Health services/clinical implementation/ public health delivery?
4. What are the major obstacles and difficulties in management of diabetes in India? *(Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others...)*
5. What are the major obstacles and difficulties in research, innovation and translational activities in India? *(Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others...)*
6. Do you have any collaboration/co-ordination mechanism for research, innovation, translational activities or management of disease? And their nature of collaboration and level of collaboration?
7. What is your opinion about evidence-based research/practice or evidence based public policy formulations?
8. According to you, which is better? Perception-based/ evidence based practices and policy making?
9. What are the clinical guidelines/policy/standard/ protocol available nationally or internationally to compact diabetes & how these guidelines being implemented at the ground level?
10. How guidelines are developed nationally or internationally? Perception based/ evidence based?
11. How often systemic review of guidelines/policy occurs at national/ international level?
12. Is there any community based lifestyle improvement programs in Diabetes? (observational/interventional/ awareness/registry/trials/ educational)
13. Can you give examples of best practices/ standard available for all patients and practitioner?

Format - 5

Questions for- Firms/ conventional and AYUSH

1. What is the basic aim and functions of your organisation?
2. Who are your major stakeholders and how do you interact with them?
3. **What is your major form of research output/capabilities?** *(Patents/ Publications/ANDA/DMFs/NCE/NBE/Protocol/Method/Manual/Policy& Guideline)*
4. Does your organisation fill any DMF/ANDA/NDA in last 5/10 years? In which category?
5. What is/are your major form/s of production portfolio? *(APIs/Proprietary drugs/ Bulk drugs (intermediates)/ Formulations/ Blockbusters/ Branded generics/essential drugs/ Plain vanilla generics/devices-in-vitro/diagnosis/assistive/Biological*)
6. **What is status (demand) for products/market growth for life-style segment (diabetes) in recent years?** *(Extremely negative/ negative/ stagnant/ positive/ extremely positive)*
7. Do you have any idea about new entrant in life-style segment (diabetes) in recent years? Or an existing company with new product portfolio/diversification towards life-style segment?
8. Do you have any idea about new categories of technology/ drug/ formulation/ diagnostic device/ assistive devices in life-style segment (diabetes) in recent years? *(Nano based/ stem cell based/ mode of delivery-nasal insulin/non-invasive/diabetic-pen)*
9. As per your experience, does the consumer/patient have empowered enough to decide for their product/services? Who create demands for new product? (Clinician/patients/other) How the decision power changes over the different segments? *(prescription drug, life-threatening diseases, life-style diseases, OTC drugs, nutritional products)*
10. **What types of R&D and innovation activities occurs in your organisation?**
11. What are your major sources of fund for research, innovation & translational activities?
12. What is the percentage of R&D expenditure of your firms? And what percentage devoted to life- style segment?
13. **What types of collaboration (formal & informal linkages) do you have and the nature of those collaborations?**
14. Do you have any collaboration with university or hospital and the nature of those collaborations?
15. What are the major obstacles and difficulties in R&D, innovation and translational activities? *(Knowledge/ Guidance / Finance/ Human Resources / Infrastructures/ Others)*
16. What are the major obstacles and difficulties in production activities? Technical and non-technical *(Land/water/electricity/transport/Tax-GST/Subsidies/ tax holiday/ import-export duty/ FDI/FII/ Competition/ Compliances/Regulatory issues)*
17. **How research capabilities/output in herbal medicine/AYUSH is different to conventional firms? And how to measure them?**
18. Could you elaborate the prognosis methods and treatment process for diseases in AYUSH? (Emphasis on life-style disease/diabetes)
19. What is the market size of AYUSH products in total? In lifestyle segment? International market?
20. What are the major obstacles and difficulties related to AYUSH and herbal industries? (Technical and non-technical issues)
21. **Does your organisation engaged in any form of life-style improvement programs/ CSR/awareness drive/Community based integrated life-style intervention program in the areas of diabetes?**

