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Patents and Patent Expiry: Impact on Innovation and Market Competition in the Drug Development Process - A Real-World Case Study of the Antidiabetic Drug Januvia® (Sitagliptin)

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Abstract

Intellectual Property (IP) protection is central to pharmaceutical innovation, providing exclusivity that enables recovery of research and development investments while delaying generic competition. This study explores the critical role of patents across the drug development lifecycle using a real-world case study of Januvia® (Sitagliptin Phosphate Monohydrate), the first DPP-4 inhibitor approved by the USFDA for the treatment of Type 2 Diabetes Mellitus. The analysis encompasses various patent types like compound, formulation, process, polymorph, and methods of use, and evaluates their impact on regulatory timelines, market exclusivity, and pricing strategies. Through comprehensive literature and patent database reviews, this study traces Januvia's development from target identification to post-marketing surveillance and eventual generic entry, highlighting key patents and their expiry timelines. It further discusses the implications of the Hatch-Waxman Act, patent term extensions, and Paragraph IV certifications in shaping market dynamics. Findings demonstrate how strategic patenting extends market control beyond primary patent expiry, influencing competition and access. The case of Januvia underscores the dual nature of patents: fostering innovation while potentially delaying affordability. A balanced regulatory and IP framework is essential to encourage drug discovery while ensuring timely availability of generics for broader public health benefits.

Keywords: Diabetes Mellitus, IP patent, Regulatory Framework, Drug Development Process, Januvia.

Introduction

Intellectual property (IP) patents play a vital role in the drug development process, ensuring innovation, market exclusivity, and commercial viability for pharmaceutical companies. This study explores the importance of IP protection in drug development, with a specific focus on Januvia® (Sitagliptin Phosphate Monohydrate), a widely used Dipeptidyl Peptidase-4 Inhibitor (DPP-4I) for Type 2 Diabetes Mellitus (T2DM). The U.S. patent landscape surrounding Sitagliptin illustrates how patent strategies, regulatory frameworks, and lifecycle management influence drug availability, pricing, and competition.

Understanding these elements is crucial for branded companies and stakeholders to navigate the balance between innovation and market access.

Januvia® (Sitagliptin Phosphate Monohydrate)

Januvia® (Sitagliptin Phosphate Monohydrate), approved by the USFDA on October 17, 2006, is the first DPP-4 inhibitor for T2DM. It enhances incretin hormones (GLP-1, GIP) to boost insulin and suppress glucagon in a glucose-dependent manner. It is used alone or with metformin or TZDs for improved glycemic control. [1]

The drug was initially protected by U.S. Patents 6,699,871 and 7,125,873, both expiring on January 26, 2023. Later, U.S. Patent 7,326,708 provided extended protection, now expiring on May 24, 2027 after a patent term extension. Januvia is available in 25 mg (pink), 50 mg (light beige), and 100 mg (beige) film-coated tablets, each marked for easy identification. [2]

As of April 2025, the prices for Januvia in the US vary based on dosage, quantity, location of the pharmacy, and available discounts. These data are collected based on IQVIA pricing.

Table 1: Price of Januvia in US as of 2025

Dosage	Quantity	Price (USD)	Price Per Tablet (USD)
25 mg	30 tablets	~$409.37	~$13.64
50 mg	30 tablets	~$516.57	~$17.21
100 mg	30 tablets	~$370.10	~$12.33

Materials and Methods

A strategic literature review was conducted using databases including Scopus, PubMed, Google Scholar, Google Patents, USPTO, Espacenet, WIPO, USFDA, FDA Orange Book, drugs@FDA, ClinicalTrials.gov, and DailyMed. The study examined various patent types like compound, formulation, process, polymorph, and method of use patents and included case studies across preclinical, clinical, and post-marketing (Phase IV) stages. [3]

Drug Development and Patent Lifecycle: From Drug Discovery to Generic Entry

Target Identification (Find biological target for disease)
Lead Compound Search (Screen potential drug candidates)
Lead Optimization (Modify for better efficacy/safety)
↓
Patent Filing: Compound (Protects novel drug structure)
Preclinical Studies (Test in vitro & in vivo for safety)
↓
Patent Filing: Process/Formulation Patents (Covers drug synthesis & delivery)
IND Submission (Application for conducting clinical trials)
Phase I Clinical Trial (Test safety)
Phase II Clinical Trial (Test efficacy)
Patent Filing: Method of treatment/use (New use or indication)
Phase III Clinical Trial (Confirm safety/efficacy)

