

Global Harmonization of Excipient Standards: A Comparative Study of USA, UK, and India using Itraconazole Formulations as Case Study

Rajaganapathy Kaliyaperumal*, Dhinesh Pandian Pandian

Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, INDIA.

ABSTRACT

Pharmaceutical excipients are no longer regarded merely as inactive ingredients but are recognized as critical functional components that can significantly influence the safety, stability, quality, and therapeutic performance of drug products. However, differences in excipient regulatory requirements and quality standards among countries can create challenges for pharmaceutical development, manufacturing, and global supply chains. This study aimed to compare pharmaceutical excipient standards and regulatory approaches in the USA, UK, and India and to examine the need for greater global harmonization. Itraconazole formulations were used as a case study to demonstrate how excipient selection and functionality can influence the performance of a poorly soluble drug. A comparative review of excipient regulatory frameworks and quality requirements in the USA, UK, and India was conducted, with emphasis on the approaches of the FDA, MHRA, and CDSCO, respectively. International guidance relating to Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) for pharmaceutical excipients was also considered. Various oral itraconazole formulations were comparatively evaluated from the published literature, focusing on the roles of excipients such as cyclodextrins and pH-sensitive polymers in modifying drug solubility, absorption, and therapeutic performance. The comparison identified differences in regulatory oversight, quality requirements, and approaches to excipient control across the three regulatory systems. International initiatives, particularly those promoted by IPEC, provide an important framework for reducing such regulatory divergence. The itraconazole case study demonstrated that excipient selection and formulation technology can substantially affect drug solubility, bioavailability, pharmacokinetic behavior, and ultimately therapeutic performance. These findings support the importance of functionality-related excipient specifications in addition to conventional quality requirements. Greater global harmonization of pharmaceutical excipient standards is necessary to support consistent product quality, patient safety, and efficient international pharmaceutical development and supply. Adoption of scientifically justified, functionality-based specifications, strengthened GMP and GDP requirements, and improved supply-chain transparency could promote regulatory convergence among the USA, UK, India, and other regions. The itraconazole case study further demonstrates that excipient quality and functionality should be considered integral determinants of drug-product performance rather than merely secondary formulation factors.

Keywords: BCS, CDSCO, Class II drugs, Excipient quality control, Excipient standards, FDA, Global harmonization, Good Manufacturing Practices (GMP), IPEC, Itraconazole, MHRA, Pharmaceutical excipients, Regulatory convergence.

Correspondence:

Prof. Rajaganapathy Kaliyaperumal

Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai, Tamil Nadu, INDIA.

Email: rajaganapathy249@gmail.com

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INTRODUCTION

The current pharmaceutical industry is based on the delivery of safe, effective, and stable medicinal products. While the Active Pharmaceutical Ingredient (API) is fairly recognized for its

therapeutic effect, it is associated substances known as excipients that enable its transformation into a feasible dosage form. These materials, which can constitute as much as 90% of a finished product's mass, are essential for a multitude of functions, from providing bulk and aiding manufacture to controlling drug release and ensuring stability (Abrantes *et al.*, 2016; Rowe *et al.*, 2009). Despite their criticality, pharmaceutical excipients exist in a complex regulatory space across major global jurisdictions such as the United States (USA), the United Kingdom (UK), and India. This regulatory disharmony presents difficult challenges to pharmaceutical development, global manufacturing strategies,



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and the integrity of the international supply chain (Strickley, 2004).

Historical perceptions of excipients as pharmacologically "inert" or "inactive" substances are the root cause of this regulatory lapse (Sheskey *et al.*, 2017). Early pharmacological and regulatory science focused mainly on the API, viewing excipients as mere vehicles or processing aids (Katdare and Chaubal, 2006). These views led to the development of vigorous, dedicated regulatory frameworks for APIs, while oversight for excipients remained largely indirect, managed through the review of the final drug product application. This historical view was terribly challenged by the elixir of sulfanilamide tragedy in the United States in 1937, where the untested excipient Diethylene Glycol (DEG), used as a solvent, resulted in over 100 deaths. This event was a turning point moment, demonstrating clear views that excipients are not universally harmless. It is directly leading to the passage of the landmark Federal Food, Drug, and Cosmetic Act of 1938, which mandated pre-market proof of safety for all new drugs. The persistence of such risks into the modern age is evidenced by more recent global incidents involving DEG and Ethylene Glycol (EG) contamination in excipients like glycerin and propylene glycol, which have led to hundreds of fatalities, mostly among children (Pifferi *et al.*, 1999). These events urge as a clear reminder that rigorous control of excipient quality is a contemporary and urgent public health imperative.

As formulation science has progressively developed, the role of excipients has emerged far beyond that of simple fillers. Modern drug delivery systems depend on highly functional excipients, such as permeation enhancers, solubilizing agents, and sustained-release materials, which actively modify the pharmacokinetic and pharmacodynamic behaviour of the API (Allen *et al.*, 2014). The "inert" label has thus become a blatant misrepresentation. However, regulatory frameworks have often been slow to adapt to this scientific reality, resulting in the current fragmented global landscape. A further complication arises from the economic nature of the excipient supply chain. Many excipients are large-volume, multi-use chemicals sourced from the food, cosmetic, or industrial chemical sectors, which may not operate under the stringent Good Manufacturing Practices (GMP) expected by the pharmaceutical industry (Dave *et al.*, 2015). This creates a fundamental contrast between an excipient's status as a low-cost commodity in its primary market and its high-impact, high-risk role within a pharmaceutical formulation, introducing major vulnerabilities that regulators and manufacturers must mitigate.

This article tries to address these complex issues by pursuing four primary objectives. First, it will provide a basic overview of excipient science, classify these materials and detail their multifunctional roles in ensuring drug product quality, safety, and efficacy. Second, it will conduct a comprehensive, in-depth comparative analysis of the regulatory frameworks for excipient

control in the USA, UK, and India, highlighting key points of convergence and divergence. Third, it will evaluate the vital role of the International Pharmaceutical Excipients Council (IPEC) as a global industry body working to establish harmonized quality standards in a field lacking formal international regulation. Finally, through a detailed case study of oral Itraconazole formulations, this article will empirically demonstrate the direct impact of excipient selection on a drug's biopharmaceutical performance. By linking regulatory principles and scientific realities to tangible clinical outcomes, this work aims to emphasize the critical and non-negotiable need for vigorous, harmonized, and scientifically-informed quality control of pharmaceutical excipients.