Format - 6

Questions for- Contact Research Organizations

1. What is the basic aim and functions of your organisation?
2. What is structure and composition of your team? (both institutional & external experts)
3. Who are your major stakeholders and how do you interact with them?
   (Only institutional/outsider experts)
4. What types of collaboration (formal & informal linkages) do you have and the nature of those collaborations?
5. **Disease wise, in which area maximum Clinical Trials going on?**
   (Lifestyle/NCD - Cancer/ Diabetes/ CVD/.. other)/ (Communicable-HIV/TB/hepatitis... others) (Areas of research drug/diagnostic/ process)
6. Who are the major actors in CTs in India? (inventors/sponsors)
7. **Who are the major sponsors in CTs and in what categories? variation in categories?**
   (Govt/ Indian Firms/Foreign Firms/ Venture/ Int. Donor/agencies/ others.....)
   (How different is it in category wise- ifestyle/neglected/communicableetc.)
8. **Are you aware of any CTs deals with life-style improvement programme?**
   (Observational/ interventional /target-based/ community based/ life-style intervention etc..)
9. **What are the major obstacles and difficulties you face while conducting and implementing clinical trials?** Technical/ non- technical issues-
   (Ethical/Moral/Patients/Sponsor/Finance/ Human Resources / Infrastructures/Policy & Guidelines/Regulations/ Others.....)

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Original Article

Challenges in diabetology research in India

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ABSTRACT

Background: Diabetes emerges out to be a major epidemic in recent years that engulfs both developed and developing countries across the globe. India, a country witnessing rapid socioeconomic progress and urbanization carries a considerable share of the global diabetes burden. There has been an incongruity between disease burden and the technical capacity to make use of existing knowledge or to generate new knowledge to combat diabetes in India.
Aim: This paper examines the role of different actors, organizations & institutions in shaping diabetology research in India using arrays of scientific indicators such as research output (publications and patents), research finance and role of policy-making bodies. This paper also identifies research gaps and challenges pertinent to this sector.
Methodology: A combination of three methods patent data analysis, publication data analysis and primary survey corroborated with secondary data to obtain desire objectives. We made an in-depth study of the patent and publication data (2000–2016) to know the research output and direction of Indian actors, institutions and organizations in the area of diabetes research.
Results: This paper identifies some key structural barriers and institutional challenges pertinent to diabetology research in India that will help in canvassing and formulating science, technology and policy guidelines for diabetology research in India
Conclusion: Multilevel intervention requires bridging the gap between knowledge and action hence policy-making should align to balance resources with innovation capabilities.
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1. Introduction

The current trends in global health burden appear shifting gear gradually. On one hand, diseases like cholera, plague, polio, leprosy, malaria, HIV and tuberculosis are declining [1,2] due to timely interventions and effective management, specific target oriented interventions by government & international agencies, massive immunization, improved sanitation and lifestyle of individuals; on other hand chronic diseases like cancer, diabetes, cardiovascular diseases (heart diseases) are increasing exponentially [2]. Over the last decade due to focused action to attain Millennium Development Goals, India had made steady progress in improving and strengthening her health care system. The National Health Policy of 1983 and the National Health Policy of 2002 have served well, in guiding the health sector through Five-Year Plans and different schemes (Central, states sponsor & Public Private Partnership) [3]. However, in the contemporary scenario, India's health priorities are changing. More than sixty percent of all global deaths are reported due to chronic diseases [4,5]. The rising problems of these diseases have widespread social and economic impacts, affecting all levels of society, including households, healthcare systems and national and global economies [1,6,7].

In the contemporary world, diabetes is recognized as a major lifestyle disease. Globally, 415 million adults have diabetes and 318 million adults have impaired glucose tolerance (IGT), which puts them at high risk of developing the disease in the future. Every one in 15 adults is estimated to have IGT and one in seven births is affected by gestational diabetes [4]. The scenario of diabetes in a country like India is also not different from the larger picture. It's genetic profile of the population, sedentary lifestyles, high-stress levels, insomnia and deteriorating eating habits are some of the major factors contributing to its galloping figure of the diabetic population. India is currently undergoing a demographic transition which reflects both quantitative as well as qualitative changes in the population profile. She has world's second-largest pool of diabetic patients with 69.2 million people were affected till 2015

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[4] and high blood glucose attributed to more than 0.67 million death in the country [8].

The issue of diabetes, as an emerging problem of India's health scenario, poses an important question that goes well beyond the specific problem of diabetes and includes in its reach the whole of health schema. There has been an incongruity between disease burden and the technical capacity to make use of existing knowledge or to generate new knowledge to combat diabetes in India. In addition, social determinants such as disparity among rich and poor, inequalities, poverty, accessibility, affordability, political instability, policy uncertainty & inefficient policies implementation are hindering the effective management of diseases in India. Is the increasing rate of diabetes in contemporary Indian situation imply an inadequate intervention on the part of the Government? Or are there other factors? On the preceding context, the present study is an attempt to find out the research and innovation gaps while assessing diabetes research in India.

