Peptide-based Pharmaceuticals: How to Strengthen Generics and Invigorate Innovation Ecosystems to Make 'Self-reliant India'

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This article summarizes the presentation at the Industrial Leadership Conclave: The role of pharmaceutical Industry in the development of India since independence organized by the National Institute of Pharmaceutical Education and Research (NIPER), Mohali, which was sponsored by the Government of India, Department of Pharmaceuticals. The generic pharma industry of India, including peptides, is a major contributor to the world pharmaceutical economy and is considered the world's third largest by volume. Marching towards 100 years of independent India, it is time to reinvigorate innovation towards discovering novel drugs, self-reliant clinical development programs, and commercialization of innovative drugs. Peptide (smaller fragment of protein) therapeutics have continued to be an innovative strategy for the development of biopharmaceutical pipelines in the developed world, such as the USA. 'Peptide therapeutics' is still an untapped innovative area in India. This article covers (a) the status of biopharmaceuticals, including peptides in India, (b) paving the way from generic to innovative drugs and future directions for India, and (c) why peptide is an innovative approach to build a pipeline of patient-centric and first-in-class peptide-based drugs.

INTRODUCTION

The Status of Biopharmaceuticals in India

The increasing trend towards economics and biopharmaceutical assets in India is remarkable. Based on the published articles,[1-2] the generic pharma industry of India is considered the world's third-largest by volume. It has made a significant contribution to the world's pharmaceuticals economy. India is also the world's third-largest producer of recombinant Hepatitis B vaccine (a recombinant hepatitis B vaccine (GeneVac-B) manufactured by the Serum Institute of India, Pune. India supplies over 80% of the antiretroviral drugs used globally to combat AIDS.[1-3] The Indian biotechnology industry was valued at ~$64 billion in 2019 and is projected to reach~$150 billion by this decade.[2,3] India's domestic pharmaceutical industry includes a network of ~10,500 manufacturing units, ~3,000 drug companies,and ~5000 biotech companies.[3,4]

During the last decade, the Indian Government has taken initiatives and provided investment in building infrastructure for pharmaceutical development. For example, the Department of Pharmaceuticals of Government of India initiated a Production Linked Incentive (PLI) scheme to promote domestic manufacturing; and has taken many steps to reduce the cost of the drug production and cost of drugs to patients. Recently, the Government of India has set aside approximately $230 million for biotechnology R&D to set up nine biosafety level-3 (BSL-3) laboratories to advance biologics. State Governments such as Uttar Pradesh are also making a pitch for building a "bulk drug park" and a "medical device park" and investing in start-up India and make-in-India initiatives. All this funding support is to make India a hub for end-to-end drug manufacturing.[5]

Are these government initiatives and incentives good enough to make 'Atamnirbhar Bharat'? Is the R & D budget increase good enough to develop innovative drugs leading India to the 100th year of Independence? Given the innovations and initiatives, I believe India will surely boost and strengthen generic manufacturing for the short term but may not be sustainable for the long term to lead India to be self-reliant by its centennial.

Paving the Way from Generic to Innovative Drugs

The data from the United State's FDA and company members of the Pharmaceutical Research and Manufacturing Association (PRMA) reported

$83 billion for R & D expenses in 2019, including inflation cost, which is nine folds incremental increase from the 1980s and 1990s.[6] Drug approvals declined during the last four decades, despite steadily rising R&D spending over the preceding years. However, between 2015-2019 increased R&D spending resulted in increased new drug approval,[2] to which during this period, a large number of biologics were developed. The 'Atmanirbhar Bharat' resonates with innovative biotechnology and novel technologies assisting health care advancement.

Five vital disruptive technologies (Figure 1), in my opinion, could lead to self-reliant India - (1) Artificial Intelligence (AI) & Machine Learning (ML) both go hand in hand. For example, '*InVivo* AI', a Canadian startup developing a novel algorithm for drug discovery for central nervous system diseases; Peptilogic, Inc, a USA based start-up is designing computational algorithms for peptide-based drug design. (2) Precision Medicine: treating each patient as a unique individual, personalized medicine, neoantigen vaccine, e.g., The MEDi platform for rapid identification of tumor-specific antigens from the patient such as human leukocyte antigens. (3) Digital Therapeutics - non-pharmacological, tech-driven solutions as stand-alone or used in conjunction with medications and devices. For example, Dopavision, a German start-up, is making a smartphone-based digital therapeutic for myopia, eye treatment by activating dopamine. (4) Curative Therapeutics such as Cell Therapy. It is a paradigm shift in treating illnesses from managing diseases to curing diseases altogether. Mogrify Ltd., a British startup, is developing novel cell therapies for musculoskeletal, auto-immune, cancer immunotherapy and respiratory diseases. (5) Peptide Therapeutics is becoming an innovative strategy to develop novel drugs. Peptide Therapeutics is covered in detail in the subsequent sections.