METHODOLOGY

This comparative narrative approach to examine pharmaceutical excipient standards, regulatory requirements, and harmonization practices in the United States of America (USA), United Kingdom (UK), and India. The literature assessment focused on the regulatory control, quality requirements, safety considerations, Good Manufacturing Practices (GMP), Good Distribution Practices (GDP), pharmacopoeial standards, and functional performance of pharmaceutical excipients. Particular attention was given to the regulatory approaches of the United States Food and Drug Administration (FDA), Medicines and Healthcare products Regulatory Agency (MHRA), Central Drugs Standard Control Organisation (CDSCO), and relevant international organizations involved in excipient quality and harmonization. Relevant published literature and regulatory information concerning pharmaceutical excipients were reviewed to identify similarities and differences among the selected regulatory systems. The review considered information relating to established and novel excipients, excipient safety evaluation, pharmacopoeial specifications, labelling requirements, supplier qualification, manufacturing controls, distribution practices, and international harmonization initiatives. Particular consideration was given to guidance and standards associated with the United States Pharmacopeia-National Formulary (USP-NF), British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), Indian Pharmacopoeia (IP), International Pharmaceutical Excipients Council (IPEC), and other regulatory and quality frameworks discussed in this review.

Literature relevant to itraconazole formulations was additionally evaluated as a case study to demonstrate the functional importance of excipients in drug-product performance. The comparison focused on conventional itraconazole capsules, oral solution, and SUBA-itraconazole formulations. Particular emphasis was placed on the roles of functional excipients, including hydroxypropyl- β -cyclodextrin and hypromellose phthalate, and their influence on drug solubility, dissolution, absorption, bioavailability, pharmacokinetic variability, food

effects, and sensitivity to gastric pH. Evidence relevant to the regulatory and pharmaceutical objectives of the review was included, whereas information unrelated to excipient regulation, quality, functionality, harmonization, or itraconazole formulation performance was excluded from the comparative synthesis. The extracted information was synthesized descriptively rather than subjected to quantitative meta-analysis. Regulatory requirements were compared across the USA, UK, and India to identify areas of convergence, divergence, and potential opportunities for harmonization. Findings from the itraconazole case study were subsequently integrated with the regulatory comparison to illustrate why excipient quality specifications should consider functional performance in addition to conventional identity, purity, and safety requirements

THE MULTIFACETED ROLE OF EXCIPIENTS IN PHARMACEUTICAL FORMULATIONS

A complete understanding of excipient regulation necessitates a firm grasp of their scientific purpose and impact. Formally, an excipient is defined as any substance other than the API or pro-drug that is purposely included in the manufacturing process or is contained in a finished pharmaceutical dosage form (Aulton and Taylor, 2018). This definition, reiterated by major pharmacopoeias and regulatory bodies like the International Pharmaceutical Excipients Council (IPEC), the United States Pharmacopeia-National Formulary (USP-NF), and the European Pharmacopoeia (Ph. Eur.), encompasses a vast and diverse array of materials. While traditionally classified by their origin—such as animal (e.g., lactose, gelatin), vegetable (e.g., starch, cellulose), mineral (e.g., calcium phosphate, talc), or synthetic (e.g., polyethylene glycols, povidone)—a more practical and scientifically relevant classification is based on their function within the dosage form (Abrantes *et al.*, 2016).

Functional Classification and Impact on Product Attributes

Excipients are selected to perform specific roles that are important for the manufacturability, stability, and performance of the final drug product. Their functions are diverse and often synergistic, as detailed in Table 1.

Key functional categories include

Diluents and Fillers: These agents, such as Microcrystalline Cellulose (MCC) and lactose, provide the necessary bulk for formulations containing highly potent APIs, where the dose of the active substance is too small to be handled conveniently during manufacturing. They ensure accurate and uniform dosing (Abrantes *et al.*, 2016; Thoorens *et al.*, 2014).

Binders: Substances like povidone, starch paste, and hypromellose are used to impart cohesive qualities to the powdered material

in solid dosage forms, ensuring that tablets remain intact after compression (Abrantes *et al.*, 2016).

Disintegrants: These excipients, including croscarmellose sodium and sodium starch glycolate, are added to tablets and capsules to facilitate their breakup into smaller particles upon contact with gastrointestinal fluids. This process is critical for initiating drug dissolution and subsequent absorption (Sheskey *et al.*, 2017).

Lubricants, Glidants, and Anti-adherents: This group of materials improves the manufacturing process. Lubricants like magnesium stearate reduce friction between the tablet and the die wall during ejection in compression. Glidants such as colloidal silicon dioxide improve the flow properties of the powder blend, ensuring uniform filling of the tablet die. Anti-adherents prevent the formulation from sticking to the punches and dies.

Solubilizers and Wetting Agents: For APIs with poor aqueous solubility (a characteristic of many modern drug candidates), excipients like surfactants (e.g., polysorbates) and cyclodextrins are essential. They enhance the dissolution rate and extent of the drug, thereby directly improving its bioavailability (Zarmpi *et al.*, 2017).

Modified-Release Agents: Polymers such as hypromellose, ethylcellulose, and various methacrylic acid copolymers are used to control the rate or site of drug release. They can be used to create sustained-release formulations that maintain therapeutic drug levels over an extended period or enteric-coated formulations that protect the drug from the acidic stomach environment and release it in the intestines (Allen *et al.*, 2014).

Stabilizers: To ensure the drug product maintains its quality, potency, and safety throughout its shelf life, various stabilizers are employed. Antioxidants (e.g., ascorbic acid, butylated hydroxytoluene) prevent oxidative degradation of the API. Buffering agents maintain the pH of liquid formulations, while chelating agents like Edetic Acid (EDTA) make complex with metal ions that can catalyze degradation reactions (Zarmpi *et al.*, 2017).

Preservatives: In multi-dose liquid and semi-solid formulations, antimicrobial preservatives such as parabens and benzalkonium chloride are necessary to prevent the growth of bacteria and fungi that may be introduced during use.

Organoleptic Agents: Excipients such as sweeteners, flavors, and colorants are used to improve patient acceptance and compliance by masking unpleasant tastes or odors and providing a consistent and identifiable appearance.

The development of pharmaceutical manufacturing, particularly the shift towards more efficient processes like direct compression and continuous manufacturing, has driven the development of "high-functionality" and "co-processed" excipients. A single high-functionality excipient, such as hypromellose, can serve multiple roles as a binder, viscosity-increasing agent, film-coater,

and suspending agent. Co-processed excipients are engineered combinations of two or more excipients designed to possess superior physical properties (e.g., flowability, compressibility) compared to a simple physical mixture. This trend emphasizes the increasing complexity and criticality of excipients; the performance of an entire formulation can now depend on the sophisticated, engineered properties of a single excipient raw material. Consequently, any variability in these complex excipients can have a magnified and detrimental effect on the quality of the final drug product.

Impact on Drug Safety and Efficacy

The assertion that excipients are "inactive" is an oversimplification. Their impact on the safety and efficacy of a medicinal product is direct and significant. Beyond their intended technological functions, excipients can interact with the API, with each other, and with the patient's physiological systems in ways that fundamentally modify the drug's performance.

The most critical influence is on bioavailability, the rate and extent to which the API reaches the systemic circulation (Zarmpi *et al.*, 2017). For poorly soluble drugs, the choice of functional and solubilizing excipients can be a determining factor in improving drug dissolution and bioavailability (Van der Merwe *et al.*, 2020). Conversely, an inappropriate excipient can affect bioavailability. A classic and cautionary example occurred in Australia in the late 1960s with the anticonvulsant drug phenytoin. A manufacturer replaced the excipient calcium sulfate dihydrate, which is poorly soluble and acted as a matrix-former to slow drug release, with the highly soluble lactose. This seemingly minor change caused a rapid and massive release of phenytoin, leading to toxic plasma concentrations and severe adverse events in patients.

