IJPSR (2026), Volume 17, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 July 2025; received in revised form, 08 October 2025; accepted, 10 October 2025; published 01 February 2026

ELUCIDATION OF PATENTABILITY CONSIDERATIONS FOR SGLT-2 AND DPP-4 INHIBITOR ANTI-DIABETIC DRUG PRODUCTS IN INDIA *VIS-À-VIS* USA

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Keywords:

Drug product, Type 2 diabetes mellitus, Improve glycemic control, Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, Dipeptidyl peptidase 4 (DPP-4) inhibitors, Patent, Patentability, Invention

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ABSTRACT: Increasing number of Diabetes mellitus (DM) has become a global public health concern. There are several drug products approved by USFDA and regulatory agency of India for the effective treatment of diabetes mellitus. Subsequently, innovator companies, applied for Patent protection with various primary and secondary attributes of the drug product. Through this Exploratory Research, we precisely investigated drug products which are SGLT-2 and DPP-4 inhibitors by mechanism, and for which the innovator failed to secure grant of patent in India for secondary inventions such as for salt of a compound, crystalline polymorph, combination of drug products, because of objections raised by Controller in view of provisions in Indian Patent Act such as Section 2(1) (j) or (ja), Section 3. On the other hand, innovator could successfully obtain patent grant for corresponding family equivalent patent in the USA despite of objections under USC (102), (103). During our exploratory research, it is observed that the technical advancements and surprising effect which were admissible and considered by the USPTO, was not "Weighed equally" by India patent office in order to justify "enhanced efficacy" or "synergistic effect" of the drug product. It should also to be noted that there is no explicit guidance in the India Patent Act to define consideration limits and acceptance criteria for data with 'Enhanced efficacy' or "Synergistic effect". Hence, there is a need of harmonization of certain provisions of Indian Patent Act with expanded view for considerations of scientific evidence, while evaluating patentability (Novelty and inventive step) for pharmaceutical products.

INTRODUCTION: Diabetes or Diabetes mellitus (DM) is a group of metabolic diseases distinguished by hyperglycemia resulting from defects in insulin secretion or insulin action. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and multiple organ failure, particularly the eyes, kidneys, nerves, heart, and blood vessels [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.17(2).550-71

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(2).550-71

The incidence of T1D is increasing worldwide, with significant geographic and ethnic variations. The Type 1 diabetes (T1D) is an autoimmune disease leading to destruction of insulin-producing pancreatic beta cells [2].

Similarly, Type 2 diabetes (T2D) mellitus (previously called non-insulin-dependent diabetes) is a condition that results in the abnormal metabolism of carbohydrates, lipids and proteins, which is linked to insulin resistance and the defective insulin secretion. Insulin resistance is the main factor in development of the disease and in the occurrence of the complications of diabetes [3]. The diabetes mellitus type 2 (T2DM) is a condition that depicts both progressive β-cell dysfunction and

peripheral insulin resistance. Continued hyperglycemia can cause more deterioration of β-cell dysfunction and aggravate the insulin resistance. In conjunction, T2DM patients are mostly obese and have some other cardiovascular risk factors, such as hyper tension and dyslipidemia [4]. The treatment of type 2 diabetes (T2DM) is still challenging with a significant portion of patients being unsuccessful in achieving and/or maintaining glycemic targets. Although many types of oral antidiabetic drugs are available, the therapeutic efficacy is diminished by side effects such as weight gain and hypoglycemia. Hence, the continuous search for new therapeutic agents with a better benefit-risk profile goes on. Reportedly, the focus of recent studies has shifted to the kidney as the prime therapeutic target, more so because maximal renal glucose reabsorption is raised in T2DM [4].

In general, the treatment consisting of glucose-lowering agents is correlated with the lack of efficiency over the period of time, which is the consequence of progressive β-cell dysfunction. Therefore, there is a continuous demand for new good-tolerated products, that can be used at any stage of the disease. Aiming at a process, which is not related to β-cell function, would be more desirable, as it would interrupt the vicious circle of the continuous glucotoxicity [4]. In recent time the newer classes of drugs used for treatment for T2DM are as following i) Alpha glucosidase inhibitor, ii) Amylin agonists, iii) In cretin mimetics [glucagon-like peptide-1 (GLP-1) receptor agonists and Dipeptidyl peptidase 4 (DPP-4) inhibitors] and iv) sodium-glucose cotransporter 2 (SGLT2) antagonists/ inhibitors [5].

Reportedly, the recent research approaches have been based on receptors targeting, islet cell transplantation, gene expression profiling, glucagon-like peptide-1, dipeptidyl peptidase IV inhibitors, insulin therapy, modulators of peroxisome proliferator-activated receptors (PPAR), glucagon receptor antagonists, insulin analogues, sensitizers and combination therapies, and identifying new anti-diabetic regimens with novel mechanism of action are being developed [6]. Evidently, there is a considerable research and innovation happening across the globe for the effective treatment of diabetes mellitus.

The researchers are continuously developing new scaffolds and active moieties to develop next generation antidiabetic drug substances. Similarly, the drugs products are also been tested for stable formulations, effectiveness against additional indications, chemically stable salts and so on. Hence, at the same time there is need to provide adequate techno-legal protection to such inventions, for example PATENT rights.

The effective Patent protection not only encourage the innovations but also triggers the higher investments by companies into the research. The patent protection is a territorial right given by the respective patent office of the country to the inventors. The patentability of the subject matter is governed by the enacted Patent Act of the respective country. For instance, we shall refer to the patentability considerations in India vis-à-vis USA for the SGLT-2 and DPP-4 inhibitor anti-diabetic drug products related inventions.

Patentability in India: In general, a patent is granted for an invention, and the person seeking patent protection has to establish in the patent office that the subject matter on which he seeks protection is an invention. There is a considerable difference between invention in the eyes of a scientist and in the eyes of law (Patent Law). Accordingly, in order to secure a patent protection, an invention must fulfil the patentability criteria as per the requirements of the Patents Act [7]. In India, the patent applications and patents are being evaluated, tested and govern by certain provisions of The Patents Act, 1970. As a primary requisite, an applicant for patent protection has to meet the three basic substantive requirements of patent law:

New Invention/Novelty: a product or process on which protection is sought must not be published or available in prior art of the country or elsewhere in the world before the date of patent filing.

Inventive Step: Invention which can be done by any ordinary skilled person is obvious and cannot be patentable.

Capable of Industrial Application/ Usefulness: invention must be capable of being made or used in an industry [7]. The Patents ACT, 1970 (of India) defines as under Section 2 (1) (j), "invention" means a new product or process involving an

inventive step and capable of industrial application; and as under Section 2 (1) (ja), "inventive step" means a feature of an invention that involves technical advancement as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art [8]. There is one more critical and most debated provision in The Patents ACT, 1970 of India, is the Section (3); that defines Inventions Not Patentable in India. The Section 3 summarizes 'What are not inventions' despite it qualifies the basic patentability criteria in India. One of the crucial subsection is Section 3 (d) of the India patent act that defined as: "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. (Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy) [9].

Patentability in the USA: According to the United States Patent and Trademark office (USPTO) guidance, the US patent gives, the inventor, the right to "exclude others from making, using, offering for sale, or selling" an invention or "importing" it into the US. Also, a plant patent gives you additional rights on the "parts" of plants (e.g., a plant patent on an apple variety would include rights on the apples from the plant variety). The guidance further depicts that, what is granted is not the right to make, use, offer for sale, sell or import the invention, but the right to stop others from doing so. The US patents are effective only within the US and its territories and possessions in the USA, hence if someone infringes on your patent, you may initiate legal action [10]. In the USA, legally, a utility patent may cover "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." A design patent may cover "any new, original, and ornamental design for an article of manufacture," and a plant patent may cover a "distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber-propagated plant or a plant found in an uncultivated state," invented. So, for a patent to be issued, your invention must meet three conditions: Able to be used (the invention must work and cannot just be a theory) A clear description of how to make and use the invention; New or "Novel" (something not done before); "Not obvious," as related to a change to something already invented [11]. According to Manual of Patent Examining Procedure (MPEP) and United States Code Title 35 – Patents Consolidated Patent Laws; defines: 35 U.S.C. 101 Inventions patentable: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful provement thereof, may obtain a patent there for, subject to the conditions and requirements of this title; 35 U.S.C. 102 Conditions for patentability: Novelty: A person shall be entitled to a patent unless the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; and 35 U.S.C. 103 Conditions for patentability: non-obvious subject matter: A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made [11].