PEPTIDE THERAPEUTICS OPPORTUNITIES

Why Peptide Therapeutics

Peptides are small fragments of proteins, a string of up to 40 amino acids. In recent years, peptides have received increased interest in pharmaceutical, food, cosmetics, and other fields. Therapeutics peptides are endogenous ligands that are efficacious and safe. Because of the safety and efficacy advantage, the attrition rate of biologics is very low. Out of 100 drugs entered into the clinical trials, 25% peptide-based make it to market, compared to only 13% small molecules because of their unpredictable safety profile.[7]

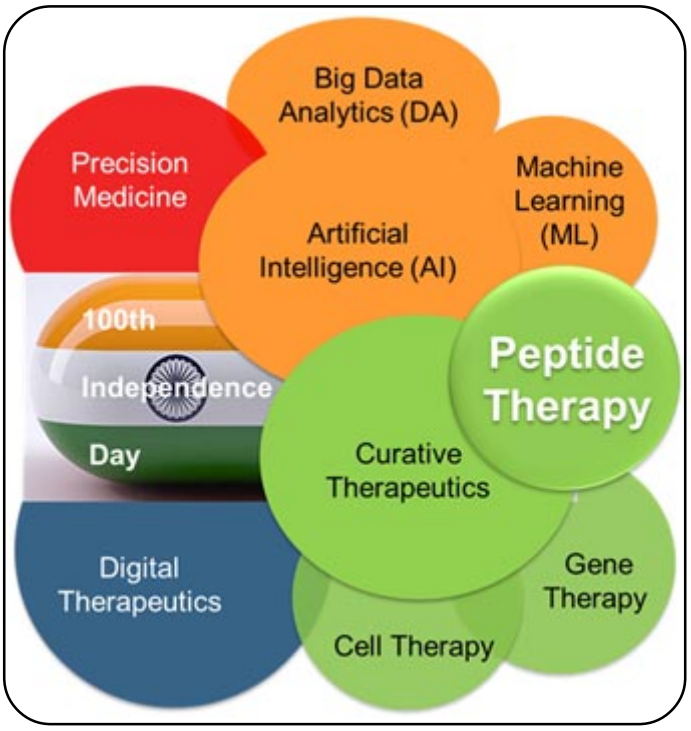

Figure 1- Future trends: disruptive technologies for self-reliant India.

During the last four decades, the discovery and development of peptide therapeutics have grown exponentially. More than one thousand peptide molecules are currently being studied for therapeutic indications in various disease areas, such as metabolic diseases, infectious diseases, cancer, and neurological disorders. More than 70 peptide drugs have been approved for marketing. More than 150 peptide molecules have entered into clinical trials for a wide variety of therapeutic indications, including metabolic, cardiovascular, oncology, and central nervous system diseases.[8] Most of the clinical and commercial successes of peptide therapeutics have been seen in metabolic diseases, and for peptide drugs acting on extracellular targets such as GPCRs, include the insulin analogs NovoLogs (insulin aspart). Some of the blockbuster drugs includes Humalogs (insulin lispro), Victozas (liraglutide), Byetta (exenatide), Luprons (leuprolide), Sandostatins (octreotide) and Forteo (teriparatide). The approved peptide-based drugs are listed in Table 1.

Peptide Discovery: The use of peptide therapeutics directed at intracellular targets such as transcription factors, kinases, and intracellular receptors, has been limited[9,10] due to challenges in investigating intracellular targets, target effectiveness /validation, and challenges in discovering and developing cell-penetrating peptides and understanding protein-protein interactions. Macrocyclic peptides have the ability to disrupt intracellular protein-protein interactions such targets are often considered 'undruggable.' The use of macrocyclic peptides opens new

Table 1. Approved Peptide Therapeutics (2020). The list is adopted from the book, Peptide Therapeutics: Strategy for Chemistry Manufacturing and Control (CMC)[10], Ed, Ved Srivastava, RSC, 2019.