NDA Submission (Apply for market approval with USFDA)
Patent Filing: Dosage regimen/Combination Use (If applicable)
Drug Approval (Approval, rejection, or additional studies)
Market launch, Post-Marketing (Phase IV) (Monitor long-term safety)
Patent Expiry (~20 years after filing, generics enter market)
ANDA submission (Can be submitted after NCE approval)
Generic entry
Note: The patent filing sequence in drug development varies based on the brand owner's IP strategy, regulatory needs, and commercial goals. While a general framework exists, companies may adjust the order of filing composition, process, formulation, and indication patents to maximize protection. Generic firms can file an ANDA after NCE approval, but market entry is barred until patent expiry unless challenged or waived.

Results

1. Target Identification

The first step in drug discovery is identifying a biological target associated with a disease. This target can be a protein, enzyme, receptor, or gene that plays a crucial role in the disease mechanism. Scientists use genomic, proteomic, and bioinformatics approaches to study disease pathways and identify suitable drug targets. [4]

2. Lead Compound Search

The goal is to identify a lead compound with promising activity against a target. Once the target is selected, compounds are screened using:

- High-throughput screening (HTS): Rapid testing of large compound libraries.
- Computational screening: AI and molecular modeling to predict target interactions.
- Natural product screening: Isolation of active compounds from natural sources like plants, microbes, or marine organisms. [4]

3. Lead Optimization

After identifying a lead compound, researchers optimize its structure to enhance efficacy, safety, and pharmacokinetic properties while minimizing deficiencies. This involves experimental techniques like NMR and mass spectrometry, along with in silico methods such as pharmacophore modeling, molecular docking, molecular dynamics, and QSAR analysis, supporting rational drug design. [5]

4. Patent Filing: Primary Blocking Patent

A Primary Blocking Patent is a foundational patent that grants exclusivity for the Active Pharmaceutical Ingredient (API), preventing competitors from making or marketing the same compound during the patent term. It acts as a key barrier to generic entry, ensuring prolonged market exclusivity. For example, Sitagliptin, a DPP-4 inhibitor by Merck & Co., is protected under such a primary compound patent. [6]

Patent No. 1: Compound Patent (Generic) of Sitagliptin by Merck & Co.

- Title: Beta-amino Heterocyclic DPP-4I for The Treatment or Prevention of Diabetes
- Patent / Publication No.: US6,699,871B2
- Legal Status: OB Expiry: Jan 26, 2023 (w/PED) (Expired)

The patent claims a compound of Formula I wherein: Ar is a phenyl group (unsubstituted or substituted with 1-5 R3 groups including halogen, C1-6 alkyl, OC1-6 alkyl, or CN); X is nitrogen (N) or CR2; R1

and R2 are hydrogen, CN, C1-10 alkyl, phenyl, or 5-/6-membered heterocycle; R4 is C1-6 alkyl (may be substituted). [7]

Patent No. 2: Compound Patent (Specific) of Sitagliptin by Merck & Co.

- Title: Phosphoric acid salt of a DPP-4I
- Patent / Publication No.: US7,326,708B2
- Legal Status: OB Expiry: May 24, 2027 (w/PED)

Claims the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I. [8]

5. Preclinical Studies

Preclinical studies are the first stage of drug development, conducted to assess a drug candidate's safety, efficacy, and pharmacokinetics before human trials. Their main goal is to determine if the drug is safe for clinical testing. Once a candidate is identified, a preclinical development program begins, including safety pharmacology and toxicology studies, which are crucial for filing an IND application. [9]

- Pharmacokinetics and Metabolic Studies
- Safety Pharmacology Studies
- Toxicity Studies

Study 1: Preclinical Toxicology and Safety Assessment of Sitagliptin

Species	Study Duration	No. of Animals	Study Type
Rats	2 weeks, 3 months–2 years	~600	Toxicity & long-term safety
Mice	3 months, 2 years	~550	Toxicity & long-term safety
Dogs	2 weeks, 3 months–1 year	96	Toxicity & chronic exposure
Dogs	3 months	45	Sitagliptin + Metformin
Cynomolgus Monkeys	3 months	24	Toxicity study

Observations: Non-diabetic animal studies showed no pancreatic toxicity with sitagliptin, as standard histological analysis revealed no damage or pancreatitis in monkeys (3 months), dogs (12 months), or rodents (up to 2 years). [10]