MATERIALS AND METHOD: For the purpose of present research and investigations, we have studied the various approved drugs products effective for the treatment of diabetes mellitus; precisely the drug products which are Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and Dipeptidyl peptidase 4 (DPP-4) inhibitors. The instant investigation further focused on elucidation of patentability considerations for said SGLT-2 and DPP-4 inhibitor Anti-diabetic drug products in India *vis-à-vis* USA. For the purpose, we complied

the patent information for some representative drug products approved by United States Food and Drug Administration (USFDA) as well as approved by FDA India. Subsequently, we investigated the patent scenario wherein we highlighted that certain patent application were granted by the USPTO however rejected / refused by India patent Act. In particular, we analyzed the difference in Novelty and inventive step considerations by different jurisdictions in parallel such as India and USA, considering pharmaceutical product at center. Accordingly, we refer to the drug approval data published on USFDA databases such as The Center for Drug Evaluation and Research (CDER); Drugs@FDA: FDA-Approved Drugs and Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Similarly, the relevant patent(s), patent application(s) and its family equivalent searches performed using patent office official websites such as INPASS (Indian Patent Advanced Search System) by Patent office India; and the web-based Patent Public Search tool by United States Patent and Trademark Office. The patent prosecution history of the respective patent application also investigated using the corresponding patent office public databases.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors: Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are antihyperglycemic agents, and by mechanism acting on the SGLT-2 proteins expressed in the proximal convoluted tubules (PCT) [12], Sodium-glucose co-transporter-2 (SGLT2) inhibitors are considerably the new and improved class of oral antihyperglycemic agents that have been approved for the treatment of diabetes mellitus. SGLT2 inhibitors are medications that have a unique mechanism of action and that lower glucose independent of insulin [13].

There are several anti-diabetic drugs which are approved by U.S. Food and Drug Administration, consisting of SGLT-2 inhibitor as active ingredients, for example, Dapagliflozin (Farxiga®), Canagliflozin (Invokana®), Sotagliflozin (Inpefa®), Empagliflozin (Jardiance®), Ertugliflozin (Steglatro®), Bexagliflozin (Brenzavvy®) And the like. Evidently, by inhibiting SGLT2, the Dapagliflozin and Empagliflozin reduces reabsorption of filtered glucose and thereby promotes urinary glucose excretion and increases the delivery of sodium to the distal tubule [14, 15]. This may influence several physiological functions including, but not restricted to, lowering both pre- and after load of the heart and down-regulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback [14, 15]. This may influence several physiological functions including, but not restricted to, increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and after load of the heart and downregulating sympathetic activity [15]. Similarly, the Canagliflozin and Ertugliflozin inhibiting SGLT2, reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion (UGE) [16, 17]. Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure [16].

Another active ingredient, Sotagliflozin is an inhibitor of SGLT2 and SGLT1. Inhibiting SGLT2 reduces renal reabsorption of glucose and sodium which may influence several physiological functions such as lowering both pre-and afterload of the heart and downregulating sympathetic activity. Inhibiting SGLT1 reduces intestinal absorption of glucose and sodium which likely contributes to diarrhoea [18]. Similarly, Bexagliflozin is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorption of the majority of glucose from the renal glomerular filtrate in the renal proximal tubule. By inhibiting SGLT2, Bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose and thereby increases urinary glucose excretion [19].

Farxiga® (Dapagliflozin): The Product Farxiga® (Dapagliflozin) tablets, for oral use having initial U.S. Approval in 2014. The Active ingredient 'Dapagliflozin' is an inhibitor of SGLT2, is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro3-[(4-ethoxyphenyl) methyl] phenyl]-, (1S), compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The structural formula of Dapagliflozin is as depicted below [14]:

FIG. 1: FARXIGA® (DAPAGLIFLOZIN)

Farxiga® (Dapagliflozin) is indicated for: (i) to reduce the risk of sustained eGFR deslins, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression; (ii) to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure; (iii) to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors; (iv) as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus [14]. Farxiga® (Dapagliflozin) is available as a film-coated tablet for oral administration containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol, and several other inactive ingredients [14]. It is marketed as Bottles of 30 Tablets as depicted herein above.

Below Tablet-1 summarizes the list of US patents and patent applications relevant for the drug product FARXIGA® (Dapagliflozin) [20], and its family equivalent patent in India. The Tablet-1 further provides the legal status andoutcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 1: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT FARXIGA® (DAPAGLIFLOZIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
C-aryl glucoside SGLT2 inhibitors and method	Dapagliflozin Compound generically	US 6,414,126 Patent Granted	IN 205147 Patent Granted
C-aryl glucoside SGLT2 inhibitors and method	Dapagliflozin Compound Specifically	US 6,515,117 Patent Granted	IN 235625 IN 269610 Patent Granted
Pharmaceutical formulations containing an SGLT2 inhibitor	Immediate release composition comprising Dapagliflozin propylene glycol hydrate	US 7,851,502 US 8,221,786 US 8,361,972 US 8,716,251 Patent Granted	IN 291392 Patent Granted
Crystal structures of SGLT2 inhibitors and processes for preparing same	Crystalline Dapagliflozin propylene glycol solvates	US 7,919,598 US 8,501,698 Patent Granted	IN10757/DELNP/2008 Abandoned
Methods for treating extreme insulin resistance in patients resistant to previous treatment with other anti-diabetic drugs employing an SGLT2 inhibitor and compositions thereof	Indication 1: Methods for treating type 2 diabetes	US 8,685,934 Patent Granted	No India family equivalent found

Methods of treating heart failure with reduced ejection fraction	Indication 2: A method of reducing the rate of cardiovascular death and worsening heart **failure** in a patient with heart failure with reduced ejection fraction	US 10,973,836 US 11,903,955 Patent Granted	No India family equivalent found
Methods of treating heart failure with preserved ejection fraction employing dapagliflozin and compositions comprising the same	Indication 3:A method for treating heart failure with preserved ejection fraction	US 11,826,376 Patent Granted	No India family equivalent found
Methods of treating chronic kidney disease with dapagliflozin	Indication 4: Method for treating chronic kidney disease	US 12,21,3988 Patent Granted	No India family equivalent found
Polymer-based sustained release device	A sustained release composition of biologically active polypeptide consisting of a biocompatible polymer	US 7,456,254 US 8,431,685 US 8,461,105 Patent Granted	IN 264309 Patent Granted
Methods for treating diabetes and reducing body weight	A method for reducing body weight comprising exendin peptide	US8329648 US8906851 Patent Granted	No India family equivalent found

Jardiance® (Empagliflozin): The product Jardiance® (Empagliflozin) tablets, for oral use having initial U.S. Approval: 2014. The Active ingredient 'Empagliflozin' is an inhibitor of the SGLT2 [15]. The chemical name of empagliflozin is D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl) oxy] phenyl] methyl] phenyl]-(1S). The structural formula of Empagliflozin is as depicted below [15]:

FIG. 2: JARDIANCE® (EMPAGLIFLOZIN)

Jardiance® (Empagliflozin) is indicated for: (i) to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, (ii) to reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression, (iii) to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease, (iv) as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus [15]. Each film-coated tablet of Jardiance® contains 10 mg or 25 rng of empagliflozin (free base) and other inactive ingredients [15]. It is marketed as Bottles of 30 and 90 Tablets as depicted herein above. Below Tablet-2 summarizes the list of US patents and patent applications relevant for the drug product Jardiance® (Empagliflozin) [23], and its family equivalent patent in India. The Tablet-2 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 2: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT JARDIANCE® (EMPAGLIFLOZIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Glucopyranosyl-substituted phenyl derivatives	Empagliflozin Compound	US 7,579,449 Patent Granted	IN268846 Patent Granted
Crystalline form of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene	Crystalline polymorph	US 7,713,938 Patent Granted	IN 7213/DELNP/2007 Patent application objected, under opposition
Pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivate	Combination of Empagliflozin and Linagliptin	US 8,551,957 Patent Granted	IN1006/DELNP/2010Patent application Refused
Pharmaceutical composition, methods for treating and uses thereof	A method to reduce the risk of cardiovascular death in a patient with type 2 diabetes mellitus	US 9,949,997 Patent Granted	No India family equivalent found
Pharmaceutical composition, methods for treating and uses thereof	A method for improving glycemic control in a patient with type 2 diabetes mellitus	US 10,258,637 Patent Granted	No India family equivalent found
Pharmaceutical composition, methods for treating and uses thereof	A method of treating, reducing the risk of, delaying the occurrence of and/or delaying the progression of chronic kidney disease	US 11,666,590 Patent Granted	No India family equivalent found
Pharmaceutical composition, methods for treating and uses thereof	Method for slowing the progression of, delaying or treating a metabolic disorder comprising administering combination of SGLT2 inhibitor, a DPP IV inhibitor and a third antidiabetic agent	US 12,115,179 Patent Granted	IN 320937 Patent Granted
Pharmaceutical composition, methods for treating and uses thereof	A method for reducing the risk of cardiovascular death in a patient with chronic kidney disease	US 12,263,153 Patent Granted	No India family equivalent found