Excipients can also involve in physical and chemical interactions with the API, providing drug stability. For example, reducing sugars like lactose can react with APIs containing primary amine groups via the Maillard reaction, leading to degradation and loss of potency (Crowley *et al.*, 2001). The presence of impurities in an excipient, such as peroxides in povidone or polyethylene glycols, can initiate oxidative degradation of sensitive APIs.

Moreover, new research indicates that certain excipients are not completely inert pharmacologically. Certain surfactants and polymers can inhibit or induce the activity of metabolic enzymes, such as the Cytochrome P450 (CYP) family, or drug transporters like P-glycoprotein (Jivraj *et al.*, 2000). Such interactions can significantly change the Absorption, Distribution, Metabolism, and Excretion (ADME) profile of an API, leading to unexpected drug-drug-like interactions and affecting both efficacy and toxicity. Finally, certain excipients can pose direct safety risks to specific patient populations. For example, excipients like lactose, gluten, or certain azo dyes can trigger adverse reactions in intolerant or allergic individuals, making their declaration on product labelling a matter of public health (Elder *et al.*, 2016).

The selection and control of excipients are therefore not simply a matter of formulation technology but a fundamental aspect of ensuring the overall quality, safety, and therapeutic effectiveness of any pharmaceutical product.

A COMPARATIVE ANALYSIS OF GLOBAL REGULATORY FRAMEWORKS FOR EXCIPIENT CONTROL

The global pharmaceutical market operates under a mixed regulation of national and regional regulatory systems. While significant harmonization has been achieved for APIs and finished drug products through initiatives like the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), however, the regulatory scenario for excipients remains notably fragmented. This section provides a comparative analysis of the frameworks in three key markets: the United States, the United Kingdom (representing the post-Brexit adoption of the European Union model), and India.

The United States Food and Drug Administration (FDA) Framework

In the United States, the regulation of excipients is mainly governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) and detailed in Title 21 of the Code of Federal Regulations (CFR) (Allen *et al.*, 2014). An excipient, termed an "inactive ingredient," is defined as "any component other than an active ingredient". The FDA's approach is characterized by a system of indirect control, where excipients are reviewed for safety and suitability within the context of a specific New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA).

In the US system, Inactive Ingredient Database (IID) is the basic foundation on excipient regulations. This publicly available database lists containing the details of excipients used in FDA-approved drug products, organized by route of administration and dosage form. It also provides the maximum potency (highest amount per unit dose) and Maximum Daily Exposure (MDE) for each excipient in an approved product. The IID serves as a critical reference for drug developers; to choose an excipient at or below a level previously approved for the same route of administration is generally considered acceptable and may require less extensive justification in a new application. This system effectively creates a precedent-based qualification pathway for established excipients.

For novel excipients which are defined as those not previously used in an FDA-approved drug product and without an established use in food, the regulatory requirement is substantial (Baldrick, 2000). With respect to evaluating pharmaceutical excipients, the FDA has provided guidance on "Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" that outlines a comprehensive set of toxicology studies to establish a safety

profile (Allen *et al.*, 2014). This includes studies on safety pharmacology, pharmacokinetics (ADME), genetic toxicology, repeat-dose toxicity (with duration dependent on the intended clinical use), and reproductive toxicology. For long-term use, carcinogenicity studies may also be required. The significant investment required to generate this data has been cited as a barrier to innovation, as drug developers may be hesitant to use a novel excipient into a product, fearing that a negative review of the excipient could delay or disrupt the entire drug application (Baldrick, 2000). Recognizing this challenge, the FDA recently launched the Novel Excipient Review Pilot Program (also known as PRIME) as part of its Innovative Science and Technology Approaches for New Drugs (ISTAND) initiative. This program provides a new pathway for excipient manufacturers to submit toxicology and quality data for a novel excipient to be reviewed by the FDA prior to its inclusion in any specific drug application. A successful review provides a degree of regulatory certainty, thereby encouraging the development and use of innovative excipients that could enable new drug delivery technologies or address formulation challenges (Jadaun *et al.*, 2023).

Regarding quality, there are no specific, legally mandated GMP regulations for excipients analogous to ICH Q7 for APIs (Amidon *et al.*, 1995). Instead, the FDA places the responsibility squarely on the drug product manufacturer to ensure that all components, including excipients, are of appropriate quality and purity. This is a core tenet of Current Good Manufacturing Practices (CGMPs) for finished pharmaceuticals (21 CFR Parts 210 and 211). Manufacturers are expected to qualify their suppliers, establish appropriate specifications, and perform testing to confirm the identity and quality of incoming excipients. This includes testing for high-risk contaminants, and the FDA has issued specific guidance on testing for DEG and EG in excipients like glycerine and propylene glycol. The official public standards for excipient quality are provided by the

United States Pharmacopeia-National Formulary (USP-NF), which contains monographs that establish specifications for identity, strength, quality, and purity (Haywood and Glass, 2011).

The United Kingdom (MHRA) and European Union (EMA) Framework

The regulatory framework for excipients in the UK and the EU is highly harmonized, with the UK's Medicines and Healthcare products Regulatory Agency (MHRA) having transposed the majority of EU legislation into UK law, such as the Human Medicines Regulations 2012, following its departure from the EU. The legal foundation is Directive 2001/83/EC, which governs medicinal products for human use (Leuner and Dressman, 2000).

Similar to the US, the primary mechanism for excipient control is through the review of the Marketing Authorisation Application (MAA). The "Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product"

is a key document that specifies the extensive information required in the Common Technical Document (CTD) (Janssens and Van den Mooter, 2009). Applicants must provide a detailed description of each excipient, its function in the formulation, its quality control specifications, and a justification for its choice and concentration (Hancock and Zografi, 1997). For novel excipients, a full data package equivalent to that of a new API, including manufacturing, characterization, control, and comprehensive safety data, is required.

A specific provision of the EU/UK system is the explicit requirement for the labelling of excipients with a "known action or effect." An annex to the European Commission's guideline on excipients in labelling lists specific substances (e.g., ethanol, lactose, gluten, aspartame, parabens, propylene glycol) that must be mentioned on the outer packaging and detailed in the package leaflet, along with specific warning statements (Vasconcelos *et al.*, 2007). This requirement is required to ensure the safe use of medicines by providing critical information to healthcare professionals and patients, particularly those with known allergies, intolerances, or specific medical conditions (e.g., phenylketonuria) (Serajuddin, 1999).