Various attempts were made to study and evaluate research output of a scientific organizations' nationally [9,10] and internationally in the past [11,12]. Most popular methods were scientometrics analysis, bibliometrics analysis, patent analysis, evaluating R&D expenditure [13,14] and human resources capitals etc. Scientometrics analysis also focused on research evaluation of a specific field. Some of the important contributions of scientific evaluation in the specific areas are medicine [9,11], endocrinology research [12,15], diabetes research [16–19] etc. In contrast to bibliometrics analysis, the patent analysis was more focused on determining the efficacy of individual compounds New Chemical Entities (NCE), New Biological Entities (NBE), drugs families, combination drugs etc. except some attempt to determine the patent portfolio of the organization [20]. A few patent studies specific to individual diabetes molecules are oral combined drug formulations [21], SGLT inhibitors [22], alpha1- antitrypsin (AAT) [23], Thiazolidinediones (TZDs) [24] and herbal compound in India [25]. Most of these studies were focused on analysing publication trends, patenting activities, R&D expenditure, human resources etc., however, linking research output to identifying gaps & challenges in a specific sector and its linkage with policy formulation is missing.

2. Methodology

The foundation of this study was built keeping in view some of the key concepts that have prime importance in understanding the problems, issues and challenges related to diabetes research and the whole healthcare innovation system. For a system where actors, organizations and institutions play a diverse role in different conditions, the measurement problems are more significant. A single indicator is not sufficient to capture all actors and their innovation activities. However, while focusing on research evaluation method, it is important to notices that the research output is different as per the mandate of the different organization. While hospital, research organization focuses more on publication, protocols, standards, On contrary firms' motivation are to obtain patents, abbreviated new drug applications (ANDAs), in-licensing and out-licensing due to their commercial importance. Therefore, several measures have been combined to address this problem.

A mixed methodology is used in this study. It has the flexibility of being fixed or emergent, as per requirement [26] and quite popular in health research [27,28]. This study involves three major methods: analysis of patent data, publication data and follow-up with a survey. While combining various methods this study drew inspiration from various other similar studies [29,30]. Snowball method for identifying actors complimenting with a patent-based method or citation based method reduces the risk of alienation of a population with a single method. The qualitative & quantitative data were used for preliminary & follow-up purposes simultaneously. The motives behind taking a wide range of indicators are to link and analysis both the quantitative and qualitative data. The following data sources were used to retrieve relevant information.

2.1. Study design & data sources

Patent data were retrieved from *WIPO-PatentScopus databases*, *Derwent Innovation Index* and *InPASS* (Indian Patent Advanced Search System), IP-India. The search terms used were diabet*, OR Type 1 Diab * OR Type 2 Diab * OR Type 1.5 Diab*, Double Diab* OR NIDDM OR IDDM OR MODY OR FCPD OR Hypoglycem* OR Hyperglycem* OR "Islet transplant*" OR "Islet encapsulation" OR "Insulin resist*" OR Retinopath* etc. [16]. The final analysis was made from IP-India database. These data include all patent application registered in Indian patent office including foreign applicants in the area of diabetes research from the period of 2000–2016. Publication data were retrieved from *SCOPUS database- Elsevier*. Except for a broad analysis of global trend (Fig. 1), all other data and detail analysis were based on the publication data of 2000–2016. Further, data were corroborated from institutional web sources, annual reports, financial data, product and institutional portfolio of institutions and organizations.

In addition to the above processes, set of the questionnaire were sent to actors including scientist, doctors, clinician, researcher, policy maker in the field of diabetology. The main purpose of the survey is to identify and gather knowledge from experts about different sectoral experience, perception, priorities, barriers and facilitators etc. at different stages of research. The response rates were poor only 47 actors responded positively. However, primary survey corroborated with other methods for attending research objectives.

3. Diabetology research & innovation in India

This section is a systematic, holistic analysis of various actors and organizations involves in diabetes research in India. Although our primary focus is to study various aspects of diabetes research confines to the national geographical boundary; however, sometimes, it is inevitable to take the international scenario for a comparative analysis and to draw attention towards policy direction.