Invokana® (Canagliflozin): The product Invokana® (Canagliflozin) tablets, for oral use having initial U.S. Approval: 2013. The active ingredient 'Canagliflozin' is an inhibitor of SGLT2, the transporter responsible for reabsorbing the majority of glucose filtered by the kidney [16]. Canagliflozin, the active ingredient of Invokana®, is chemically known as (1S)-1, 5-anhydro-1-[3-[[5-(4- fluorophenyl)-2-thienyl] methyl]-4-methylphenyl]-D-glucitol hemihydrate. The structural formula for Canagliflozin is as depicted below [16]:

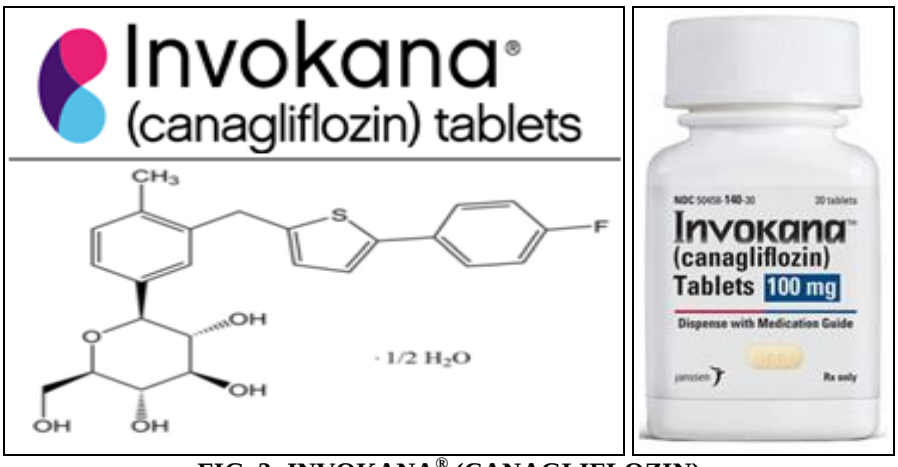

FIG. 3: INVOKANA® (CANAGLIFLOZIN)

Invokana® (Canagliflozin) is indicated for: (i) as an adjunct to diet and exercise to improve glycemic control in adults and paediatric patients aged 10 years and older with type 2 diabetes mellitus; (ii) to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular

disease (CVD); (iii) to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day [16]. Invokana® is supplied as film-coated tablets for oral administration, containing 102 and 306 mg of Canagliflozin in each tablet strength, corresponding to 100 mg and 300 mg of Canagliflozin (anhydrous), respectively. It is marketed as Bottles of 30, 90 and 500 Tablets as depicted herein above[16]. Below Tablet-3 summarizes the list of US patents and patent applications relevant for the drug product Invokana® (Canagliflozin) [24], and its family equivalent patent in India. The Tablet-3 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 3: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT INVOKANA® (CANAGLIFLOZIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Glucopyranoside compound	Canagliflozin compound	US 7,943,788 Patent Granted	IN232231 Patent Granted
Crystalline form of 1-(β-D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2- thienylmethyl] benzene hemihydrate	Crystalline polymorph hemihydrate	US 7,943,582 Patent Granted	IN 286412 Claims amended to process IN 2536/CHENP/2015 Patent application Refused
Pharmaceutical formulations	Tablet formulation of Canagliflozin	US 10,617,668 Patent Granted	IN 10381/DELNP2012 Patent application Refused

Steglatro® (Ertugliflozin): The product Steglatro® (Ertugliflozin) tablets, for oral use having initial U.S. Approval: 2017 [17]. The Active ingredient 'Ertugliflozin' is known as Ertugliflozin L-Pyroglutamic Acid of chemical name, as (1S, 2S, 3S, 4R, 5S)-5-(4-chloro-3-(4- ethoxybenzyl) phenyl)-1-(hydroxymethyl)-6, 8-dioxabicyclo [3.2.1] octane-2,3,4-triol, compound with (2S)-5-oxopyrrolidine-2-carboxylic acid. The chemical structure is as depicted below [17].

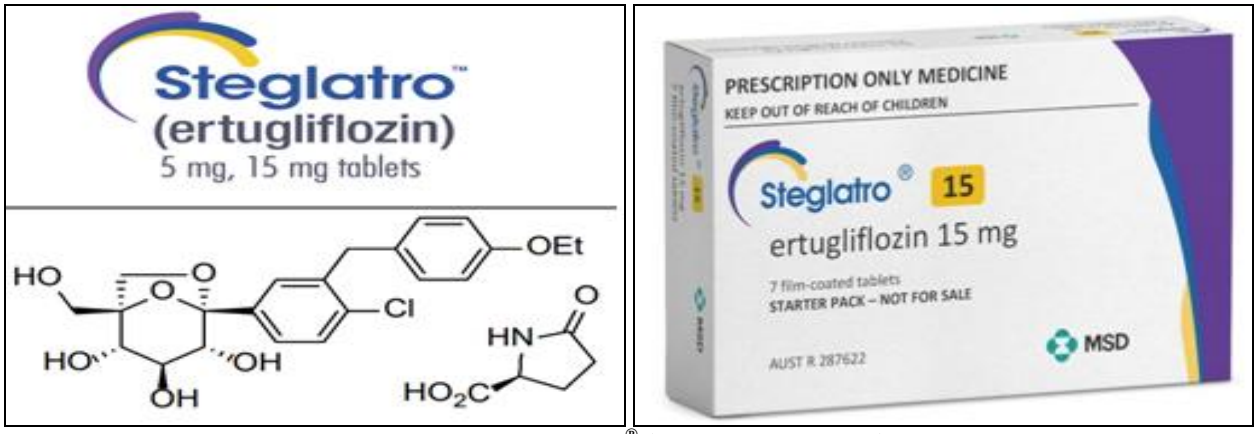

FIG. 4: STEGLATRO® (ERTUGLIFLOZIN)

Steglatro® (Ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [17]. Steglatro® (ertugliflozin) tablets for oral use contain ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor. Steglatro is supplied as film-coated tablets, containing 6.48 or 19.43 mg of Ertugliflozin L-pyroglutamic acid, which is equivalent to 5 and 15 mg of Ertugliflozin. It is marketed as Bottles of 30 and 90 Tablets as depicted herein above [17]. Below Tablet-4 summarizes the list of US patents and patent applications relevant for the drug product steglatro® (Ertugliflozin) [25], and its family equivalent patent in India. The Tablet-4 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 4: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT STEGLATRO® (ERTUGLIFLOZIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives	Ertugliflozin compound	US 8,080,580 Patent Granted	IN 331468 Patent Granted

Inpefa® (Sotagliflozin): The product INPEFA® (Sotagliflozin) tablets, for oral use having initial U.S. Approval: 2023. INPEFA® (Sotagliflozin) tablets for oral administration contain Sotagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor. The chemical name of Sotagliflozin is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)- 6-(methylthio) tetrahydro-2H-pyran-3,4,5-triol. The structural formula of Sotagliflozin is as depicted herein below [18]:

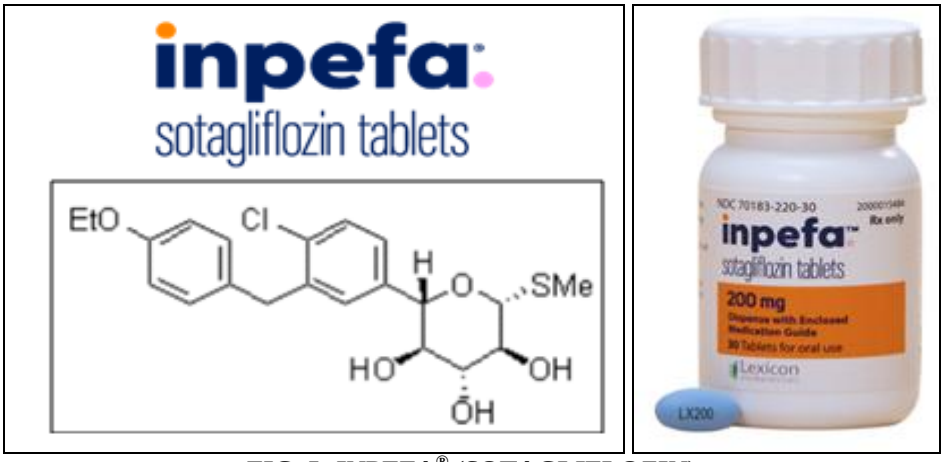

FIG. 5: INPEFA® (SOTAGLIFLOZIN)

Inpefa® (Sotagliflozin) is indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with: (i) heart failure or (ii) type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors [18]. Each film-coated tablet of INPEFA® (Sotagliflozin) contains 200 mg or 400 mg of Sotagliflozin and other inactive ingredients. It is marketed as Bottles of 30 and Tablets as depicted herein above [18].