With respect to quality standards, the Marketing Authorisation Holder (MAH) is accountable for ensuring that all excipients comply with appropriate GMP and quality standards. The officially recognized standards are provided by the European Pharmacopoeia (Ph. Eur.). The British Pharmacopoeia (BP) is the national pharmacopoeia of the UK and is legally effective. It incorporates all monographs from the Ph. Eur., and also includes additional national monographs (Baghel *et al.*, 2016). Therefore; compliance with the BP ensures compliance with the Ph. Eur.

The Indian Central Drugs Standard Control Organisation (CDSCO) Framework

India's regulatory system for pharmaceuticals is governed by the Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetics Rules, 1945. Historically, the regulation of excipients has been less direct than in the US or EU. Excipients are not explicitly defined as 'drugs' under Section 3(b) of the Act unless they possess a therapeutic claim, meaning their control has been largely indirect and managed through the final product license. Manufacturers of excipients are expected to adhere to the quality standards outlined in the Indian Pharmacopoeia (IP), but a dedicated manufacturing license for excipients is not typically required (Shi *et al.*, 2022).

However, the Indian regulatory landscape is undergoing a significant and proactive transformation. In a major step towards greater transparency and patient safety, the Union Health Ministry has notified the Drugs (Second Amendment) Rules, 2025. This amendment to Rule 96 will, effective from March 1, 2026, mandate the disclosure of the qualitative details of all excipients on the label of the innermost container of the drug product (Williams *et al.*, 2013). This move, prompted by

recommendations from the Drugs Technical Advisory Board (DTAB), aligns India more closely with global best practices and provides critical information to both prescribers and patients.

With respect to imported excipients, particularly those that may also function as APIs (e.g., Mannitol, dextrose), registration of the substance and its manufacturing site with CDSCO is mandatory, along with an import license (Shi *et al.*, 2022). However, the same requirement is not required for import of bulk inactive substances intended for manufacturing of a drug formulation, with or without pharmacopoeial conformity. The Indian Pharmacopoeia (IP) is the official book of standards for all drugs and their components manufactured and marketed in India (Dressman *et al.*, 1998). The Indian Pharmacopoeia Commission (IPC) is actively engaged in modernizing the IP and harmonizing its standards with other major global pharmacopoeias through its participation in the Pharmacopoeial Discussion Group (PDG), signalling a clear intent to align with international quality benchmarks.

Synthesis of Regulatory Divergence and Convergence

A comparative analysis of these three major regulatory systems reveals that a common foundational principle i.e. the ultimate responsibility for excipient quality and safety persist with the manufacturer of the finished drug product. All three regions are heavily depending on their respective pharmacopoeias (USP-NF, BP/Ph. Eur., IP) to define the baseline quality standards. However, significant differences in approach exist, as summarized in Table 2.

The US relies on a precedent-based system via the IID, which is a powerful tool for established excipients but creates a high barrier for novel ones. The EU/UK system is more prescriptive regarding dossier content and has a specific, risk-based focus on labelling excipients with known physiological effects. India's framework is rapidly evolving from a less direct system to one that will soon feature some of the most transparent labelling requirements in the world.

This analysis shows a common trend in regulatory thinking on excipient that shifting from a traditionally reactive approach to an increasingly proactive, risk-based approach. The current systems in the US and EU/UK, which require pre-market review of excipients within a drug application, represent a more developed, proactive model. India's new labelling requirement is a further positive step towards more transparency and patient empowerment. The FDA's Novel Excipient Pilot Program creating a mechanism to qualify an excipient's safety profile independent of, and prior to, its use in a specific drug, thereby de-risking and encouraging innovation. This global development pathway indicates a growing recognition among regulators that excipient quality is a critical attribute that must be regulated proactively and transparently throughout the entire pharmaceutical supply chain and product lifecycle.

The Harmonizing Influence of the International Pharmaceutical Excipients Council (IPEC)

As the regulatory requirements for excipient regulation differs from country to country, it required a globally harmonized regulations for pharmaceutical excipients. The International Pharmaceutical Excipients Council (IPEC) which is a voluntary industry association has emerged and dedicated to address the above. It formed as a global federation of regional industry associations which including IPEC-Americas, IPEC Europe, IPEC Japan, IPEC China, and IPEC India. It brings together excipient manufacturers, distributors, and pharmaceutical users to develop and advocate for voluntary, harmonized quality standards (Lipinski *et al.*, 2001). IPEC's work provides a key framework for ensuring excipient quality and safety, effectively functioning as a "regulatory proxy" enforced not by law, but by the quality requirements of the pharmaceutical industry itself.

The need for such a body is rooted in the structure of the global supply chain. As regulators in the US, EU and India place the legal responsibility for excipient quality on the finished drug manufacturer, these manufacturers require a consistent, reliable standard against which to qualify and audit their numerous suppliers (Allen *et al.*, 2014). It would be a difficult process for each pharmaceutical company to develop its own proprietary set of standards. IPEC, through its collaborative, consensus-building process, has created a harmonized set of guidelines that are broadly accepted by both suppliers and users, establishing a common language and a predetermined set of expectations for quality.

The IPEC-PQG Good Manufacturing Practices (GMP) Guide

The major contribution of IPEC is "The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients" (International Council for Harmonisation [ICH], 2023) developed in collaboration with the Pharmaceutical Quality Group (PQG). This guideline is the globally recognized standard for applying GMP principles to the manufacture of excipients (International Council for Harmonisation [ICH], 2019). It is not a simple copy of the GMPs for APIs (ICH Q7) or finished drugs; rather, it is prepared on the specific requirement of the excipient industry. The guideline also extracts the ISO 9001 standard for quality management systems, which many chemical manufacturers already have in place, and integrates relevant GMP principles from ICH Q7 (Lipinski *et al.*, 2001). This approach makes the effective implementation of appropriate GMPs more accessible to excipient manufacturers who may also serve non-pharmaceutical industries. The guide covers all important aspects of a quality management system, including risk management, change control, documentation, process controls, facility and equipment management, and handling of materials. The most recent revision, published in 2022, was updated to align

with the requirements of ISO 9001:2015, ensuring its continued relevance.

Other Foundational IPEC Guidelines

Apart from GMP, IPEC has developed a set of guidelines that address other critical issues of the excipient life cycle, creating a comprehensive quality ecosystem:

IPEC Good Distribution Practices (GDP) Guide

Recognizing the importance of the supply chain of the excipients, this guide establishes requirement for the storage, transport, and handling of excipients after distribution from the manufacturing site. Its principles are designed to maintain the quality of the excipient and, crucially, to ensure supply chain security, preventing contamination, adulteration, or the entry of falsified products.

IPEC Quality Agreement Guide and Template

This guide assists the development of formal Quality Agreements between excipient suppliers and pharmaceutical users. These agreements are important for clearly defining the roles, responsibilities, and quality expectations of each party, including product specifications, change control procedures, and communication protocols.

IPEC Certificate of Analysis (CoA) Guide

A Certificate of Analysis is an important document that accompanies each batch of excipient, confirming to its compliance with specifications. This guide provides recommendations for the content and format of CoAs, aiming to ensure they are accurate, reliable, and consistent across the industry.

Table 1: Classification and Function of Common Pharmaceutical Excipients.