Abeloparatide [2017]	Histrelin [1991]
ACTH [1-39] [1952]	Icatibant [2008]
ACTH [4-10] [2011], Russia	Lanreotide [2007]
Afamelanotide [2014]	Leuprolide [1984]
Alarelin, China	Linaclotide [2012]
Albuvitide [2018]	Liraglutide [2009]
Alloferon, Russia	Lisinopril [1987]
Angiotensin [1-7] [2017]	Lixisenatide [2013]
Atosiban [2000]	Lucinactant [2012]
Aviptadil [2000]	Lutathera [2018]
Bivalirudin [2000]	Macimorelin[2017]
Blenrep/Belantamabmafodotin [2020]	Mifamuritide [2009]
Bremelanotide [2019]	Nafarelin [1990]
Buserelin [1984]	Neogen, Russia
Calcitonin [human] [1986]	Nesiritide [2001]
Calcitonin [salmon] [1971]	NOV-002, Russia
Carbetocin [2001]	Octreotide [1988]
Carfilzomib [2012]	Ornithine vasopressin, Australia [1971]
Carperitide [1995]	Oxytocin [1962]
Cetrorelix [1999]	Pasireotide [2012]
Degarelix [2008]	Plecanatide [2017]
Desmopressin [1972]	Pramlintide [2005]
Detectnet/Gallium 68 PSMA-11 [2020]	Romiplostim [2008]
Dulaglutide [2014]	Scenesse [2019]
Elcatonin [1981]	Semaglutide [2017]
Eledoisin [1970s]	Setmelanotide/Imcivree [2020]
Enalapril [1985]	Somatostatin [1970s]
Enfuvirtide [2003]	Taltirelin [2000]
Eptifibatide [1998]	Teduglutide [2012]
Etelcalcetide [2016]	Teriparitide [2002]
Exenatide [2005]	Terlipressin [1978]
FAR-4043 [2010]	Tesamorelin [2010]
Felypressin [1970s]	Tetracosactide [1980]
Ganirelix [1999]	Thymodepressi, Russia
Glatiramer [1996]	Thymopentin [1985]
Glucagon [1989]	Thymosin-α_1 [2009]
GMDP, Russia	Triptorelin acetate [1986]
Golotimod, Russia	Triptorelin pamoate [2009]
Gonadorelin acetate [1989]	Vapreotide [2005]
Goserelin [1987]	Vasopressin [1962]

opportunities to address a range of human diseases such as cancer and cardiovascular disease.[11] While much progress has been made in developing peptide therapeutics over the past several decades, we still need to understand better (1) the pharmaceutical properties required for drug-like peptides, (2) the correlation of nonclinical PK/PD that can translate to humans, and (3) appropriate peptide delivery technologies.

Chemistry, Manufacturing, and Controls (CMC): Significant progress has been made toward the cost-effective manufacturing of the Drug Substance (DP or API) and Drug Products (DP).[12] There is a lack of clarity in Chemistry, Manufacturing and Controls (CMC) strategy, encompassing clinical development to commercialization. This could be one of the potential barriers to the development of novel peptide drugs. CMC can often become a rate-limiting step for peptide-based drugs owing to a deficiency in knowledge and a lack of formal policy or CMC guidelines. Despite several successes, specific regulatory challenges are often related to managing quality standards. These challenges are partly due to a lack of official regulatory guidelines for peptide drugs, as there are no current FDA or International Conference on Harmonization (ICH) guidelines that address the quality of pharmaceutical peptide products. Regulators frequently use a risk-based assessment on a case-by-case basis when reviewing NDAs (New Drug Applications) or ANDAs (Abbreviated New Drug Applications). The system for regulating medicines in Europe is unique in the world. It is based on a closely coordinated regulatory network of competent national authorities in the Member States of the European Economic Area (MS-EEA) working together with the European Medicines

Agency (EMA) and the European Commission.

Delivery Routes for Peptides Drug: Peptides are being delivered via invasive parenteral route; however, several non-invasive delivery routes such as nasal, buccal, transdermal, and pulmonary have been investigated, particularly for chronically administered drugs.[10,11,13]