3.1. Results from citation analysis

3.1.1. The growth of literature

Diabetes, no doubt became a global epidemic in the recent past engulfed equally both developed and developing countries. However, research in diabetes shows tremendous growth in last two decades due to global attention. Globally the number of peer-reviewed research articles in diabetes has increased from below 15

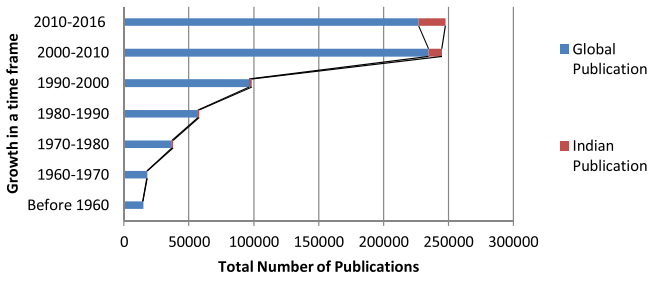


Fig. 1. India's contribution to global literature in the area of diabetology. Source: citation analysis through Scopus database, Elsevier.

thousand (before 1960), 18 thousand (1960–70) to around 245 thousand in last decade (2000–2010) clearly shows the emergence of this discipline. An additional amount of research articles more than 247 thousand in just 6 years (2010–16) indicates the trend is going to dominant in diabetes research in future (Fig. 1). Contributions of Indian actors and institutions have shown steady progress with a growth rate from 0.15% before 1960 to 4.8% in last decade (2000–10) and most interestingly in the last 6 years (2010–16) the growth rate is doubled to 8.3%. The growth rate remains less than 2% until 1990 but the post-liberalization period has shown an exponential increase in the amount of literature and research activities in diabetology in India.

A number of universities, hospitals, firms, a network of scientists, researchers and their significant contributions to global diabetology innovation made all these possible. India's contribution to these global innovations has increased many fold in the last two decades. Globally, India stood at 9th position in terms of total number of publications from 2000 to 2016, however gradually she consolidates her position as a major player in diabetes research. Detailed year-wise citation analysis from 2000 to 2016 showed an encouraging trend. From 2000 to 2005 in terms of number of publications India stood between 13th–14th positions globally, that trend showed a steady growth in next five year period of 2006–10 (12th–7th) further in 2011–13 (7th–5th) and from last 3 years 2014–16 consistently placed at 4th position in terms of volume of production of research papers.

The United States of America has hegemony in terms of research publications with more than 200 thousand papers (2000–16) that accounts for 3.3 times of total publications of the United Kingdom, which stands distinct 2nd in the list. India's publication counts less than 1/8th of USA, however, this difference has drastically reduced in last 6 years from 2010 to 16, now the margin is 1/5th of USA. Comparing the leading countries in terms of volume of publications the UK accounts for 2.6 times and Japan 1.8 times of whole Indian publications, however among others the differences are rather marginal. The annual growth rate of domestic publications are three times higher than the global growth rate. The average growth of Indian publication is 18% compared to 7% globally from the period of 2000–2016. For three consecutive years (2009, 2010, 2011) the growth rate was more than 28%, whereas the growth worldwide never seem to be more than 10% in that period.

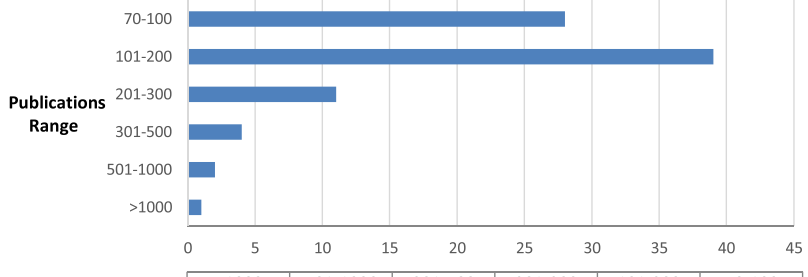
3.1.2. Role of hospitals and research organizations

The citation data of affiliated organizations revealed that only one organization (AIIMS) in India has more than 1000 numbers of peer-reviewed research publications, followed by PGIMER and MDRF (501–1000 range) in the area of diabetes research in India. Four organizations have publications in a range of 301–500, eleven organizations have publications ranges from 201 to 300. Compare to these eighteen organizations in the higher echelon of the pyramid, 67 organizations are at lower strata of the pyramid with 39 organizations have publication ranges from 101 to 200 and 28 organizations have publication ranges from 70 to 100 (Fig. 2). The organizations having publications less than seventy are not considered for detailed analysis purpose, however, the trend indicates considerably higher institutions with lesser publications. *These data indicate diabetes research in India is at the naïve stage and scattered. Specialized research organizations exclusive for diabetology research (except MDRF and DRC) are less in number in the higher echelon of the pyramid.*