Functional Category	Example Excipient	Primary Role in Formulation	Impact on Drug Product Quality
Diluent / Filler	Microcrystalline Cellulose, Lactose	Provides bulk to low-dose APIs, aids in compression.	Ensures content uniformity, tablet weight, and mechanical strength (Abrantes <i>et al.</i> , 2016).
Binder	Povidone (PVP), Starch Paste	Imparts cohesion to powders, ensuring tablet integrity.	Affects tablet hardness, friability, and disintegration time (Abrantes <i>et al.</i> , 2016).
Disintegrant	Croscarmellose Sodium, Crospovidone	Promotes rapid tablet breakup in aqueous media.	Critically controls the drug dissolution rate and onset of action (Sheskey <i>et al.</i> , 2017).
Lubricant	Magnesium Stearate	Reduces friction during tablet ejection from the die.	Can negatively impact tablet hardness and dissolution if over-mixed (film formation).
Glidant	Colloidal Silicon Dioxide	Improves the flow properties of powder blends.	Ensures uniform die filling, leading to consistent tablet weight and content.
Solubilizer	Hydroxypropyl- β -cyclodextrin, Polysorbate 80	Increases the aqueous solubility of poorly soluble APIs.	Directly enhances bioavailability for BCS Class II/IV drugs (Zarmpi <i>et al.</i> , 2017).
Modified-Release Polymer	Hypromellose (HPMC), Ethylcellulose	Controls the rate and/or location of drug release.	Defines the pharmacokinetic profile (e.g., sustained, delayed, or targeted release) (Li and Wu, 2014).
Antioxidant	Ascorbic Acid, Butylated Hydroxytoluene (BHT)	Prevents oxidative degradation of the API.	Enhances chemical stability and ensures potency throughout the product shelf life.
Preservative	Benzalkonium Chloride, Methylparaben	Inhibits microbial growth in multi-dose formulations.	Ensures microbiological safety and stability of the product during its in-use period.
Coating Agent	Opadry®, Eudragit® polymers	Protects the tablet core, masks taste, provides enteric or sustained release properties.	Affects stability, patient compliance, and drug release profile (Katdare and Chaulbal, 2006).

Table 2: Comparative Overview of Excipient Regulatory Frameworks.

Key Regulatory Feature	United States (FDA)	United Kingdom (MHRA) / EU (EMA)	India (CDSCO)
Legal Basis	FD&C Act, 1938; Title 21 CFR.	Directive 2001/83/EC; Human Medicines Regulations 2012.	The Drugs and Cosmetics Act, 1940 and Rules, 1945.
Primary Control Mechanism	Review within drug application (NDA/ANDA).	Review within Marketing Authorisation Application (MAA).	Primarily indirect; review within product license.
Key Guidance/Database	Inactive Ingredient Database (IID).	Guideline on excipients in the dossier; List of excipients with known effect.	Indian Pharmacopoeia (IP).
GMP Requirement	No specific excipient GMP; responsibility of drug manufacturer under CGMP.	No specific excipient GMP; responsibility of MAH under GMP.	No specific excipient manufacturing license; adherence to IP standards expected.
Novel Excipient Pathway	Extensive nonclinical safety data required; Novel Excipient Review Pilot Program.	Full data package similar to a new API required in MAA.	No specific pathway; reviewed on a case-by-case basis.
Labelling Requirement	Not generally required to list all excipients on the label.	Mandatory labelling of all excipients for parenteral/topical/ocular; mandatory for those with "known effect" for others.	Mandatory qualitative disclosure of all excipients on the innermost label (effective March 2026).
Primary Pharmacopoeia	United States Pharmacopeia-National Formulary (USP-NF).	British Pharmacopoeia (BP) which incorporates the European Pharmacopoeia (Ph. Eur.).	Indian Pharmacopoeia (IP).

EXCiPACT™: A Third-Party Certification Scheme

To monitor these voluntary guidelines and reduce the significant audit burden on the industry, IPEC, along with other industry bodies, developed EXCiPACT™. EXCiPACT is an independent, high quality third-party certification scheme for manufacturers and distributors of pharmaceutical excipients. It utilizes auditors who are specially trained and qualified to assess compliance with the IPEC-PQG GMP and/or IPEC- GDP standards. An excipient supplier who achieves EXCiPACT certification can provide their audit report to multiple customers, who can then use it to support their own vendor qualification requirements, thereby reducing the need for numerous on-site audits (International Council for Harmonisation [ICH], 2019). This system provides a reliable, standardized, and efficient mechanism for verifying that an excipient supplier's quality systems meet the globally accepted best practices established by IPEC.

In essence, IPEC and its associated initiatives have created a stringent system of self-regulation that has become indispensable to the global pharmaceutical industry. By providing a harmonized set of standards and a reliable certification scheme, IPEC ensures a baseline level of quality and consistency that mitigates risk, facilitates global trade, and ultimately helps to protect and promote patient safety in an area where formal legal regulations are often incomplete or inconsistent across borders.

CASE STUDY: IMPACT OF EXCIPIENT SELECTION ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF ITRACONAZOLE FORMULATIONS

To move from the theoretical and regulatory to the practical and clinical, this section presents a case study on the antifungal agent Itraconazole. This example provides a detailed demonstration of the article's central thesis: that excipients are not passive additives but are often the critical enabling technologies that determine a drug's therapeutic viability. The choice of excipients and formulation strategy are the only factors that determine the significant differences in performance among different Itraconazole formulations. Therefore, stringent quality control of these components is important.

Biopharmaceutical Challenges of Itraconazole

Itraconazole is a broad-spectrum triazole antifungal agent widely used for systemic fungal infections (U.S. Food and Drug Administration [FDA], 1997). From a biopharmaceutical view, it is a challenging molecule. It is classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, meaning it possesses high membrane permeability but suffers from very low aqueous solubility (World Health Organization [WHO], 1999). It is a weak base with a pKa of 3.7, and its solubility is pH dependent. Itraconazole solubility at pH 1.0 is

approximately 4 µg/mL, and at neutral pH, its solubility drops to < 1 ng/mL, it requires a highly acidic environment (such as that of the stomach) to achieve even minimal dissolution (International Council for Harmonisation [ICH], 2021).

This poor, pH-dependent solubility leads to several clinical problems with conventional formulations. Its absorption is highly unpredictable and variable among patients, and it is significantly influenced by the presence of food and the level of gastric acidity (U.S. Food and Drug Administration [FDA], 2017). Co-administration with gastric acid suppressors like proton pump inhibitors can drastically reduce its absorption. This unpredictability in absorption results in highly variable plasma concentrations, which can easily fall below the minimum effective concentration, leading to therapeutic failure, or rise to toxic levels, increasing the risk of adverse events such as hepatotoxicity and congestive heart failure (International Council for Harmonisation [ICH], 2023). The clinical utility of the Itraconazole molecule is therefore inextricably linked to the ability of the formulation to overcome these fundamental biopharmaceutical hurdles.