Below Tablet-5 summarizes the list of US patents and patent applications relevant for the drug product Inpefa® (Sotagliflozin) [26], and its family equivalent patent in India. The Tablet-5 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 5: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT INPEFA® (SOTAGLIFLOZIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Inhibitors of sodium glucose co-transporter 2 and methods of their use	Sotagliflozin compound	US 7,781,577 Patent Granted	IN258913 Patent Granted
Solid forms of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol and methods of their use	Polymorph crystalline form	US 8,217,156 Patent Granted	IN 504/DELNP/2011 Patent application Refused
Compounds and methods for treating or preventing cardiovascular diseases and conditions	A method of reducing the risk of cardiovascular death in a patient at risk of cardiovascular death	US2022370485 A1 Patent application under examination	No India family equivalent found

Brenzavvy® (Bexagliflozin): The product Brenzavvy® (Bexagliflozin) tablets, for oral use having initial U.S. Approval: 2023 [19]. The Brenzavvy® (Bexagliflozin) tablets for oral use

contain Bexagliflozin, an SGLT2 inhibitor. The chemical name of Bexagliflozin is (2S, 3R, 4R, 5S, 6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy) benzyl) phenyl)- 6-(hydroxymethyl) tetrahydro-2H-pyran-3, 4, 5-triol. Structural formula of Bexagliflozin is as depicted below [19]:

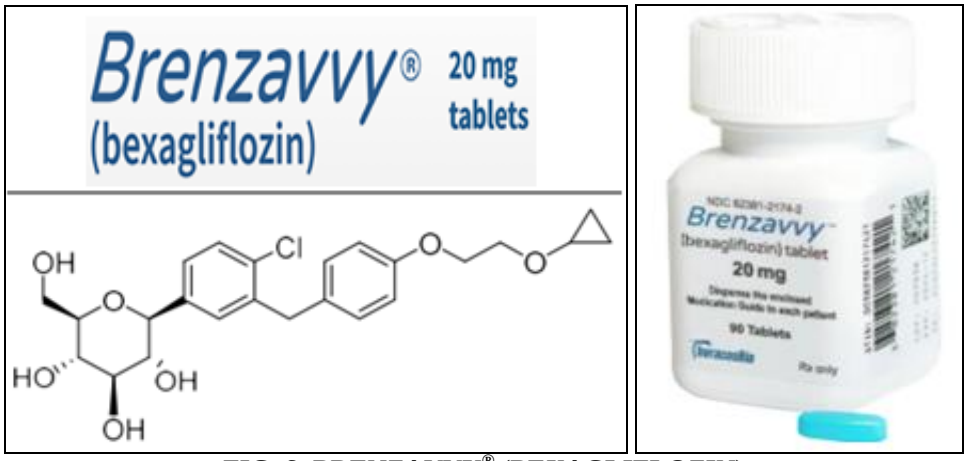

FIG. 6: BRENZAVVY® (BEXAGLIFLOZIN)

Brenzavvy® (Bexagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [19]. Each film-coated tablet contains 20 mg of Bexagliflozin and other inactive ingredients. It is marketed as Bottles of 30 and 90 Tablets as depicted herein above [19]. Below Tablet-6 summarizes the list of US patents and patent applications relevant for the drug product Brenzavvy® (Bexagliflozin) [27], and its family equivalent patent in India. The Tablet-6 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 6: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT BRENZAVVY® (BEXAGLIFLOZIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Benzylbenzene derivatives and methods of use	Benzylbenzene derivatives and methods of use	US 7,838,499 Patent Granted	IN 278347 Patent Granted
Crystalline form of benzylbenzene SGLT2 inhibitor	Crystalline polymorph	US 8,987,323 Patent Granted	IN 4041/KOLNP/2012 Patent application Refused

Dipeptidyl Peptidase 4 (DPP-4) Inhibitors: The dipeptidyl peptidase-4 (DPP-4) inhibitors, which belong to the class of incretin-based medications, are recommended as second or third-line therapies in guidelines for the management of type 2 diabetes mellitus; and they have a favourable drug tolerability and safety profile compared to other glucose-lowering agents [28]. Dipeptidyl-peptidase-4 (DPP-4) inhibitors (or 'gliptins') represent a class of oral anti-hyperglycemicagents that block the inactivation of the "incretin" hormones, namely glucagon-like peptide-1 (GLP-1)and glucose-dependent insulin tropic polypeptide (GIP), and thus affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake [29]. There are several anti-diabetic drugs which are approved by U.S. Food and Drug Administration, consisting of DPP-4 inhibitor as active ingredients, for example, Tradjenta® (Linagliptin), Januvia® (Sitagliptin), Onglyza® (Saxagliptin), Nesina® (Alogliptin) and the like. Evidently, the drug Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [30]. Thus, Linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation.

Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake [30]. Similarly, Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones [31]. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal.

These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP [31]. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in-vitro* at concentrations approximating those from therapeutic doses [31]. Also, Saxagliptin is a competitive DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus [32]. In addition, Alogliptin is a DPP-4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus [33]. Alogliptin selectively binds to and inhibits DPP-4 but not DPP-8 or DPP-9 activity *in-vitro* at concentrations approximating therapeutic exposures [33].

Tradjenta® (Linagliptin): The product TRADJENTA® (Linagliptin) tablets, for oral use having initial U.S. Approval in 2011 [30]. The Active ingredient ' Linagliptin ' is an inhibitor of the DPP-4 enzyme, is described chemically as 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3,7-dihydro-1H-purine-2, 6-dione. The structural formula of Linagliptin is as depicted below [30]:

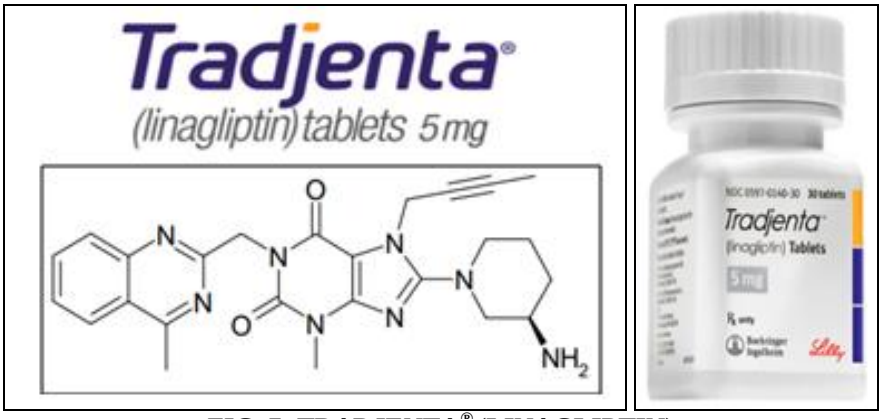

FIG. 7: TRADJENTA® (LINAGLIPTIN)

Tradjenta® (Linagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [30]. Each film-coated tablet of Tradjenta® (Linagliptin) contains 5 mg of linagliptin free base and the following inactive ingredients: Copovidone, corn starch, magnesium stearate, mannitol, and pregelatinized starch. In addition, the film coating contains the following inactive ingredients: Hypromellose, polyethylene glycol, red ferric oxide, talc, and titanium dioxide [30]. Below Tablet-7 summarizes the list of US patents and patent applications relevant for the drug product Tradjenta® (Linagliptin) [34], and its family equivalent patent in India.