Study 2: Preclinical Carcinogenicity and Fertility Studies of Sitagliptin

Study type	Species	Dose (mg/kg/day)	MRHD (100 mg/day)	Observation
Carcinogenicity	Rat	500	~60 times higher	Liver tumors were observed at high doses
		150	~20 times higher	No liver tumors
Carcinogenicity	Mouse	500	~70 times higher	No tumors observed
Fertility Study	Rat	125	~12 times higher	No effect on fertility

		250–1000	~25–100 times higher	Increased embryo resorption (in some cases)

Observation: Preclinical toxicity studies of sitagliptin in rats, mice, dogs, and monkeys showed no pancreatic abnormalities, even at doses resulting in plasma exposures much higher than those in humans. These findings suggest that sitagliptin does not cause pancreatic toxicity, even at elevated exposure levels. [11]

6. Patent Filing: Secondary Blocking Patents

Secondary blocking patents extend protection around a pharmaceutical compound by covering related innovations, such as new formulations, dosages, methods of use, or manufacturing processes. These patents help branded manufacturers preserve market exclusivity and prevent generic competition, even after the primary patent expires. [12]

- Combination Therapies: Combining the active ingredient with other drugs.
- Formulations: Developing new drug formulations, such as controlled-release versions.
- Polymorphs: Different forms of the same compound, like crystalline, amorphous, co-solvate, co-crystal and the like.
- Process: The specific method or technique to manufacture a drug or its components.
- Methods of Use/Treatment: Claiming therapeutic uses for the drug. [13]

Patent No. 3: Process Patent of Sitagliptin by Solvias AG, Merck Sharp & Dohme LLC

- Title: Process of preparation of enantiomerically enriched beta amino acid derivatives
- Patent / Publication No.: US7,495,123B2
- Legal Status: Est. expiry: Apr 05, 2025 [14]

Table 2: Claim for the Process for the Preparation of Enantioselective Hydrogenation of Beta-Amino Acid Derivatives

Step	Details
Process	Preparation of a compound of structural formula I
Functional Group (Z)	OR_2, SR_2, or NR_2R_3
R Groups	R_1: $C_{1–8}$ alkyl, aryl, heteroaryl, or aryl-$C_{1–2}$ alkyl. R_2 & R_3: Hydrogen, $C_{1–8}$ alkyl, aryl, or aryl-$C_{1–2}$ alkyl. R_2 & R_3 (Cyclic Form): Can form 4- to 7-membered heterocyclic ring with O, S, N, NH, or $NC_{1–4}$ alkyl.
Heterocyclic Ring Fusion	Fused with a 5- to 6-membered carbocyclic/heterocyclic ring with substitutions (e.g., hydroxy, amino).
Key Reaction Step	Hydrogenation of a prochiral enamine of structural formula II in the presence of hydrogen gas
Catalyst System	Rhodium metal precursor complexed with a chiral phosphine ligand

Rhodium Metal Precursors	[Rh(monoolefin)$_2$Cl]$_2$, [Rh(diolefin)Cl]$_2$, etc., with counterions like methanesulfonate or tetrafluoroborate.

Patent No. 4: Combination Composition Patent of Sitagliptin by Merck & Co.

- Title: Pharmaceutical Compositions of Combinations of DPP-4I with Metformin
- Patent / Publication No.: US8,414,921B2
- Legal Status: OB Expiry Date: Jan 21, 2029 (w/PED) [15]

Table 3: Composition Claims for Sitagliptin-Metformin Pharmaceutical Formulationse

Claim No.	Sitagliptin (or Salt)	Metformin HCl	Lubricant	Binding Agent	Surfactant	Diluent	Additional Details
1	3-20%^	25-94%^	0.1-10%^	0-35%^	0.5-1%^	5-15%^	-
10	25-200 mg	250,500,625,750,850,1000 mg	1-2%^	~7%^	~0.5%^	~10%^	-
21	3-20%^	25-94%^	0.1-10%^	0-35%^	0.5-1%^	5-15%^	-
22	64.25 mg *	500 mg	13.8 mg SSF	48.2 mg PVP	3.45 mg SLS	59.3 mg MCC	17.2 mg film coating
23	64.25 mg *	850 mg	22.3 mg SSF	78.2 mg PVP	5.60 mg SLS	96.1 mg MCC	27.9 mg film coating
24	64.25 mg *	1000 mg	26 mg SSF	91.0 mg PVP	6.50 mg SLS	112.3 mg MCC	32.5 mg film coating
25	64.25 mg *	500 mg	6.89 mg MS	48.2 mg PVP	-	69.6 mg MCC	17.2 mg film coating
26	64.25 mg *	1000 mg	13.0 mg MS	91.0 mg PVP	6.5 mg SLS	125.25 mg MCC	32.5 mg film coating
27	128.5 mg **	1000 mg	26 mg SSF	91.0 mg PVP	6.50 mg SLS	48 mg MCC	-