Formulation Strategies and the Decisive Role of Excipients

Over the years, three distinct oral formulation strategies have been developed for Itraconazole; each depends on a different set of excipients to modulate its delivery, as detailed in Table 3.

Formulation 1: Conventional Capsules (e.g., Sporanox®)

The innovative formulation consists of 100 mg of Itraconazole coated onto sugar spheres, which are then filled into a hard gelatin capsule.

Formulation Strategy

It is a common and basic pharmaceutical manufacturing technique wherein the drug layering onto an inert core.

Key Functional Excipients

Sugar Spheres (Sucrose, Starch)

These substances use as the inert core or substrate onto which the drug is layered.

Hypromellose and Polyethylene Glycol (PEG) 20,000

These polymers act as binders and film-formers in the drug-coating solution, ensuring the Itraconazole adheres to the sugar spheres.

Gelatin Capsule Shell

It contains spheres coated with Itraconazole and Colorants such as titanium dioxide and FD&C Blue No. 1 for identification purposes (International Council for Harmonisation [ICH], 2023).

Table 3: Composition and Role of Key Functional Excipients in Itraconazole Formulations.

Formulation Type	Formulation Strategy	Key Functional Excipient(s)	Role of Excipient(s)	Impact on Drug Delivery
Conventional Capsule (e.g., Sporanox®)	Drug layering on inert cores	Sugar Spheres (Sucrose/Starch), Hypromellose	Provide an inert surface for drug coating; act as a binder/film-former.	Presents the drug in a solid, crystalline state; does not overcome inherent low solubility, leading to poor and variable absorption.
Oral Solution (e.g., Sporanox® Oral Solution)	Molecular inclusion complexation	Hydroxypropyl-β-cyclodextrin (HPCD)	Forms a soluble complex by encapsulating the lipophilic Itraconazole molecule.	Bypasses the dissolution step by pre-solubilizing the drug, leading to rapid absorption and significantly higher bioavailability (International Organization for Standardization [ISO], 2015).
SUBA Capsule (e.g., Tolsura®)	Amorphous solid dispersion in a pH-sensitive polymer matrix	Hypromellose Phthalate (HPMCP)	Forms a solid dispersion, maintaining Itraconazole in a high-energy amorphous state; dissolves at intestinal pH.	Prevents drug recrystallization and releases it as a supersaturated solution in the small intestine, maximizing absorption and reducing variability (Kapsi and Ayres, 2001).

Table 4: Comparative Pharmacokinetic Parameters of Itraconazole Formulations.

Pharmacokinetic Parameter	Conventional Capsule (100 mg)	Oral Solution (100 mg)	SUBA Capsule (65 mg)
Relative Bioavailability	~55% (with a full meal).	30-40% higher than conventional capsules.	~85% higher than conventional capsules.
C _{max} (Max. Concentration)	Fed: ~150 - 250 ng/mL Fasted: Highly variable, often very low.	Fed: ~137 ng/mL Fasted: ~180 ng/mL.	Fed: ~100 - 150 ng/mL Fasted: ~100 - 130 ng/mL.
T _{max} (Time to Max. Conc.)	Fed: ~4-5 hr Fasted: Variable.	Fed: ~4 hr Fasted: ~1.5 - 2 hr.	Fed: ~4-5 hr Fasted: ~4-5 hr.
AUC (Total Exposure)	Fed: ~2,000 - 3,000 ng·h/mL Fasted: Significantly lower and variable.	Fed: ~2,800 ng·h/mL Fasted: ~3,700 ng·h/mL.	Fed: ~2,500 - 3,000 ng·h/mL Fasted: ~2,000 - 2,500 ng·h/mL.
Terminal Half-Life (t _{1/2})	Single Dose: ~21-24 hr Steady State: ~30-40 hr.	Single Dose: ~25-30 hr Steady State: ~35-40 hr.	Single Dose: ~30-40 hr Steady State: ~60 hr.
Inter-Subject Variability (%CV)	High (often >40% for AUC and C _{max}).	Moderate (Lower than conventional capsules).	Low (Significantly reduced, often <25%).
Effect of Food	Absorption is maximal with a full meal (positive food effect) (International Council for Harmonisation [ICH], 2023).	Absorption is highest in fasted state (negative food effect) (International Organization for Standardization [ISO], 2015).	Reduced food effect; less variability between fed and fasted states (International Council for Harmonisation [ICH], 2021).
Effect of Gastric pH	Absorption significantly reduced by acid suppressors.	Less affected by gastric pH due to pre-solubilization.	Absorption not significantly affected by acid suppressors due to pH-sensitive polymer (Thiry <i>et al.</i> , 2016).

Biopharmaceutical Outcome

This formulation helps little to address the intrinsic poor solubility of Itraconazole. The drug is presented in its crystalline form, and its dissolution is entirely dependent on the prevailing conditions in the gastrointestinal tract. This results in the well-documented low and highly variable bioavailability, with a strong positive food effect (absorption is maximal when taken with a full meal) (U.S. Food and Drug Administration [FDA], 2018).

Formulation 2: Oral Solution (e.g., Sporanox® Oral Solution)

In order to improve bioavailability, an oral solution was developed that directly tackles the solubility problem.

Formulation Strategy

It is based on the principle of molecular inclusion complexation and increases the solubility of Itraconazole.

Key Functional Excipients

Hydroxypropyl-β-cyclodextrin (HPCD)

It is the important excipient in this formulation. HPCD is a cyclic oligosaccharide which having hydrophilic exterior and a lipophilic interior cavity. The lipophilic Itraconazole molecule

is encapsulated within the HPCD cavity, forming a soluble inclusion complex. This dramatically increases the concentration of Itraconazole that can be dissolved in the aqueous solution (International Organization for Standardization [ISO], 2015).

Propylene Glycol

It used as a co-solvent to further increase solubilization.

Hydrochloric Acid

Used to adjust the pH of the solution to approximately 2, which also supports to keep the weakly basic Itraconazole in its more soluble, ionized form (International Organization for Standardization [ISO], 2015).

Sorbitol and Flavoring Agents

Added to improve palatability and act as sweeteners (International Organization for Standardization [ISO], 2015).

Biopharmaceutical Outcome

This formulation bypasses the dissolution rate-limiting step of absorption, by pre-diluting the drug. It has a significantly higher and more consistent plasma concentration than the capsule formulation. The bioavailability in solution form is highest when taken in the fasted condition, as food can interfere with

the absorption of the complex (International Organization for Standardization [ISO], 2015).

Formulation 3: SUBA-Technology Capsules (e.g., Tolsura®)

The most recent innovation is a solid dosage form that utilizes advanced polymer science to improve bioavailability. SUBA stands for "Super Bio-Available."

Formulation Strategy

It is based on amorphous solid dispersion of the drug within a pH-sensitive polymer matrix (Thiry *et al.*, 2016).