Further detailed analysis of affiliated institutions having a minimum of 100 or above publications revealed some interesting trends. Hospital/medical colleges based research publications consist of 55%, University-based basic and applied research based publications consist of 34% and rest 13% of publications belong to specialized research institutes in India. Within top 58 institutions having more than 100 publications, lion shares of publications are by top 27 medical colleges and institutes in India, followed by 23 universities based research and only 8 specialized research organizations. The citation data also pointed out the nature of work being done in the field of diabetology in India. Out of all publications more than 54% were in the field of medicine and allied subjects while applied science research fields such as biochemistry, genetics, molecular biology and immunology have contributed a little more than 20%. The research fields concern with therapeutic segment such as pharmacology, toxicology, pharmaceutical sciences contribute 13% and agricultural & biological sciences disciplines that deal with nutritional and diet-related diabetes research contribute mere 3.5%. Basic science, chemistry, chemical engineering and engineering field that are essential for drug development and diagnostic instruments consist of only 5% of literature. *Hence this trend may indicate that research in India involves at a later stage of innovation activity to assess clinical efficacy or patient-related epidemiological studies rather than drug development and discoveries which are marked at earlier stages of development.*

3.2. Results from patent analysis

Patents holding are important indicators for measuring research output of organizations. Novelty, non-obviousness and capability of industrial application are three major criteria for granting a patent. Due to its industrial applications and protections, patents have economic and commercial importance. Filling of patents in the jurisdiction of Indian patent office indicates an entirely different trend then publications. Patent analysis of both



	>1000	501-1000	301-500	201-300	101-200	70-100
No. of Organizations	1	2	4	11	39	28

Fig. 2. Research output (publications) of organizations in the area of diabetology in India.
Source: citation analysis through Scopus database, Elsevier.

granted and published patents shows the dominance of foreign players in patenting activities.

There are 70 granted patents through the period from 2000 to 2016, out of which 70% belongs to the foreign assignees and only 30% belongs to Indian assignees. Similar trends were observed in the published patents, criteria that also show the patent filling trends of innovators. Out of approx. 500 patent applications filled at Indian patent offices in the area of diabetes between the time periods of 2000–2016, 73% are foreign applicants while only 23% are domestic applicants (Fig. 3). Patenting trend also gave a glimpse of the type of patent holders. Out of all the granted foreign patents, 90% belongs to pharmaceutical firms, 5% belongs to research organizations and rest 5% are individual patentees. However, trends in Indian patent holders are entirely different 38% belongs to firms followed by 33% individual patent holders and rest 28% belongs to research organizations and institutes. These trends also indicate the foreign firms are active in filing patents and protecting their innovations and also taking benefit of commercial advantage from patents in the form of royalties by filling through Patent Cooperation Treaty (PCT) route. whereas Indian firms show dismissal trends with only 8 patents belongs to Indian firms among 70 granted patents. Similar trend is observed in the published patents from 2000 to 2016, only 38 patents in the pool of 492 registered patents belongs to Indian assignees. There is also an interesting trend in Indian filling patents where individual or group of individual assignee percentage exceed institutional/ research organizational patent holding in both granted and published patents.

Global patenting trends and national patenting trends also indicate the research potentials, present activities and future directions of innovations. Global patent trends showed 69%

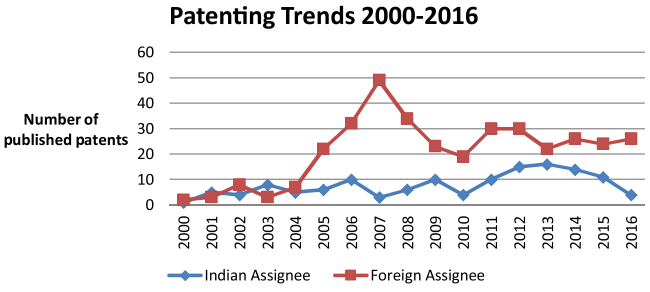


Fig. 3. Year-wise patenting trends in the area of diabetology in India.
Source: patent analysis of published patents through IP-India database.

research in core pharmaceutical research, followed by 12% in advanced applied biological research areas of nanotechnology, molecular biology and procedural innovation such as islet transplantation, islet encapsulation etc. Diagnostic sectors have a healthy contributions of 11% and rest 8% belongs to neutraceutical and research in alternative medicines. However, detailed analysis of Indian patent filling trends showed around 56% of research activities are in traditional knowledge, alternative medicines or plants based research followed by core pharmaceutical research 24%, but in other areas, lesser number of patents were filled such as neutraceutical (8%), procedural innovation, advanced technology (7%). One of the important sector in terms of disease prevention and controlling epidemic, the diagnostic sector received the least attention in the country with only 5% of domestic patents.