28	128.5 mg **	500 mg	15.4 mg SSF	53.8 mg PVP	3.84 mg SLS	66.5 mg MCC	-

^- % by weight, * Equivalent to 50 mg free base anhydrate, ** Equivalent to 100 mg free base anhydrate

Patent No. 5: Polymorph (Amorphous) Patent of Sitagliptin by Merck Sharp & Dohme Corp.

- Title: Amorphous form of a phosphoric acid salt of a DPP-4I
- Patent / Publication No.: US7,612,072B2
- Legal Status: Est. expiry: Sep 09, 2025 + 355 days [16]

Claims an amorphous form of the dihydrogenphosphate salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I, characterized by the X-ray powder diffraction pattern of Figure 1.

Patent No. 6: Polymorph (Crystalline) Patent of Sitagliptin by Merck & Co.

- Title: Novel Crystalline Salts of a DPP-4I
- Patent / Publication No.: US2008/0227786A1
- Legal Status: Abandoned - Failure to Respond to an Office Action [17]

Claims a crystalline salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8h)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine or a hydrate thereof; wherein HX is an acid selected from hydrochloric acid, tartaric acid, benzenesulfonic acid, p-toluenesulfonic acid, and 10-camphorsulfonic acid.

7. Investigational New Drug Application (IND)

It is an application filed to the FDA prior to human testing. It gives a full description of chemistry, manufacturing and controls, pharmacology and toxicology information, and any previous human experience.

Types of IND

- Investigator IND: Initiated by a physician to study approved or unapproved drugs.
- Emergency Use IND: Allows drug use in urgent cases without prior IND approval.
- Treatment IND: Grants access to promising drugs during FDA review for serious conditions.
- Exploratory IND: Phase 1 studies drug behavior (PK/PD) at low doses.
- Expanded Access IND: Provides investigational drugs for life-threatening conditions with no alternatives. [18]

IND Categories

- Commercial IND: Submitted by companies intending to market the product; marked in Field 6B of FDA Form 1571.
- Research IND: Submitted by investigators or institutions for scientific study, with no commercial intent; often results in publications. [19]
- Submission Format: Commercial INDs are usually submitted electronically in eCTD format; non-commercial INDs have more flexibility.

- Review Period: Sponsors must wait 30 days post-submission for FDA review. Trials may be delayed if a clinical hold is issued.

IND Content and Format

A sponsor who intends to conduct a clinical investigation shall submit an IND including, in the following order:

- Cover sheet (Form FDA 1571)
- Table of contents
- Introductory statement and general investigational plan
- Investigator's brochure
- Protocols
- Chemistry, manufacturing, and control (CMC) information
- Pharmacology and toxicology information
- Previous human experience with the investigational drug
- Additional information
- Drug dependence and abuse potential
- Radioactive drugs
- Pediatric studies
- Other information [20]

8. Clinical Studies

A prospective study evaluates interventions versus a control by following participants forward in time. Clinical trials, conducted in four phases under strict protocols, assess investigational agents. Human studies begin after FDA and IRB approval of an IND. An NDA is submitted only after successful completion of Phases I-III, with the FDA's CDER reviewing all data and risk-benefit analyses.

Exploratory IND (Phase 0) studies are early-stage trials focusing on pharmacokinetics and pharmacodynamics with minimal human exposure and subtherapeutic doses, aiming to identify ineffective candidates. Phase I trials, also known as dose-escalation studies, assess safety, maximum tolerated dose, PK, PD, and drug interactions in a small group of volunteers. Phase II trials, also called "therapeutic exploratory," involve a larger patient group to gather data on safety, PK, PD, and preliminary efficacy, while determining optimal dosage and treatment regimens. Phase III trials, known as "therapeutic confirmatory" with 300-3000 participants, confirm efficacy, monitor adverse effects, and use randomization, blinding, and intention-to-treat analysis to ensure validity and reliability. [21]

Study 3: Glycemic Outcomes in Clinical Trials of Januvia (Sitagliptin Monotherapy)

- Sample size: Over 1,200 patients (Januvia + Placebo)
- Objective: To evaluate the efficacy and safety of the drug in patients with T2D
- Study Design: Double-blind, placebo-controlled
- Study Duration: 18 weeks, 24 weeks
- Population: Patients with inadequate glycemic control, representative of real-world treatment candidates.