The Tablet-7 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 7: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT TRADJENTA® (LINAGLIPTIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
8-[3-amino-piperidin-1-yl]-xanthines, the preparation thereof and their use as pharmaceutical compositions	Linagliptin compound	US 7,407,955 Patent Granted	IN 243301 Patent Granted
Uses of DPP-IV inhibitors	A method of treating type II diabetes mellitus using Linagliptin + metformin	US 8,673,927 Patent Granted	IN 9501/DELNP/2008 Patent application Refused IN201718031279 Patent application Refused
DPP IV inhibitor formulations	Linagliptin Formulation	US11,033,552 Patent Granted	IN291136 Patent Granted
Treatment for diabetes in patients inappropriate for metformin therapy	A method for treating type 2 diabetes mellitus using Linagliptin wherein metformin therapy for said patient is ineligible due to contraindication against metformin.	US9,486,526 Patent Granted	IN 858/DELNP/2011 Patent application withdrawn
Treatment for diabetes in patients with inadequate glycemic control despite metformin therapy comprising a DPP-IV inhibitor	A method for treating type 2 diabetes mellitus in a patient with inadequate glycemic control despite therapy with metformin	US8,846,695 Patent Granted	IN 5224/DELNP/2011 Patent application Abandoned
Pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivate	composition comprising Linagliptin + Empagliflozin	US8,551,957 Patent Granted	IN1006/DELNP/2010 Patent Application Refused
Pharmaceutical composition, pharmaceutical dosage form, process for their preparation, methods for treating and uses thereof	composition comprising Linagliptin + SGLT2 inhibitor	US2022331326A Patent application under examination	IN 6148/DELNP/2011 Patent Application Refused

Januvia® (Sitagliptin): The product Januvia® (Sitagliptin) tablets, for oral use having initial U.S. Approval in 2006 [31]. The active ingredient 'Sitagliptin' is in the form of 'Sitagliptin phosphate' salt. The Sitagliptin phosphate is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, and is chemically known as 7-[(3R)-3-amino-1-oxo-4-(2,4,5- trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine phosphate (1:1) monohydrate. The structural formula of Sitagliptin phosphate is as depicted below [31]:

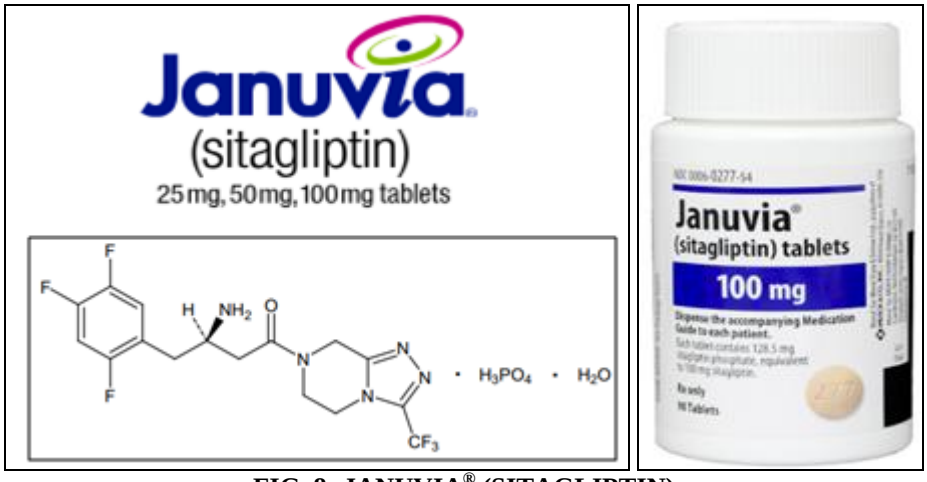

FIG. 8: JANUVIA® (SITAGLIPTIN)

Januvia® (Sitagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [31]. Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate [31]. Each film-coated tablet of Januvia® (Sitagliptin) contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50, or 100 mg, respectively, of free base and the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, sodium stearyl fumarate, and propyl gallate [31]. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide. It is marketed as Bottles of 30 / 90 Tablets as depicted herein above [31]. Below Tablet-8 summarizes the list of US patents and patent applications relevant for the drug product Januvia® (Sitagliptin) [35], and its family equivalent patent in India. The Tablet-8 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 8: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT JANUVIA® (SITAGLIPTIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Beta-amino heterocyclic dipeptidyl peptidase inhibitors for the treatment or prevention of diabetes	Sitagliptin compound	US6,699,871 Patent Granted	IN209816 Patent Granted
Phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor	Sitagliptin phosphate salt compound	US7,326,708 Patent Granted	IN 5948/DELNP/2005 Patent application abandoned
Pharmaceutical compositions of combinations of dipeptidyl peptidase-4 inhibitors with metformin	Formulation Sitagliptin + Metformin	US8,414,921 Patent Granted	IN 2710/CHENP/2008 Patent application abandoned
Pharmaceutical compositions of sitagliptin	stable pharmaceutical composition comprising sitagliptin base and at least one beneficial agent	US 10,925,871 Patent Granted	IN366205Patent Granted
Process for the preparation of chiral beta amino acid derivatives by asymmetric hydrogenation	API / intermediate manufacturing process	US7,468,459 Patent Granted	IN 235426 Patent Granted

Onglyza® (Saxagliptin): The product Onglyza® (Saxagliptin) tablets, for oral use havinginitial U.S. Approval in 2009 [32]. The active ingredient 'Saxagliptin' is in the form of 'Saxagliptin monohydrate'. Saxagliptin is an orally-active inhibitor of the DPP-4 enzyme. 3,7 Saxagliptin monohydrate is described chemically as (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo [3.3.1.1] dec-1-yl)acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile, monohydrate or (1S,3S,5S)-2-[(2S)-2-Amino-2-(3- hydroxyadamantan-1-yl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate [32]. The structural formula of Sitagliptin phosphate is as depicted below:

FIG. 9: ONGLYZA® (SAXAGLIPTIN)

Onglyza® (Saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [32]. Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400) [32]. Each film-coated tablet of Onglyza® (Saxagliptin) for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose [32]. In addition, the film coating contains the following inactive ingredients: iron oxides, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. It is marketed as Bottles of 30 / 90 Tablets as depicted herein above [32]. Below Tablet-9 summarizes the list of US patents and patent applications relevant for the drug product Onglyza® (Saxagliptin) [36], and its family equivalent patent in India. The Tablet-9 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 9: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCT ONGLYZA® (SAXAGLIPTIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV and method	Saxagliptin compound	US RE44186E Patent Granted	IN 206543 Patent Granted
Coated tablet formulation and method	Tablet formulation	US 7951400 Patent Granted	IN 275601 Patent Granted

Nesina® (Alogliptin): The product Nesina® (Alogliptin) tablets, for oral use having initial U.S. Approval in 2013 [33]. The active ingredient 'Alogliptin' is in the form of 'Alogliptin Benzoate' salt. The Alogliptin Benzoate is a selective, orally bioavallable inhibitor of the enzymatic activity of DPP-4. Chemically, alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl} methyl) benzonitrile monobenzoate. The structural formula of Sitagliptin phosphate is as depicted below [33]:

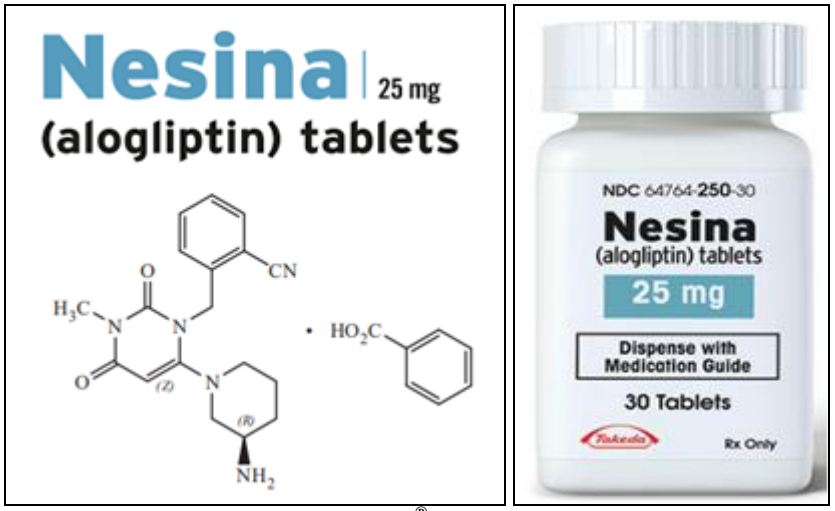

FIG. 10: NESINA® (ALOGLIPTIN)

Nesina® (Alogliptin) is indicated as an adjunct to diet and exercise to improve glycernic control in adults with type 2 diabetes mellitus [33]. Alogliptin benzoate is a white to off-white crystalline powder containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethylsulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol and very slightly soluble in octanol and isopropyl acetate[33]. Each NESINA® (Alogliptin) tablet contains 34 mg,

17 mg or 8.5 mg Alogliptin benzoate, which is equivalent to 25 mg, 12.5 mg or 6.25 mg, respectively, of Alogliptin and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, mannitol, and microcrystalline cellulose [33]. In addition, the film coating contains the following inactive ingredients: ferric oxide (red or yellow), hypromellose, polyethylene glycol, and titanium dioxide and is marked with printing ink (Gray F1). It is marketed as Bottles of 30 / 90 Tablets as depicted herein above [33]. Below Tablet-9 summarizes the list of US patents and patent applications relevant for the drug product Nesina® (Alogliptin) [37], and its family equivalent patent in India. The Tablet-9 further provides the legal status and outcome of the respective Patent or Patent application after examination from respective patent offices, such as USPTO [21] and India Patent office [22].