3.3. Research financing in India

3.3.1. Role of private and public investments

Research and innovation funding are critical factors for any developmental activities. India's overall R&D expenditure in terms of percentage of GDP is 0.6 in 2015 [31] least among BRICS countries except for South Africa. Although the national goal of increasing GERD to 2% for quite some time [32] it has never crossed beyond 1%. The funding mechanism is different among institutions and actors depending upon their nature of innovations. Privates' organizations especially domestic firms invest more in research activities than foreign firms. The prime focuse of foreign firms are market capture rather than R&D activities as their research activities are mostly based in their host countries. Indian pharmaceutical companies have begun to aggressively invest in their R&D activities. R&D spending by India's leading drug makers grew nearly 17% in 2008–2009, with a number of firms increasing their investments by over 40%. Indian companies spend roughly 7–15% of their top line into R&D [33]. Besides building on the traditional generic products pipeline, companies are now investing in research on complex generics, specialty and differentiated products and biosimilars. The result reflects the strong presence of Indian pharmaceutical companies in highly regulated markets like US, Canada and European markets. Indian companies received approval for 201 Abbreviated New Drug Applications (ANDAs) from the United States Food and Drug Administration (FDA) in 2016, approx 34% of total approvals for the year [34].

Public sector infusion of the fund in diabetology research occurs through concern ministries, departments and funding agencies. All major S&T and healthcare institutions and funding agencies in

Table 1
Extramural funding of research programmes in the area of diabetology.

Funding agencies	Programmes/Extramural funds	Number of diabetology related projects	Areas of research funding
BIRAC-DBT	BIPP	9	Drug discovery, Neutraceuticals, Diagnostics
	BIG	3	Molecular biology, Pharmacology
	CRS	1	Diagnostics
	SPARSH	1	Diagnostics
	SIBRI	7	NCE, Drug discovery, Stem cell, Herbal, Diagnostics
DST	DPRP	9	NCE, Drug discovery, Herbal
CSIR	NMITLI	2	Nanotechnology, Herbal
AYUSH	CCRAS	12	Clinical research
	CCRUM	6	Clinical research
	CCRH	13	Clinical research
	CCRS	1	Clinical research
	CCRYN	1	Clinical research

Sources: Compiled from institutional repositories, financial reports & annual reports.

India such as DBT, DST, ICMR, UGC, CSIR, AICTE, DIPP, DHR, DoP support diabetology research through the intramural and extramural projects, institutional funding, various schemes & programmes, collaborating projects and Public-Private Partnerships (PPP). Department of AYUSH provides guideline and funds for research in Indian system of medicines such as ayurveda, homeopathy, yoga, unani, siddha etc.

However, there are specific innovative programmes initiated in the recent past to address specific challenges pertinent to Indian research and innovation eco-system. These are CSIR's *New Millennium Indian Technology Leadership Initiative* (*NMITLI*) and *Special Drug Development Research Initiatives* (*SDDRI*), DST's *Small Business Innovation Research Initiative* (*SBIRI*), *Biotechnology Industry Partnership Programme* (*BIPP*), *Biotechnology Ignition Grant* (*BIG*), *Contract Research and Services Scheme* (*CRS*), *Social Innovation programme for Products: Affordable & Relevant to Societal Health* (*SPARSH*) and DST's *Drugs & Pharmaceutical Research Programme* (*DPRP*). These specific government initiatives focuses on Public-Private Partnerships (PPP) model of funding with more industry-academia linkages promoting venture funds, providing financial and technical assistance for pre-commercialization related activities such as scale-up, pilot plants, field trials, market seeding of products, market surveys, acquisition of early-stage relevant knowledge/IP for portfolio building-critical to chain of innovations etc. SBIRI, BIPP and BIRAP promote R&D in the biotech industry and support high-risk pre-proof-of-concept research and late-stage developments in small and medium companies led by innovators with scientific backgrounds. DPRP promotes collaborative R&D in the pharmaceutical sector in emerging and challenging areas of research. Table 1 *shows a glimpse of nature of public funding in diabetology research in India.*

4. Issues and challenges in diabetology research in India

4.1. Research & innovation challenges

4.1.1. Quality of research

India's contribution to the global literature on diabetology has increased exponentially in last two decades which shows growing awareness among the researcher and clinical practitioner in this field. However, there is large-scale disparity among quantity and quality of research papers. The number of research papers with Indian affiliation in internationally acclaimed highest Impact Factor (IF) Journals such as *Diabetes Care, Diabetes, Diabetologia, Diabetic Medicine, Diabetes Research and Clinical Practices* are limited. Among top 30 journals where most Indian authors/institutions have contributed in the field of diabetology, only 4 journals out of 30 have an IF > 3 and it further reduced to 3 journals where the IF > 5. Concerning some of the articles contributed by Indian authors, only 13% belongs to journals with IF > 3 rest, 87% articles published in journals having IF < 3.