Parameter	18-Week Study	24-Week Study

	Januvia	Placebo	Januvia	Placebo
A1C (%)	N= 193	N= 103	N= 229	N= 244
Baseline Mean	8.0%	8.1%	8.0%	8.0%
Change from Baseline	-0.5%	0.1%	-0.6%	0.2%
Difference from Placebo	-0.6%		-0.8%	
% Achieving A1C < 7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	N= 201	N= 107	N= 234	N= 247
Baseline Mean (mg/dL)	180	184	170	176
Change from Baseline	-13	7	-12	5
Difference from placebo	-20 mg/dL		-12 mg/dL	
2-hour PPG (mg/dL)	*Data not available*		N= 201	N= 204
Baseline Mean (mg/dL)	*Data not available*		257	271
Change from Baseline			-47 mg/dL	
Effect on Body Weight	No effect with Januvia, Small loss with the placebo			
Effect on Lipids	Similar to placebo			
Dose Comparison (100 vs 200 mg)	No additional benefit from 200 mg			

Observation: Clinical studies of Januvia showed significant improvements in glycemic control, with greater reductions in A1C, FPG, and PPG compared to placebo. More patients achieved the target A1C goal, with no weight gain or adverse lipid changes. The 100 mg dose proved effective, with no added benefit from the 200 mg dose. In T2D patients with chronic renal insufficiency, Januvia maintained a favorable safety profile, though a slight increase in serum creatinine was observed in those with moderate renal insufficiency.

Study 4: Comparative Efficacy of Januvia 100 mg + Metformin vs. Placebo + Metformin

- Sample size: 701 patients with T2D
- Objective: To evaluate the efficacy and safety of Januvia in combination with metformin
- Study Design: Randomized, double-blind, placebo-controlled
- Study Duration: 24 weeks
- Comparison: Januvia 100 mg + metformin vs. placebo + metformin
- Population: Patients with inadequate glycemic control (A1C 7%-10%) on metformin, on combination therapy, or previously untreated (converted to metformin monotherapy)

Parameter	Placebo + Metformin	Januvia 100 mg + Metformin
A1C (%) — N	N = 224	N = 453
Baseline	8.0	8.0
Change from baseline	-	-0.7
Difference	-0.7	
Patients achieving A1C <7%	41 (18%)	213 (47%)

FPG (mg/dL) — N	N = 226	N = 454
Baseline	174	170
Change from baseline	+9	-17
Difference	-25	
2-hour PPG (mg/dL) — N	N = 182	N = 387
Baseline	272	275
Change from baseline	-11	-62
Difference	-51	

Observation: Januvia® 100 mg once daily with metformin significantly improved glycemic control in T2D patients, reducing A1C, FPG, and 2-hour PPG. A higher percentage achieved the target A1C (<7%) with Januvia, and fewer required rescue therapy (5% vs. 14% with placebo). Both groups had similar body weight changes, with no weight gain on Januvia. The combination therapy was well tolerated with no unexpected safety concerns.

9. Patent Filing: Patent No. 7: Methods of Use/Treatment Patent of Sitagliptin by Pfizer

- Title: Dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives
- Patent / Publication No.: US9,439,901B2
- Legal Status: OB Expiry: Oct 21, 2030 [22]

Table 4: Claims for Pharmaceutical Composition Containing Sitagliptin for Obesity and T2DM Treatment

Claim no.	Claims
1, 2	A method for treating obesity T2DM in humans comprising: (i) (1S,2S,3S,4R,5S)-5-[-4-chloro-3-(4-ethoxy-benzyl)-phenyl]-1-hydroxymethyl-6,8-dioxa-bicyclo[3.2.1]octane-2,3,4-triol; (ii) A pharmaceutically acceptable excipient, diluent, or carrier and (iii) Sitagliptin, or a pharmaceutically acceptable salt thereof.