Peptide drug molecules are generally not delivered orally because of their poor aqueous solubility and poor membrane permeability in the gastro-intestinal (GI) tract, leading to unacceptably low oral bioavailability. The oral route is a better option because of its patient-friendly delivery and increases the drug's therapeutic value. However, a few peptide drugs are approved for oral delivery, but they are intended for the GI restricted therapeutic targets, e.g., Vancomycin (Vancocin®), cyclic peptide, modified amino acids, 1449 Da, as gelatin capsule for Staphylococcus enterocolitis and Clostridium difficile-Associated Disease (CDAD), Staphylococcus enterocolitis. Fidaxomycin (Dificid®), macrolide compound, 1058 Da, as tablet for CDAD, Linaclotide (Linzess®), cyclic peptide, 1525 Da, as gelatin capsule for CIC and IBS-C. A few peptide drugs targeted for systemic delivery are currently marketed, e.g., Desmopressin (DDAVP®),1128 Da, as a tablet for central diabetes insipidus, nocturnal enuresis; Cyclosporine (Neoral®), 1202 Da, as self-emulsifying system, for organ transplant rejection and Taltirelin hydrate (Ceredist®) 477 Da, as orally dissolving tablets, for spinocerebellar degeneration. Several biotech and large pharma companies are investing in developing the technologies for oral delivery of peptides, and most recently Semaglutide, (RYBELSUS®), 4113 Da as tablets was approved by FDA for lowered blood sugar and body weight.

Implantable technologies can facilitate delivery of a controlled concentration of drug to a patient by controlling the rate of drug release.[13] There are three critical components of implantable drug delivery systems: (1) a highly potent drug payload (peptides), (2) a formulation providing long-term thermal stability to the payload, and (3) precisely controlled drug release mechanisms via zero-order kinetic release, or pulsatile. Significant progress has been made toward developing various implantable technologies to deliver drugs via intracranial, intrathecal, or intravaginal routes. However, the most promising developments have been in intraocular and subcutaneous implants. Some of these technologies have gained FDA approval in recent years. Research and development in this area continue to focus on the need for both implantable devices and in situ-forming implant technologies. These implantable technologies may contain therapeutic agents in nanomaterial formulations of non-bioabsorbable and biodegradable polymers.

PEPTIDE THERAPEUTICS IN INDIA

Why Peptide Therapeutics in India ?

Based on the 2017 Indian market report,[14] sales of peptides manufactured in India, including Heparin were approximately $380 million and expected to reach over $800 million by 2022. A Compound Annual Growth Rate (CAGR) of 15.0% was registered. India manufactures more than 30% of the generic peptide-based drugs, including Active Pharmaceutical Ingredients (API). Some of the peptide-based generic drugs include Insulin, Liraglutide, and Exenatide for Diabetes; Eptifibatide for infectious diseases; Leuprolide and Octreotide for prostate cancer; Bivalirudin and Glatiramer for cardiovascular (CV); and Forte and calcitonin for Osteoporosis; and Oxytocin for Uterine contraction.[15] India is the largest supplier of Oxytocin and Bivalirudin and is expected to register the highest- CAGR during this decade.

The key players in India for peptide-based drugs include Aurobindo, Biocon, Cadila, Cipla, Dr. Reddy, Natco Pharma, Neuland, SunPharma, USV, Wockhardt and Zydus. Hemmo Pharmaceuticals, the largest producer of oxytocin, recently acquired by Piramal Pharma Ltd. Neuland Ltd, is an expert in manufacturing of starting-material for peptide drugs and is believed to be one of the largest suppliers of Pseudoproline, an intermediate for complex peptide manufacturing. ISSAR Pharma (now Cadila), to my knowledge, was India's first-ever company to conduct Phase-1 clinical trials and launch the first-ever indigenous peptide drug, Melgain for the treatment of Vitiligo, a skin disorder that causes the skin to lose its color, in 2004. ISSAR has patented novel formulation for a few other drugs, e.g., Xylentra® contains an active drug substance called Genopep®, a 23 amino acid peptide, and Novoskin (10 aa), a Basic Fibroblast Growth Factor (BFGF) as topical formulation.[16,17]

The patent expiry of blockbuster prescription drugs will provide additional growth to India. More than 70 peptide-based drugs are on the market worldwide, and more prescription-based peptide drugs may soon become generic due to potential patent expiry, such as Byetta or Victoza.

HOW TO BUILD INNOVATIVE PEPTIDE PIPELINES IN INDIA

India has the capabilities, capacity, infrastructure, know-how, and technical expertise to strengthen and expand the generic peptide drugs and API

manufacturing to enhance its revenue. With 25% of the revenue earned and supplemented by the Government initiative, now it is the time to leverage these assets to develop India's own innovative peptide drugs and build a self-reliant India by its centennial.