Key Functional Excipients

Hypromellose Phthalate (HPMCP)

This is the most important excipient for manufacturing of SUBA-Technology. Itraconazole is molecularly dispersed within the HPMCP matrix using a spray-drying process, which prevents the drug from crystallizing and holds it in a higher-energy amorphous state (Kapsi and Ayres, 2001). HPMCP is an enteric polymer, meaning it is insoluble in the low pH of the stomach, however, rapidly dissolves at the more neutral pH of the small intestine.

Colloidal Silicon Dioxide, Magnesium Stearate, Sodium Starch Glycolate

These are traditional excipients used to ensure good powder flow, prevent sticking during manufacturing, and help the capsule contents disperse.

Biopharmaceutical Outcome

This sophisticated delivery system protects the amorphous drug from the stomach's acidic environment. Upon reaching the small

intestine, the polymer matrix dissolves, releasing Itraconazole as a supersaturated solution of nanoparticles at the primary site of absorption. This leads to a dramatic increase in bioavailability compared to the conventional capsule, allowing a lower dose (e.g., 65 mg of SUBA-Itraconazole) to achieve plasma concentrations equivalent to or greater than a 100 mg conventional capsule (International Council for Harmonisation [ICH], 2023). This formulation also shows considerably reduced pharmacokinetic variability and is less affected by food or changes in gastric pH (International Council for Harmonisation [ICH], 2021).

Comparative Analysis of Pharmacokinetic and Clinical Profiles

The selection of key functional excipients in various itraconazole formulation technologies directly influences their pharmacokinetic profiles, as summarized in Table 4 and illustrated in Figure 1. Studies have shown that the relative bioavailability of SUBA-Itraconazole is approximately 173% of the conventional capsule formulation, with 21% less inter-subject variability. The oral solution demonstrates absorption that is roughly three times greater than that of the capsule.

These pharmacokinetic differences have direct pharmacodynamic and clinical consequences. The higher and more reliable drug exposure achieved with the oral solution and SUBA-capsule leads to improved clinical efficacy and more predictable outcomes in the treatment of serious fungal infections (Sóti *et al.*, 2015). The significant differences in bioavailability mean that these dosage forms are not interchangeable (Ye *et al.*, 2007). A milligram-for-milligram substitution could lead to dangerous under-dosing or over-dosing. This case study clearly explains that for a drug like Itraconazole, the excipient is not an accessory; it is the core technology that leads the product's performance and clinical utility. It elevates the quality control of excipients from a simple

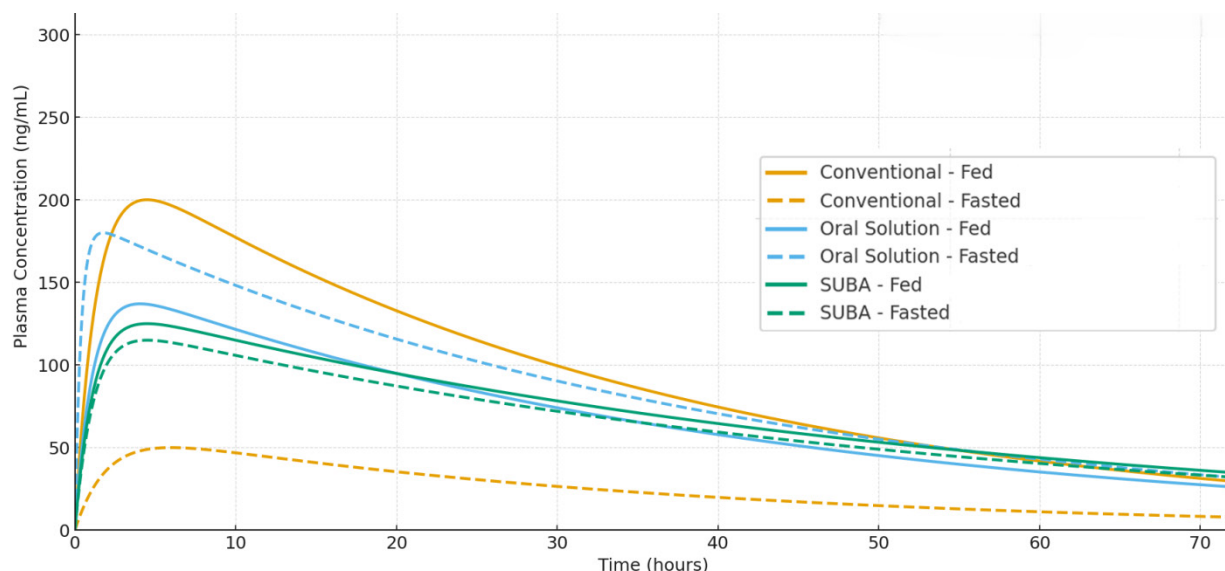


Figure 1: Pharmacokinetic Profiles of various dosage forms of Itraconazole formulations.

check of identity and purity to a critical assessment of functional performance, which must be rigorously controlled to ensure batch-to-batch consistency and predictable therapeutic outcomes.

DISCUSSION AND SYNTHESIS OF FINDINGS

Based on the analysis of above data, three critical points have been established: first, that global regulatory frameworks for excipients, while evolving, remain fragmented; second, that industry-led bodies like IPEC play a vital role in establishing baseline quality standards; and third, that the scientific and clinical impact of excipients on drug performance is significant. This section synthesizes these findings, arguing that the biopharmaceutical realities demonstrated by the Itraconazole case study provide a compelling rationale for accelerating the move towards more stringent and harmonized global regulatory oversight of excipients.

The regulatory gaps identified between the USA, UK, and India is not merely administrative differences. They create a complex and challenging environment for the global pharmaceutical industry. A Pharmaceutical firm developing a new drug for worldwide distribution must cross over the different requirements of the FDA's IID-based system, the EU/UK's dossier-centric approach with its specific labelling for "known effect" excipients, and India's emerging framework of mandatory qualitative disclosure. This lack of uniform regulatory requirements increases the cost and complexity of drug development and can make barriers to market access. More importantly, it can also lead to inconsistencies in the quality and control of excipients used in medicines intended for different parts of the world, potentially impacting patient safety.

The Itraconazole case study elaborates the excipient importance from a theoretical concept to a tangible clinical reality. The development of Itraconazole from a poorly-absorbed compound with unpredictable efficacy (conventional capsule) to a reliable therapeutic agent (oral solution and SUBA-capsule) by the impact of excipients. The use of hydroxypropyl- β -cyclodextrin and hypromellose phthalate were not minor formulation tweaks; they were fundamental technological interventions that "rescued" the API for oral delivery. This shows that for a significant portion of modern drug substances particularly those in BCS Class II and IV-the excipient is the primary factor of the product's success. Therefore, inadequate or inconsistent regulatory control over the quality of these critical functional excipients is not a theoretical risk but a direct risk to therapeutic efficacy and patient safety. A batch of HPMCP with inconsistent viscosity or pH-solubility profile, for example, could lead to a batch of SUBA-Itraconazole with altered drug release, resulting in sub-therapeutic exposure and treatment failure in a patient with a life-threatening fungal infection.