TABLE 9: PATENT(S) ASSOCIATED WITH THE DRUG PRODUCTNESINA® (ALOGLIPTIN)

Patent title	Patent claim scope	Patent or Patent application number and status after examination	
		USA	India
Dipeptidyl peptidase inhibitors	Alogliptin compound	US7807689 Patent Granted	IN 244233 Patent Granted
Tablet preparation without causing a tableting trouble	Tablet formulation	US8697125 Patent Granted	No India equivalent patent found

RESULTS AND DISCUSSION: It is evident from above discussion that, there are several approved drugs approved for the treatment of type 2 diabetes mellitus; that precisely shows Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors or Dipeptidyl peptidase 4 (DPP-4) inhibitors activity. It is also evident that, the innovator filed considerable number of patent applications to protect his invention that covers above drug products and its attributes. The innovator had attempt to protect the technical attributes as invention, such as compound 'Genus', compound 'Species', specific active Salt, crystalline polymorphic form, Method of Treatment, Indication, Dosing regimen, Formulation, pharmacokinetics (PK) and pharmacodynamics (PD) profile, AUC / Cmax and so on.

As depicted above, **Table 1** to **Table 9** of this article, the innovator filed patents to protect invention in USA and extended the patent filing to India as family equivalent patent in India. It is to be noted that, the US patent application was examined in accordance with provisions in USA patent act and the corresponding Indian Patent application was examined as per provisions of Indian Patent act. Wherein, during the patent examination at respective patent office, the primary objections were related to justify the patentability of the invention based on Novelty, Obviousness / Inventive step, Industrial applicability of the patentable subject matter. For instance, the **Table 1** provides list of Patent(s) associated with the drug product FARXIGA® (Dapagliflozin) which is a SGLT2 inhibitor; wherein innovator could obtain patent for Drug substance (compound) and immediate release formulation in the USA as well as in INDIA. Further, the innovator obtained patent grant for crystalline polymorph in the USA (US 7,919,598) but the corresponding Indian family equivalent patent application (IN 10757/DELNP/2008) was objected and finally abandoned by the innovator. The India Patent application No: IN 10757/DELNP/2008 (Applicant: BRISTOL-Myers Squibb Company) of Title: (Crystalline Solvates And Complexes of (1s)-1, 5-Anhydro-1-C-(3-((Phenyl) Methyl) Phenyl-D-Glucitol Derivatives with Amino Acids as Sglt2 Inhibitors for the Treatment of diabetes; was filed in India dated on Dec 30, 2008; which was derived from PCT international application - pct/us 2007/071749, having pct international filing date June 21, 2007. The request for examination was submitted at India patent office by June 17, 2010. The pending claims submitted for examination were predominantly covering the Crystalline Dapagliflozin and it's solvates such as propylene glycol solvates. In the first examination report; the Controller objected the subject matter for the reason as "Product claim(s) 1-15, 32-35, 42-43 and process claims 22-31, 36-41, 44-56 fall within the scope of such clause (d) of section 3 of Indian Patents Act as claimed compounds are mere discovery of new form of known substance

disclosed in cited documents with no improvement in therapeutic efficacy of claimed compounds over known compounds and claimed processes are mere use of known processes as disclosed in the cited documents" it was also further objected that "Subject matter of the claims does not constitute an invention under Section 2(1) (j) as the claims lack Novelty and Inventive step" [38].

Similarly, the **Table 2** provides list of Patent(s) associated with the drug product Jardiance® (Empagliflozin) which is a SGLT2 inhibitor; wherein innovator could obtain patent for Drug substance (compound) and pharmaceutical composition in the USA as well as in INDIA. Further, the innovator obtained patent grant for crystalline polymorph in the USA (US 7,713,938) but the corresponding Indian family equivalent patent application (IN 7213/DELNP/2007) was objected. Similarly, the innovator obtained patent grant for Combination of Empagliflozin and Linagliptin in the USA (US 8,551,957) but the corresponding Indian family equivalent patent application (IN1006/DELNP/2010) was refused by the controller. The India Patent application No : IN 7213/DELNP/2007 (Applicant: Boehringer Ingelheim International GMBH) of Title: "Crystalline form of 1-Chloro-4-(ß-D-Glucopyranos-1-Yl)-2-[4-((S)-Tetrahdydrofuran-3-Yloxy-Benzyl]-Benzene, a method for its preparation and the use thereof for preparing medicaments" was filed in India dated on Sep 19, 2007; which was derived from PCT International Application - PCT/EP2006/061956, having PCT International Filing Date May 02, 2006. The Request for Examination was submitted at India patent office by Apr 29, 2009.

The pending claims submitted for examination were predominantly covering the Crystalline polymorphic Form-I of Empagliflozin. In the first examination report; the Controller objected the subject matter for the reason as "Subject matter of claims lack inventive step under section 2(1)(j) of Patents Act, 1970" and "Subject matter of claims falls under section 3 of the Patent Act, 1970 and are not inventions under the said section / clause: Claims 1 and 2 falls within the scope of such clause (d) of section 3 of Patents Act 1970-as the claimed compound does not differs significantly with respect to efficacy compare to the prior art as an inhibitor of the sodium-dependent glucose transporter and etc. The data should be provided in the application showing the compound have enhanced activity as an inhibitor of the sodium-dependent glucose transporter compare to the prior art" [39]. However, it should be noted that there is no explicit guidance in the Act to define the consideration limits for data with 'Enhanced efficacy'.

The India Patent application No: In 1006/Delnp/2010 (Applicant: Boehringer Ingelheim International Gmbh) of Title: "Pharmaceutical Composition Comprising a Glucopyranosyl-Substituted Benzene Derivative" was Filed in India Dated On Feb 15, 2010; which was Derived from PCT International Application - PCT/Ep2008/060736, having PCT International Filing Date Aug 15, 2008. The Request for Examination was submitted at India patent office by Aug 11, 2011. The pending claims submitted for examination were predominantly covering the Combination of Empagliflozin and Linagliptin. In the first examination report; the Controller objected the subject matter for the reason as "Subject matter of claims fall under Section 3 of the Patent s Act, 1970 and are not patent able subject matter under the said section/Clause: because Claims 1-10 do not contain synergistic ratios of the constituents and fall within the scope of such clause (e) of 1970 and therefore, not allowable. Claims fall within the scope of such clause (d)of section 3 of Patents Act, 1970 the components in the composition as disclosed is known in the prior art for the same use and thus appears to be new use of known substance.