4.1.2. Performance of firms

Innovation indicators showed contrasting figures while assessing performances of Indian firms. Indian firms performed poorly in terms patenting activities. Among all the granted foreign patents registered in IPO, 90% belongs to foreign pharmaceutical firms, Indian firms shows dismissal trends with only 8 patents belongs to Indian firms among 70 granted patents. If we take a closer look at the patent filling trend from 2000 to 2016, only 38 patents in the pool of 492 registered patents belong to Indian assignees. However, the competence of Indian generic firms is evident with the dominance of Abbreviated New Drug Applications (ANDAs) filling at US-FDA in 2016, approx 34% of total approvals for the year [34]. One of the most interesting trends showed where major Indian firms such as Dr. Reddy's Research Foundation & Glenmark Pharma out-licensed their original molecules to foreign firms Novo Nordisk and Merck KGaA respectively. The Indian pharma companies are more active in in-licensing and out-licensing processes to build their portfolios rather than focusing on research and patenting activities.

4.1.3. Research in emerging areas

Both research publications and patent data revealed that the diagnostic sector received the least attention (5%) in terms of research and innovation in India. Diagnostic is the most important sector for controlling the epidemic by earlier detection and addressing the issue of affordability. Patenting trend showed that core pharmaceutical research and drug development are major sources of innovations worldwide while in India research focuses towards plant-based research, traditional and alternative medicines (55%) with maximum patentee by the individual inventors. Institutional support, motivation and effective policy direction requires to draw attention towards the development of new chemical entities or new biological entities. Traditional Knowledge-based industries also required institutional support for further development and global acceptance.

University and research organizations play a major role in the advancement of knowledge and research in niche areas such as nanotechnology, molecular biology and procedural innovation such as islet transplantation, islet encapsulation etc. Patent data shows some encouraging results with Indian patent holders with diverse research portfolio in frontier areas such as stem cells, proteomics, nanoparticle-based formulations, in-situ gelling drug delivery systems, non-invasive devices etc. However, research in advance areas account for only 7% compared to 12% in global patents. Just a few top-notch organizations are actively involved in such research.

4.2. Research finance and allied challenges

4.2.1. Private funding

The route of private investment has seen a lot of activities already mostly in the generic industries but it is relatively small ticket and specific to the biotech and other niche pharmaceutical molecules. India is a relatively new player in innovation market, it has not really taken off. Another challenge is the incubation period; private equity usually has a 4–7 year return period whereas in the drug discovery enterprise the return horizon is a minimum of 7 years. Thus, only late-stage drugs or drugs with lower risks of failure are likely to be invested in. This is particularly true of venture funds where investments are made in companies already generating some source of revenue. Hence, pure drug discovery firms are not as attractive to them. This might be the one biggest reason most pharma companies are taking in-licensing or out-licensing routes for revenue generation.

4.2.2. Public funding

All the major funding agencies, ministries and concerned departments in India supports diabetology research through institutional, intramural and extramural project financing to various research organizations, hospitals, universities etc. However, more than 60% respondents suggested that the funds are inadequate (Fig. 4). There are also handful projects sanctioned through innovative PPP schemes such as BIPP, NMITLI, SBIRI and DPRP mode on diabetology but the duration of the projects are mostly between 1 and 3 years or maximum 5 years. For research in strategic sectors such as biotechnology, drug development the amount of time is insufficient for drug development or major discovery.

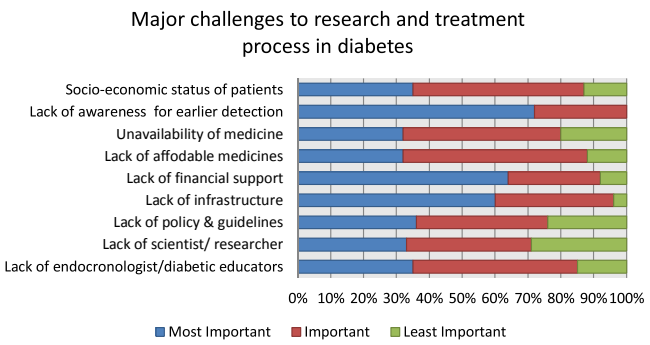


Fig. 4. Challenges in diabetology research and treatment of the disease.
Sources: Based on primary data collected through online survey & interview.