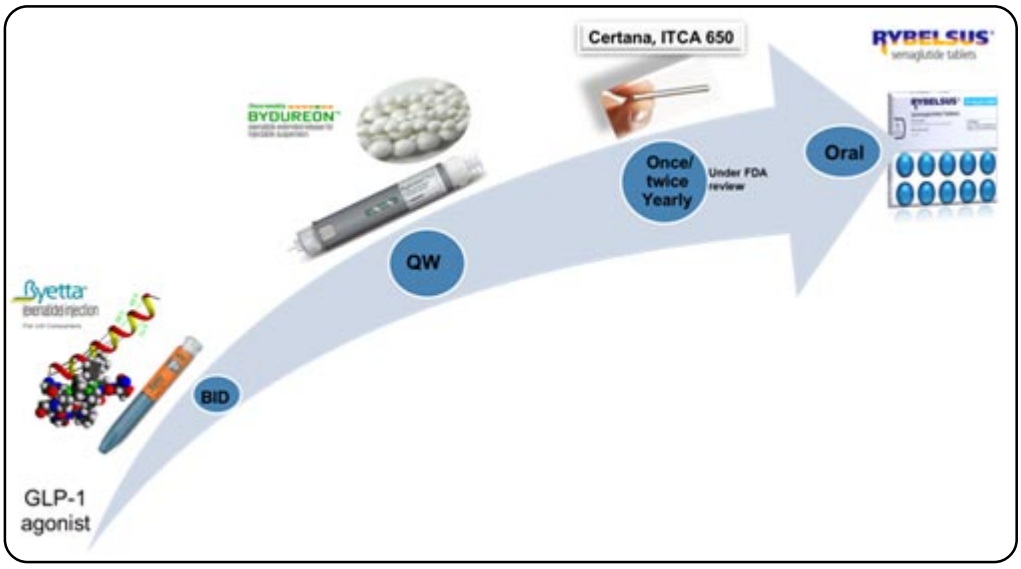

Figure 3. GLP-1 agonists form twice-a-day (BID) injection to oral delivery via innovative formulation. The logo images of the drugs taken from their website.

Strategy and Technology

One of the approaches to build innovative peptide pipelines in India could be as illustrated in Figure 2. The horizontal scale represents the Risk and Revenue, and the vertical scale represents Reward and Self-reliant. There could be three phases to progression path for a self-reliant India (a) during the next five years, India continues to develop cost-effective production, increase larger-scale production of Generic peptides by volume,expand generic peptides or API products beyond the current pipeline. It is a low risk and rewarding effort, (b) in the second phase of five years, develop novel formulations of the currently marketed generic peptide drugs for alternative delivery such as nanoparticle-based delivery or oral delivery. For example, formulation-based new innovative products of Exenatide, as life cycle management, illustrated in Figure 3, and (c) in a third phase of five years, India should take a leadership role in innovative, first-in-class commercialization peptide-based drugs using disruptive technologies. This ultimate phase would lead to a high risk, high reward, and high revenue value. These three phases mentioned above could be executed sequentially or as staggered to ram up towards self-reliant India by centennial. Of course, it requires aggressive efforts and time to make a self-reliant India in the prescription of peptide-based medicine.

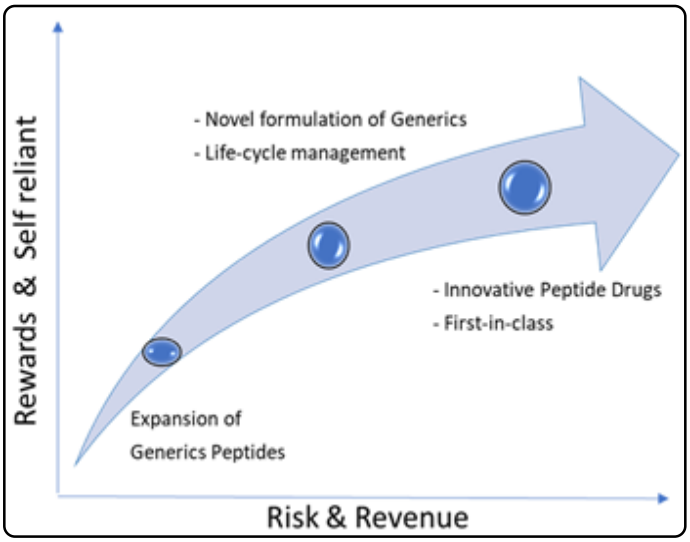

Figure 2. Progression path of peptide drugs development towards revenue and self-reliant India.