Further, the present composition does not differ significantly in properties with regard to efficacy with respect to the known compositions. Also, the subject matter of the claims does not constitute an invention under section 2[1(j)] of the Patents Act,1970[40].In reply the innovator submitted the enhanced efficacy data as "The effect of a combination of the DPP-IV inhibitor and the SGLT-2 inhibitor according to the invention on active GLP-I was tested in Zucker diabetic fatty (ZDF) in comparison to vehicle, the DPP-IV inhibitor only and SGLT-2 inhibitor only administration" and the data was provided in the form of graph as follows [40]:

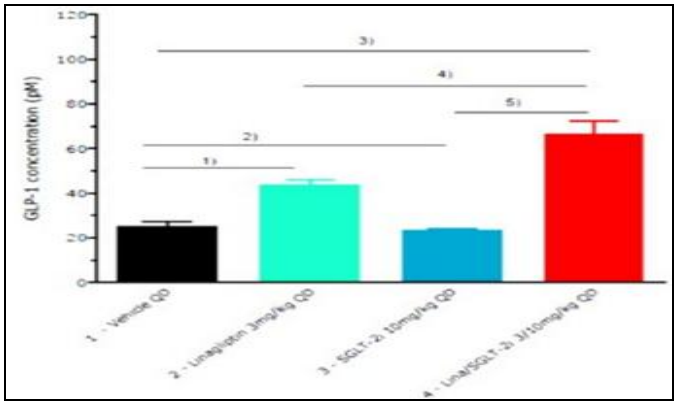

FIG. 11: TAKEN FROM THE SUBISSION BY THE INNOVATOR DURING EXAMINATION OF INDIAN PATENT APPLICATION IN 1006/DELNP/2010)

Even though, the innovator tried to convince the Controller on the objections related to enhanced efficacy and synergistic effect of combination, the Patent application IN 1006/DELNP/2010 was finally ordered as Refused. However, it should once again to be noted that there is no explicit guidance in the Act to define the consideration limits for data with 'Enhanced efficacy' or enhanced "Synergistic effect". In other words, there is no explicit guidance in the Act to clearly demark, what set of data to be submitted and what the acceptance criteria to be applied in order to overcome the Rejection raised by the Controller.

For instance, the **Table 6** provides list of Patent(s) associated with the drug product Brenzavvy® (Bexagliflozin) which is a SGLT2 inhibitor; wherein innovator could obtain patent for Drug substance (compound) in the USA as well as in INDIA. Further, the innovator obtained patent grant for crystalline polymorph in the USA (US 8,987,323) but the corresponding Indian family equivalent patent application (IN 4041/KOLNP/2012) was objected and finally Refused by the Controller. The India Patent application No: IN 4041/KOLNP/2012 (Applicant: Theracos SUB, LLC) of Title: "Crystalline Form Of Benzylbenzene SGLT2 Inhibitor"; was filed in India dated on Dec 19, 2012; which was derived from PCT International Application - PCT/CN2011/075554, having PCT International Filing Date June 10, 2011. The Request for Examination was submitted at India patent office by June 03, 2014. The pending claims submitted for examination were predominantly covering the crystalline polymorphic form of Bexagliflozin. In the first examination report; the Controller objected the subject matter for the reason as "lacks Inventive Step under section 2(1)(j) Claim(s) (1-45) lack(s) inventive step, being obvious in view of teaching (s) of cited document(s) and Sufficiency of Disclosure that Claim 1 seeks to protect a "crystalline form", it maybe contain many different crystal forms. It is well-known that a crystalline form of compounds is unexpectable. So the person skilled in the art can not foresee that how many crystalline forms there are in claim 1 from the disclosure of the description. Accordingly, the said claim 1 cannot be supported by the description and the description does not set forth the invention sufficiently [41].

Additionally, the **Table 8** provides list of Patent(s) associated with the drug product JANUVIA® (Sitagliptin) which is a DPP-4 inhibitor; wherein innovator could obtain patent for Drug substance (compound) and pharmaceutical composition in the USA as well as in INDIA.

Further, the innovator obtained patent grant for Sitagliptin phosphate salt in the USA (US 7,326,708) but the corresponding Indian family equivalent patent application (IN 5948/DELNP/2005) was objected. Additionally, the innovator obtained patent grant for Formulation Combination of Sitagliptin + Metformin in the USA (US 8,414,921) but the corresponding Indian family equivalent patent application (IN 2710/CHENP/2008) was objected by the controller. The India Patent application No: IN 5948/DELNP/2005 (Applicant: MERCK & CO. INC.) of Title: Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitors";was filed in India dated on Dec 20, 2005; which was derived from PCT International Application - PCT/US2004/019683, having PCT International Filing Date June 18, 2004. The Request for Examination was submitted at India patent office by June 07, 2006. The pending claims submitted for examination were predominantly covering the dihydrogenphoshate salt of Sitagliptin. In the first examination report; the Controller objected the subject matter for the reason as "Claims 1 falls within the scope of such clause (d) of section 3 of the Patent Act and the claim which are the property of product claimed as worded hence not an invention and not allowable under section 2(1)j of the Act" [42]. The India Patent application No: IN

2710/CHENP/2008 (Applicant: Schering Corporation) of Title: "Pharmaceutical Compositions of Combinations of Dipeptidyl Peptidase-4 Inhibitors with Metformin" was filed in India dated on May 30, 2008; which was derived from PCT International Application - PCT/US2006/047380, having PCT International Filing Date Dec 12, 2006. The Request for Examination was submitted at India patent office by Nov 03, 2009. The pending claims submitted for examination were predominantly covering the Formulation Combination of Sitagliptin + Metformin. In the first examination report; the Controller objected the subject matter for the reason as "Subjectmatter of claims 1-22 does not constitute an invention in view of below cited documents under section 2(1)(j) of Indian Patents Act,1970 and the subject matter of claims 1-18 and 20-22 appears to fall under section 3(e) of Indian Patents Act, and it appears to be a mere admixture of a known compounds which does not result in the synergism of that substance. The dose ratio of DPP-4 inhibitors (sitagliptin etc,) and metformin is taught in prior art documents, the additional definition of a lubricant and a binding agent does not appear to bring any technical effect" [43].

Further, the **Table 5** provides list of Patent(s) associated with the drug product INPEFA® (Sotagliflozin) which is a SGLT-2 inhibitor; wherein innovator could obtain patent for Drug substance (compound) and pharmaceutical composition in the USA as well as in INDIA.

Further, the innovator obtained patent grant for crystalline Polymorphic form of Sotagliflozinin the USA (US 8,217,156) but the corresponding Indian family equivalent patent application (IN 504/DELNP/2011) was refused by the Controller. The India Patent application No: In 504/DELNP/2011 (Applicant: Lexicon Pharmaceuticals, INC) of Title: "Solid Forms of (2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-Ethoxybenzyl) Phenyl)-6-(Methylthio) Tetrahydro-2h-Pyran-3,4,5-Triol And Methods Of Their Use"; was filed in India dated on Jan 21, 2011; which was derived from PCT International Application - PCT/US2009/050636, having PCT International Filing Date July 15, 2009. The Request for Examination was submitted at India patent office by July 02, 2012. The pending claims submitted for examination were predominantly covering the crystalline polymorphic form of Sotagliflozin and its composition. In the first examination report; the Controller objected the subject matter for the reason as Inventive Step as Claim(s) 1-22 lack(s) inventive step, being obvious in view of teaching (s) of cited document(s) and NON Patentability as Claim(s) 1-22 are statutorily non-patentable under the provision of clause ([3(d)) of Section 3 for the following reasons: Subject matter of claims 1-22 describes the different solid form of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(methylthio) tetrahydro-2H-pyran-3, 4, 5-triol and its characterization properties which is disclosed in document D1 and falls u/s 3(d) of the Patent Acts, 1970. Section 3(d) of the Patents Act, 1970 explains that the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance is not patentable" [44].

On the other hand, the corresponding USA patent family equivalent patents were objected under the provision of 35 U.S.C. 102 Conditions for patentability as Novelty and 35 U.S.C. 103 Conditions for patentability as non-obvious subject matter. However, despite the objections, the patent was granted by the examiner, in view of surprising effects identified by the innovator over prior art.

For example, the US patent No 8,551,957 is as granted patent after successful examination, which claims combination of Empagliflozin and Linagliptin. In order to justify the inventive step or to overcome obviousness rejection over existing prior art, the innovator submitted the surprising effect as "the present invention it has now surprisingly been found that a pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative of the formula (I) as defined hereinafter can advantageously be used in combination with a DPP IV inhibitor as specified hereinafter for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular in improving glycemic control in patients. This opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighbouring disease states" [45]. Also "A pharmaceutical composition according to this

invention, in particular due to the glucopyranosyl-substituted benzene derivative therein, exhibits a good safety profile. Therefore, a treatment or prophylaxis according to this invention is advantageously possible in those patients for which the mono-therapy with another antidiabetic drug, such as for example metformin, is contraindicated and/or who have an intolerance against such drugs at therapeutic doses. In particular, a treatment or prophylaxis according to this invention may be advantageously possible in those patients showing or having an increased risk for one or more of the following disorders: renal insufficiency or diseases, cardiac diseases, cardiac failure, hepatic diseases, pulmonal diseases, catabolytic states and/or danger of lactate acidosis, or female patients being pregnant or during lactation" [45].