10. New Drug Application (NDA)

The New Drug Application (NDA) is the formal request for FDA approval to market a new drug in the U.S. It includes data from preclinical studies and clinical trials under an IND application, aiming to demonstrate the drug's safety, effectiveness, and quality. The FDA has 60 days to begin the review after submission. The NDA ensures the drug's safety and efficacy, appropriate labeling, and compliance with manufacturing standards for identity, strength, quality, and purity. [23]

Contents and Format of an NDA

- Application form FDA 356
- Index
- Summary

- Technical sections: Chemistry, manufacturing and controls; Non-clinical pharmacology and toxicology; Human pharmacokinetics and bioavailability; Microbiology; Clinical data; Statistical section; Pediatric use section
- Samples and labelling
- Case report forms and tabulations
- Patent information and certification
- Claimed exclusivity
- Financial certification or disclosure statement
- Format: Archival copy, Review copy, Field copy, and Electronic format submissions [24]

11. Patent Filing: Patent No. 8: Combination Patent of Sitagliptin by Merck Sharp & Dohme Corp.

Combination patents protect formulations that include two or more active ingredients, often used to enhance therapeutic effects or reduce side effects.

1. Title: Chewable Dosage Forms Containing Sitagliptin and Metformin
2. Patent / Publication No.: US11,096,890B2
3. Legal Status: Est. expiry: Sep 25, 2038 [25]

Table 5: Composition Claims for Chewable Sitagliptin-Metformin Formulation

Claim no.	Component	Range (wt.%)
1.	Combination of active pharmaceutical ingredients (Metformin Hydrochloride and Sitagliptin or a pharmaceutically acceptable salt thereof)	15 to 40%
	Fully or partially pregelatinized starch	25 to 45%
	Polyethylene glycol 8000	0.5 to 10%
	Partially hydrogenated palm kernel oil (lubricant)	5 to 20%
	Emulsifier, Flavoring agent, Sweetener	Not specified
	Dosage form type	Chewable

12. Phase IV

Phase IV studies, or post-marketing surveillance (PMS), monitor a drug's long-term safety and effectiveness after regulatory approval. These observational, non-interventional studies assess rare adverse effects, drug performance in real-world settings, and use in special populations. They can support label expansion, safety updates, and inform clinical or regulatory decisions. While not all Phase IV studies are PMS, all PMS studies occur in Phase IV, continuing pharmacovigilance and spontaneous adverse event reporting. [26]

Study 5: A Post Marketing Safety Study of Sitagliptin (Januvia®) (MK-0431-234)

- ClinicalTrials.gov ID: NCT01354990
- Sample Size: 2,975 participants
- Objective: To obtain safety information on the use of Januvia® from endocrinologists, diabetologists, internists, and general practitioners.

- Study Design: Observational model, Cohort, Time perspective: Retrospective
- Study Duration: Up to approximately 28 months
- Comparison: No control or comparator group (observational study). Data collected retrospectively on patients prescribed sitagliptin.
- Population: Patients diagnosed with T2DM who were prescribed Januvia® and treated by endocrinologists, diabetologists, internists, or general practitioners.

Outcome Measures:

Adverse Events	Affected / at Risk (%)
All-Cause Mortality	--/--
Serious Adverse Events	0/2974 (0.00%)
Other (Not Including Serious) Adverse Events	0/2974 (0.00%)

Post-marketing Adverse Reactions

Additional adverse reactions have been reported during post-approval use of Januvia, but their frequency and causal relationship to the drug are uncertain. Reported adverse reactions include: Hypersensitivity reactions, hepatic enzyme elevations, acute pancreatitis, worsening renal function, tubulointerstitial nephritis, disabling joint pain (arthralgia), bullous pemphigoid, constipation, vomiting, headache, and pruritus (itching). [27]

13. Abbreviated New Drug Application (ANDA)

Pharmaceutical manufacturers are divided into branded companies, which develop new drugs, and generic manufacturers, which produce cost-effective alternatives after patent expiry. In the U.S., branded companies obtain approval via a New Drug Application (NDA), while generic manufacturers use an Abbreviated New Drug Application (ANDA), proving bioequivalence to a Reference Listed Drug (RLD) without full clinical trials. The ANDA process, established by the Hatch-Waxman Act of 1984, promotes affordable medications and preserves innovation incentives, with generic drugs now making up nearly 90% of U.S. prescriptions. [28-31]

Content and Format of ANDA

1. Application form
2. Table of contents
3. Basis for ANDA submission
4. Conditions of use
5. Active ingredients
6. Route of administration, dosage form, strength
7. Bioequivalence
8. Labeling
9. Chemistry, manufacturing and control
10. Samples
11. Patent certification
12. Financial certification or disclosure statement [32]

To obtain ANDA approval, applicants must demonstrate that their generic drug matches the Reference Listed Drug (RLD) in active ingredient, dosage form, strength, and route of administration, with proven bioequivalence and equivalent quality. Challenges include regulatory barriers (patents, exclusivities), financial constraints, and scientific hurdles, especially for complex formulations. NCE exclusivity grants five years of market protection, with Paragraph IV certifications allowing challenges after four years. The FDA's Office of Generic Drugs may grant tentative approval when patents or exclusivities block entry. Initiatives like GDUFA and DCAP aim to enhance generic competition.