4.3. Institutional & regulatory challenges

Patenting is an important innovation indicator while both firms and institutions in India lack patenting capabilities. The patent office also faces structural problems in the form of lack of human resources (patent examiner, attorney) that delays patent grant. Lack of patent awareness and institutional support such as patent drafting, filing, prior art search, hinders researcher abilities to file and obtain a patent. However, only a few organizations such as CSIR, DBT, ICMR, IITs and JNU have an institutional arrangement of facilitation of patents in the country. The new IPR policy gave some policy direction to address these structural problems [35,36]. More than 65% respondents strongly agree that lack of financial support and sub-optimal infrastructure are biggest barriers to diabetology research and innovation in India. More than 60% respondents of view that, for development of diabetes management and research, India need to invest in human capitals inform of the increasing number of endocrinologists, diabetes educators and also basic science researcher and scientist.

Around 72% respondents strongly agreed that lack of earlier detection of diabetes is the major barrier to this epidemic, as the chronic stage is simply avoidable with timely intervention(Fig. 4). As per IDF, everyone in two adults with diabetes is undiagnosed [4]. WHO-Diabetes India Profile 2016 indicates that basic diagnostic technology such as blood glucose measurement, foot vibration perception by tuning fork is universally available in primary care unit but OGT test, HbA1test, Dilated fundus examination, foot vascular status by Doppler, Urine strips for glucose and ketone measurements are not easily accessible in primary care centers in the country [8]. Both research publication and patent data revealed that the diagnostic sector received the least attention (5%) in term of research and innovation in India.

The out of pocket expenditure on health in India is one of the highest in the world 67% in 2014. With lesser institutional support, affordability became an important issue for effective treatment of diabetes as it now spreading across the socio-economic strata. Interviewers mostly doctors & senior residents cautioned that the financial condition of the patient often make a decision making role while prescribing medicines/treatment procedure. An institutional mechanism such as WHO *List of Essential Medicine* [37] & National Pharmaceutical Pricing Authority through *National List of Essential Medicine* [38] helps to tackle the affordability issues. Section 21.4 of NLEM 2015 mentioned *Glimepiride, Insulin* (*Soluble, Regular, Intermediate*), *Metformin* in the list of essential medicine. However, exclusion of newer OADs (*DPP inhibitors, PPAR agonist, GLP analogue*) and insulin formulations (*long-acting*) could hamper the effective treatment procedures [38]. Availability of medicine is a challenging task in a resource-poor setting. On Indian context Insulin, Metformin, Sulphonylurea [8] are easily available in the primary health care centre's, however, other formulations are not available. This also affects the accessibility of medicine for the person with weaker socio-economic status.

5. Conclusion

The diabetology research does not occur in isolation. Any structural and institutional reform or blockages at periphery affects research capabilities. Primarily, health care system is patient-centric and the end point of any research should focus to achieve a promising new, affordable treatment that can be used with practical applications. In a resource-constrained country like India, challenges are in dual forms. On the one hand, the issues of affordability, accessibility and availability of treatment for the masses are challenging on the other, research & innovation requires constant financial and institutional support for maintaining optimum standards. There should be multilevel interventions for bridging the gap between knowledge and action. Diabetology research in India seems to have a promising future, However effective policy formulation, guidance, institutional and financial support could help to achieve excellence. Policy formulation needs to align with key policy principles of SDGs such as equity, affordability, universality, patient-centric quality care and pluralism [3]. Regulatory organization and policy-making bodies require vision for balancing resources and innovation capabilities

Limitation

Only two performance indicators (patent and publications) were taken into consideration in this study. But there are other players in diabetology research such as generic firms, CROs, firms and researcher in traditional, complementary or alternative medicine whose research outputs are different and their performances cannot be measured through above indicators, hence excluded from this study.

Authors contribution

Prof. Desai (Retd.) has contributed for the design of the work, interpretation of data for the work, drafting the work or revising it critically for important intellectual content and for final approval of the version to be published.

M.r Swarup Jena has contributed to the design of the work, acquisition, interpretation of data for the work, and analysis.

Mr. Brijesh Kumar Mishra has contributed to the acquisition.

Ms. Anamika Yadav has contributed to the acquisition and the analysis.

Conflicts of interest

We have no conflicts of interest to disclose.

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