Manufacturing Advantage

The number of peptide drugs entering the clinical trial has increased exponentially during the last four decades. The market size of peptide drugs, especially APIs, has increased significantly. A few decades ago, marketed peptide drugs were smaller in length, mostly 10 amino acid sequences, but they are more than 30 or 40 amino acids in length in the current decade. We now have state-of-the-art techniques for the pharmaceutical characterization of larger peptide sequences and better manufacturing technology on kilogram scales. Based on my personal experience in the current decade, the cost for a 30 to 40 amino acid peptide sequence on 10 kilogram/batch is USD ~$600/gram compared to $2,000/gram in the 1990s.

Technical Expertise

In addition to technologies, building innovative peptide pipelines in India requires a transformation of scientific talent from peptide manufacturing toward sinnovative peptide drug discovery to make India more self-reliant.

Based on the membership of the Indian Peptide Society,[18] India has more than 300 researchers engaged in peptide science in academic institutions such as AIIMS, NIPER, ICGB, JNU, IIT, IISc, and Biotech organizations. We need to reinvigorate them by advanced training or motivate them towards application-based and patient-centric research and innovation of drug development. In my opinion, Academia prefers publications; individuals prefer discoveries but are

bound by the expectations of long-standing elitism created by the Academic industry. Academic scientists need to transform themself from a publication mindset to a patent mindset. Patents filed in Biotech subject matter by Indian residents' biotech scientists are only 30%, whereas non-resident Indian biotech scientists are 70%.[19]

Transform Talent

India's NIPER institutions have prepared their students to be a part of the state-of-the-art technologies in peptides, computer-aided drug design, and pharmaceutical sciences. The institution has transferred or licensed its technologies to drug manufacturers and secured several patents. The students' alumni have been recognized with prestigious Awards such as Thomson Reuters Innovation Awards.

In 2019, approximately 590 students graduated from all the seven NIPER Institutions with a major in Pharmaceutical Sciences.[20] Today it is fair to ask what percentage of these 2019 graduates from all the NIPERs are continuing or furthering their career towards innovative drugs discovery. If more than 50% of them retain their passion for drug discovery and development within India's Pharmaceutical Industry, it is a reasonable talent 'brain grain'. Institutions need to encourage students further the importance of professional development with cutting-edge science and to invest in self-management, communication (written and verbal), and leadership skills. It is the right time for all the NIPER students to make a global impact and stay the course every day when they come to the campus. A similar concept could be applied to other educational institutions within India.

Filling the Gap in Biotechnology

While India fosters the talents of students and cultivate their skills to further contribute to the scientific community around the world, it is time to expand the innovation scope, leverage veteran expertise and experience to fill the gap of innovative technologies or/and leadership within India. Like any other information technology (IT) or telecommunication sector, it is time for the biotechnology sector to aggressively engage Indian scientific experts settled abroad as Scientific Advisors.

Knowledgebase Resources

There is an abundance of information on peptide-based therapeutics and understanding the technology that will help to build the necessary basic knowledge to become innovative. Most recent books on peptide-based therapeutics[9-13] are excellent resources for starting or advancing peptide therapeutics in India. Collectively, these books provide (a)holistic story from molecules to medicine, combining the themes of design, synthesis, biomarkers, and clinical applications of peptide-based therapeutics, (b) regulatory process both in America and Europe, and guidelines including immunogenicity evaluation strategy, (c) the manufacturing process, and quality control strategy, novel techniques for characterization of peptide impurities and stability testing, and (d) peptide formulation, nanoparticles, peptide drug delivery (including a major emphasis on implantable drugs delivery for chronic diseases).

CONCLUSION

The Atmanirbhar Bharat resonates with advancing bio-innovation in biotechnology/peptides therapeutics as one of the avenues. The generic pharma industry, including peptides in India, is considered as the world's third largest by volume. The transformation from Generic to Innovative drugs in India includes adopting new technologies, fostering pharmaceutical talents, and filling the gap in the technology by levering peptide expertise beyond India. The peptide-based innovation could start with the innovative formulation of the current generic peptide drug to a patient-centric and patient-friendly peptide drug delivery. For example, as illustrated in Figure 3, Exendin-4 (Byetta™), a GLP-1 agonist was developed as a twice-a-day injection, it was followed by the development of Bydureon™ (once-a-week injection), and then the Certain™, (ITCA-650) (once or twice-a-year implant), still under FDA review. In 2021, Rybelsus,™ GLP-1 analogs, was approved asan oral tablet(once-a-day). These are great examples of life cycle management of a peptide-based molecule for Type 2 Diabetes treatment. The Government of India's initiatives and investments to strengthen cost-effective generics and biosimilars are admirable[6] and provide encouragement to innovative drugs and enhancing manufacturing of APIs.

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