Patent Term Extension: The Hatch-Waxman Act (1984) allows up to five years of patent term restoration to compensate for time lost during FDA review, with total market exclusivity limited to 14 years from FDA approval. The extension is based on the time spent in the testing phase (human trials to NDA submission) and the approval phase (NDA submission to approval). The FDA calculates the extension as the full approval phase plus half of the testing phase, minus any delays caused by the applicant. Most of the extension typically comes from the testing phase. [33]

Exclusivity: Exclusivity is a marketing right granted by the FDA upon drug approval to promote innovation and allow future generic competition. It blocks ANDA or 505(b)(2) submissions for a set period, depending on the exclusivity type, but does not extend a patent's term. Under the Hatch-Waxman Act, the main types are defined in 21 C.F.R. 314.108:

- Orphan Drug Exclusivity (ODE) - 7 years
- New Chemical Exclusivity (NCE) - 5 years
- New Clinical Investigations (NCI) - 3 years
- Pediatric Exclusivity (PED) - 6 months added to existing Patents/Exclusivity
- 180-Day Exclusivity - first generic applicant [34]

Table 6: ANDA Tentative Approvals for Sitagliptin

ANDA No.	Drug Name	Company	Action Date
202473	Sitagliptin Phosphate	Mylan Pharmaceuticals Inc	10/10/2012
202423	Sitagliptin Phosphate	Sun Pharma Global	04/11/2013
202425	Sitagliptin Phosphate	Apotex Inc	02/18/2014
202327	Sitagliptin Phosphate	Watson Labs Inc	04/15/2014
202487	Sitagliptin Phosphate	Teva Pharmaceuticals USA	02/23/2015
208186	Sitagliptin Phosphate	Zydus Pharmaceuticals USA	09/07/2018
214784	Sitagliptin Phosphate	Ajanta Pharma Ltd	01/05/2021
214693	Sitagliptin Phosphate	Unichem Labs Ltd	07/09/2021
202387	Sitagliptin Phosphate	Sandoz Inc	12/27/2021
214054	Sitagliptin	Intas Pharmaceuticals USA	03/02/2022
215155	Sitagliptin Phosphate	Alkem Labs Ltd	04/08/2022
214433	Sitagliptin	Lupin Ltd	12/14/2023

216919	Sitagliptin Phosphate	Mankind Pharma Ltd	01/02/2024
216886	Sitagliptin	Prinston Pharma Inc	10/03/2024
212952	Sitagliptin	Aurobindo Pharma Ltd	02/11/2025
216337	Sitagliptin	ScieGen Pharmaceuticals Inc	03/06/2025

There are 16 generic manufacturers who have received tentative FDA approval for Januvia® (Sitagliptin Phosphate Monohydrate), but cannot market their products until patent or exclusivity expiry. The first generic to gain final approval at patent expiry is granted a 180-day exclusivity, encouraging early patent challenges. During this period, the first generic is priced below the brand but maintains high margins. After 180 days, other generics enter, increasing competition, reducing prices, and improving patient access while lowering healthcare costs.

Types of ANDA Certification Clauses

- Paragraph I: No patents listed for the RLD, no patent issues.
- Paragraph II: Patent for the RLD has expired, generic can be approved immediately.
- Paragraph III: Applicant acknowledges the patent's validity and waits until expiration to launch.
- Paragraph IV: Applicant challenges the patent's enforceability or infringement, with potential for 180-day exclusivity if successful.