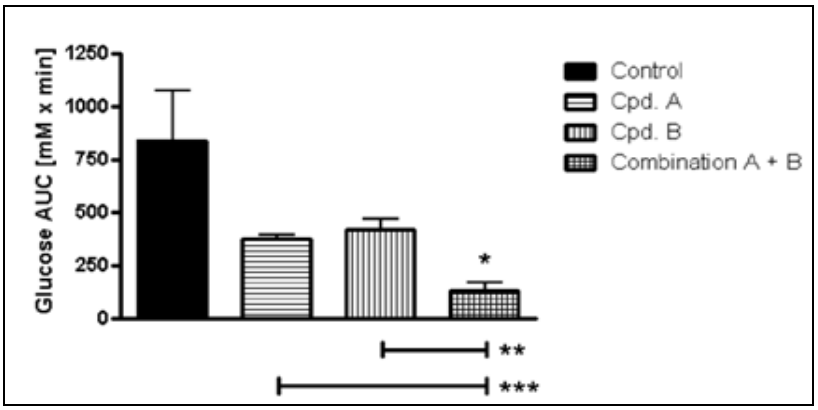

FIG. 12: TAKEN FROM THE PATENT SPECIFICATION THE US PATENT NO 8,551,957

"The result is shown in **Fig. 12.** "Cpd. A" is the DPP IV inhibitor 1-[(4-methyl-quinazolin-2-yl) methyl] - 3 – methyl – 7 - (2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine at a dose of 1 mg/kg. Cpd. B is the glucopyranosyl-substituted benzene derivative (9), i.e. 1-chloro-4-(β-D-glucopyranos-1-yl) – 2 - [4-((S) - tetrahydrofuran-3-yloxy)-benzyl]-benzene, at a dose of 3 mg/kg. Combination A+B is the combination of said DPP IV inhibitor and said glucopyranosyl-substituted benzene derivative at the same doses. P-values versus control are indicated by symbols above the bars. P-values of the combination versus the monotherapies are indicated below the figure (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$)[45]"

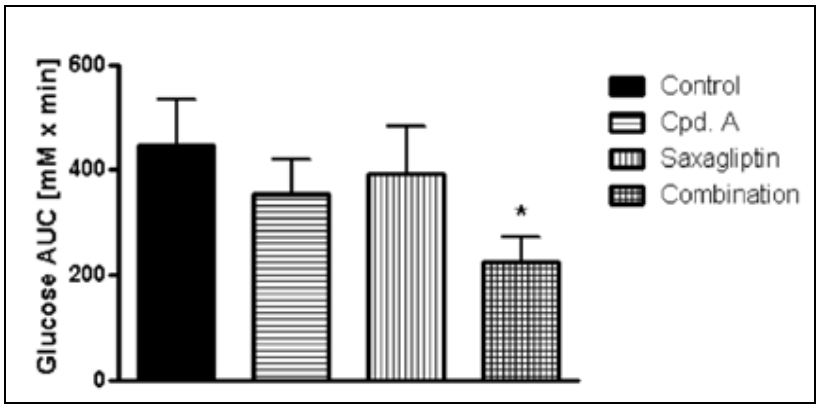

FIG. 13: TAKEN FROM THE PATENT SPECIFICATION THE US PATENT NO 8,551,957

"The result is shown in **Fig. 13**. "Cpd. A" is the glucopyranosyl-substituted benzene derivative (9), i.e. 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran – 3 - yloxy) - benzyl] - benzene, administered at a dose of 3 mg/kg. The DPPIV inhibitor Saxagliptin is administered at a dose of 0.3 mg/kg. In the combination, the glucopyranosyl-substituted benzene derivative and Saxagliptin are administered together at the same doses as in the respective monotherapies. P values versus control are indicated by symbols above the bars. (*, $p<0.05$)" [45]. In the Notice of Allowance, for patent US 8,551,957, the Examiner addressed that the prior art does not teach or fairly suggest the

instantly claimed combination and method of use thereof. The examiner acknowledged that the instant composition is seen to have improved properties when compared to each drug used in monotherapy (Example 1-3 and fig 1-3 of specification), wherein the combination of the two decreased glucose excretion in the Orla glucose tolerance test by 84%, which is statistically significant amount [45].

Similarly, in as another example of US patent No 7,326,708, which is a granted patent after examination by USPTO, covers Phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor, that is a phosphate salt of Sitagliptin. In order to justify the inventive step or to overcome obviousness rejection over existing prior art, the innovator submitted the surprising effect as "the crystalline dihydrogenphosphate salt of the present invention exhibits pharmaceutic advantages over the free base and the previously disclosed hydrochloride salt in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient.

In particular, the enhanced chemical and physical stability of the crystalline dihydrogenphosphate salt monohydrate constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient" [46] and also "A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 200 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the crystalline forms of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the crystalline forms of the present invention can be administered in intranasal form *via* topical use of suitable intranasal vehicles, or *via* transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art" [46]. The innovator also described that "the crystalline dihydrogenphosphate salt monohydrate was found to be stable under ambient condition. It was found to convert to dehydrated monohydrate if heated to above 40° C. under very dry nitrogen flow. Dehydrated monohydrate converted back to monohydrate under ambient condition" [46].

CONCLUSION: Evidently, from the above discussion and investigations, which is in the form of Exploratory Research, we could locate and study the patentability of several approved drugs products which are effective for the treatment of diabetes mellitus. We, through our Exploratory Research, precisely investigated the patentability of the drug products which are Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and Dipeptidyl peptidase 4 (DPP-4) inhibitors by mechanism of action. It is also evident from above discussion that the innovator companies, applied for the PATENT protection with various primary and secondary attributes of the drug product, concurrently in multiple jurisdictions such as USA and India.

However, in many instances, the innovator failed to secure grant of patent in India for secondary inventions such as for salt of a compound, crystalline polymorph and also combination of two or more drug products, because of objections raised by Controller in view certain provisions of Indian Patent Act such as Section 2(1)(j) or (ja), Section 3(d), Section 3(e). On the other hand, the innovator could successfully obtain patent grant for corresponding family equivalent patent in the USA despite of the novelty and inventive step related objections by the USPTO. The technical advancements and surprising effect which were admissible and considered by the USA patent office (USPTO), was not "Weighed equally" and considered by India patent office in order to justify "efficacy" or "enhanced efficacy" or "synergistic effect" of the drug product. It should again to be noted that there is no explicit guidance in the India Patent Act to define the consideration limits for data with 'Enhanced efficacy' or enhanced "Synergistic effect". In other words, there is no explicit guidance in the Indian Patent Act to clearly demark, what set of data to be submitted and what the acceptance criteria to be applied in order to overcome the Rejection raised by the Controller with respect to section 3 of India Patent Act. Hence, in order to encourage innovators to invent in India or to attract foreign innovators to develop technology in India, precisely in pharmaceutical domain, there is need to find basis for adequate provisions to protect inventions in India. For the

said purpose there may, if required, need the harmonization of certain provisions of Indian Patent Act or more expanded view for considerations of scientific evidence and admissibility of technical data. For example, there should be a consideration to be given for surprising effect or technical advancement of the drug product. Accordingly, there is need for harmonization of patent law in India from a pharmaceutical perspective. Precisely, it requires considerations for harmonization of patentability criteria such as Novelty and inventive step for pharmaceutical products in INDIA *vis-à-vis* USA.

ACKNOWLEDGEMENT: Nil

Funding Information: The authors submits that they did not receive any funding for this study.

Data Availability: The authors submits that; they refer to the drug approval data published on USFDA databases such as The Center for Drug Evaluation and Research (CDER); Drugs@FDA: FDA-Approved Drugs and Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Similarly, the relevant Patent(s), Patent application(s) and its family equivalent searches performed using patent office official websites such as INPASS (Indian Patent Advanced Search System) by Patent office India; and the web-based Patent Public Search tool by United States Patent and Trademark Office. The patent prosecution history of the respective patent application also investigated using the corresponding patent office public databases.

CONFLICT OF INTEREST: The authors certify that there are no conflicts of interest pertaining to the publication of this manuscript.

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How to cite this article:
Nighute S, Sahu N, Raut A and Jadhav S: "Elucidation of patentability considerations for SGLT-2 and DPP-4 inhibitor anti-diabetic drug products in India *vis-à-vis* USA". Int J Pharm Sci & Res 2026; 17(2): 550-71. doi: 10.13040/IJPSR.0975-8232.17(2).550-71.