IPEC plays an important role in manufacturing of quality and safety excipients by providing various guidance documents. The

IPEC-PQG GMP Guide and its related GDP standards provides globally recognized Good Manufacturing Practices for excipient and ensuring its quality. They express the industry's collective understanding of the necessary controls to ensure that excipients are manufactured and distributed in a manner that is suitable for their vital role in drugs formulation. The EXCiPACT certification scheme added additional strength to this by providing a reliable mechanism to ensure compliance. This industry-led framework plays a significant role to address the gaps left by formal regulation, creating a more liable and secure global supply chain.

Despite of strong GMPs, surprisingly significant challenges remain. An important aspect made evident through the QbD principles is variability of excipients. Even if an excipient complies with all the specification characteristics outlined in a pharmacopoeial monograph, such minor differences between one lot of material and another in physicochemical properties (e.g., particle size distribution, moisture content or polymer viscosity) can have a crucial impact on the manufacturing process performance and final product quality. From the Itraconazole case study it becomes evident that such "minor" variations are of great relevance for high-functionality excipients as HPMCP on drug release. This suggests a future where excipient control must move beyond simple compendial testing towards a deeper understanding that should see excipient control transcend more simplistic compendial testing toward controlling the specific physical characteristics which are important for an excipients function in a particular formulation.

Overall, there is clear evidence of the need for a change of perspective. It is time for the international regulatory environment to embrace a harmonized system that recognizes excipients not as inactive afterthoughts, but as critical raw materials whose quality and functional performance require a level of scrutiny commensurate with their impact on the final medicinal product

FUTURE DIRECTIONS AND RESEARCH GAPS

Despite increasing recognition of the importance of pharmaceutical excipients, substantial gaps remain in their global regulatory oversight and quality assessment. One of the major challenges is the absence of a completely harmonized international regulatory framework specifically applicable to pharmaceutical excipients. Although the USA, UK, and India share the general principle that the finished-product manufacturer is ultimately responsible for excipient quality, differences remain in regulatory pathways, documentation requirements, labelling provisions, pharmacopoeial expectations, and approaches to novel excipients. Greater regulatory convergence is therefore required to minimize duplication, facilitate international pharmaceutical development, and ensure consistent excipient quality across global supply chains.

Future harmonization efforts should extend beyond conventional pharmacopoeial specifications based primarily on identity, purity, and general quality characteristics. Greater attention should be directed toward functionality-related characteristics that can influence manufacturing performance, drug release, stability, dissolution, and bioavailability. This is particularly important for functional excipients used in poorly soluble drugs and advanced drug-delivery systems. The itraconazole case study presented in this review demonstrates that changes in excipient type and functionality can substantially influence biopharmaceutical and pharmacokinetic performance. Therefore, future regulatory approaches should encourage scientifically justified specifications that link critical excipient attributes with the critical quality attributes of the finished drug product.

Further research is also required to understand and control lot-to-lot and supplier-to-supplier variability in pharmaceutical excipients. An excipient may comply with established pharmacopoeial specifications while exhibiting variations in physicochemical or functional characteristics that can affect formulation performance. Application of Quality by Design and risk-based approaches could facilitate the identification of critical material attributes and establish appropriate control strategies for excipients used in sensitive formulations.

Another important direction is strengthening supply-chain transparency and traceability. Greater adoption of internationally recognized GMP and GDP principles, supplier qualification systems, quality agreements, standardized Certificates of Analysis, and independent certification approaches could improve consistency throughout the excipient supply chain. Continued collaboration among regulatory agencies, pharmacopoeial organizations, excipient manufacturers, pharmaceutical companies, and organizations such as IPEC will be essential for developing globally acceptable standards.

Finally, future studies should generate stronger comparative evidence linking excipient variability with clinically relevant drug-product performance. Such evidence would help regulatory authorities determine when functionality-related testing is necessary and support the development of harmonized, risk-based specifications. Continued regulatory convergence, combined with advances in excipient science and formulation technology, may ultimately establish a more consistent global framework that supports innovation while protecting product quality, therapeutic performance, and patient safety.

CONCLUSION

This extensive study has exposed the critical but inadequately regulated role of pharmaceutical excipients in current pharmaceutical products. In view of the comparative studies of the existing regulatory frameworks in the USA, UK, and India and the case study on Itraconazole formulations, it comes to the following key conclusions. First, there is considerable inconsistency and

problematic heterogeneity in the global regulatory oversight of excipients, which creates challenges for industry and potential risks for patient's safety. Second, industry-led initiatives, particularly the guidelines issued by IPEC, provide an essential, but voluntary, framework for quality that helps to mitigate these risks. Third, and most critically, the Itraconazole case study provides unequivocal evidence that excipients are not inert, but are functional components that can fundamentally determine the pharmacokinetic profile, and therefore the clinical safety and efficacy, of a drug product. The choice of excipient can transform a drug from clinically unviable to a highly effective therapy.

ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism, and Excretion; **ANDA:** Abbreviated New Drug Application; **API:** Active Pharmaceutical Ingredient; **AUC:** Area Under the Curve; **BCS:** Biopharmaceutics Classification System; **BLA:** Biologics License Application; **BP:** British Pharmacopoeia; **CDSO:** Central Drugs Standard Control Organisation; **CFR:** Code of Federal Regulations; **cGMP:** Current Good Manufacturing Practices; **CoA:** Certificate of Analysis; **CTD:** Common Technical Document; **DEG:** Diethylene Glycol; **EDTA:** Ethylenediaminetetraacetic Acid; **EG:** Ethylene Glycol; **EMA:** European Medicines Agency; **FDA:** United States Food and Drug Administration; **GDP:** Good Distribution Practices; **GMP:** Good Manufacturing Practices; **HPCD:** Hydroxypropyl- β -cyclodextrin; **HPMC:** Hypromellose; **HPMCP:** Hypromellose Phthalate; **ICH:** International Council for Harmonisation; **IID:** Inactive Ingredient Database; **IP:** Indian Pharmacopoeia; **IPC:** Indian Pharmacopoeia Commission; **IPEC:** International Pharmaceutical Excipients Council; **ISO:** International Organization for Standardization; **MAA:** Marketing Authorisation Application; **MAH:** Marketing Authorisation Holder; **MDE:** Maximum Daily Exposure; **MHRA:** Medicines and Healthcare products Regulatory Agency; **NDA:** New Drug Application; **PDG:** Pharmacopoeial Discussion Group; **PEG:** Polyethylene Glycol; **Ph. Eur.:** European Pharmacopoeia; **PQG:** Pharmaceutical Quality Group; **SUBA:** Super Bio-Available; **UK:** United Kingdom; **USA:** United States of America; **USP-NF:** United States Pharmacopoeia-National Formulary.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Dhinesh Pandian P: Conceived the research topic, conducted literature search, analysed sources, wrote the full manuscript and approved the final version. **Dr. K Rajaganapathy:** Managed all correspondence with the journal, coordinated revisions, and approved the final version. All authors have reviewed the results and approved the final version of the manuscript.

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