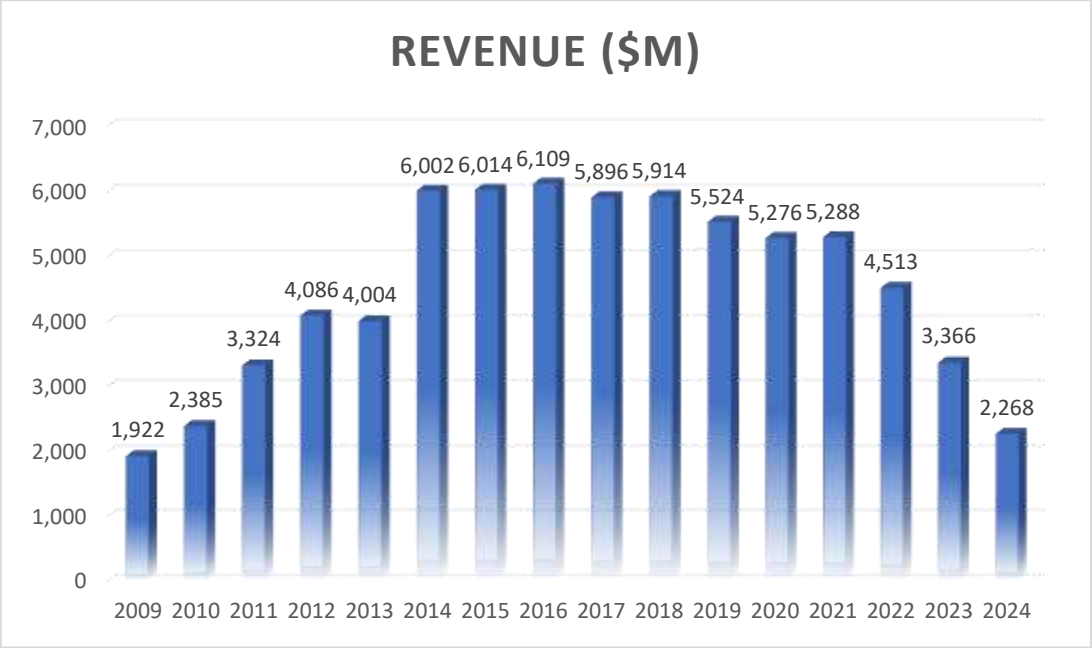
Timeline for Paragraph IV Filing

- ANDA Submission: Generic submits ANDA with Paragraph IV certification.
- Notice: Within 20 days, the generic notifies the brand and patent holder.
- Patent Holder's Response: 45 days to file a lawsuit.
- 30-Month Stay: FDA approval is delayed for 30 months if a lawsuit is filed.
- Court Decision: Approval depends on the lawsuit outcome.
- 180-Day Exclusivity: First filer receives 180-day exclusivity. [35]

Paragraph IV Patent Certifications as of 17 March 2025 for Januvia®: The P-IV Patent Certifications for Januvia® involve 6 generic manufacturers challenging its patents through ANDA submissions made on October 18, 2010. However, full generic competition is limited until the last qualifying patent expires on May 24, 2027. If the first filer succeeds in their challenge, they may receive 180-day market exclusivity. This regulatory process balances patent protection with the availability of lower-cost generics. [36]

Januvia's Financial Performance (2009-2024)

Januvia®, Merck's blockbuster DPP-4 inhibitor for T2DM, has shown strong financial performance since its 2006 launch. While early revenue data is unavailable, reports from 2009 onward show peak sales from 2010 to 2020, reflecting broad adoption and minimal generic competition. In recent years, however, revenue has declined due to rising generic threats, patent expirations, and market competition. A detailed year-wise revenue analysis highlights the drug's market trends, with data from 2006 to 2008 not available. [37]



Discussion

The development of Januvia® (Sitagliptin Phosphate Monohydrate) highlights the crucial role of IP patents in the pharmaceutical industry, especially for innovative antidiabetic drugs. Patents enabled Merck to protect its compound, formulation, usage methods, and manufacturing processes, securing market exclusivity and recouping R&D costs. This exclusivity supported profitability until patent expiration allowed generic competition, lowering costs and improving access. The U.S. Hatch-Waxman Act balances innovation incentives with generic entry, while patent disputes, as seen with Januvia, can impact market dynamics by affecting exclusivity periods and drug accessibility.

Conclusion

The case of Januvia® (Sitagliptin) illustrates the pivotal role of patents and their expiry in shaping innovation and market competition in the drug development process. Patent protection enabled Merck to safeguard its innovation, recover R&D investments, and maintain market exclusivity. However, the expiry of these patents opened the market to generics, intensifying competition while improving affordability and access. This real-world example underscores the dual impact of patents driving pharmaceutical innovation while also influencing post-expiry market dynamics. A balanced patent framework is essential to support ongoing innovation without compromising public access to essential medicines.

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