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Regulatory considerations for pharmaceutical excipient selection

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This article discusses the role and importance of excipients in medicines, focusing on regulatory aspects crucial for pharmaceutical companies. The aim of the article is to provide an overview of regulatory considerations in excipient selection and management, elucidating the complex landscape companies must navigate.

Keywords – excipients, quality, regulatory, strategy

Introduction

Excipients can be described as constituents of a medicine other than the active substance.[1] From a regulatory perspective, in the European Union excipients are defined as "any constituent of a medicinal product other than the active substance and the packaging material."[2] In more descriptive terms, excipients are components of pharmaceutical products, different from the drug substance, added to pharmaceutical formulations for many reasons, including facilitating product manufacturing, aiding in identification, modulating stability and preservation, increasing product acceptability, controlling physiochemical properties, and enhancing drug substance bioavailability. Excipients are essential for developing dosage forms of appropriate size and physical properties, thus facilitating dosing and practical drug administration. Excipient selection is therefore a key consideration in the development of a pharmaceutical product.

Excipients are not a homogeneous group, and various categories or types of excipients can be distinguished based on their function (e.g., antioxidants, preservatives, fillers), origin (e.g., synthetic or natural products), and structural composition (e.g., single chemical entities or mixtures of chemically related compounds).[3] Their chemical structures vary from small molecules to complex natural or synthetic polymeric mixtures.[4] In most cases, from a quantitative perspective, excipients constitute a larger proportion of drug products than the active ingredients. Excipient quality can impact the final quality of the drug products, including the stability and bioavailability of the drug substance. For example, instabilities caused by excipients can impact tablet hardness, disintegration and dissolution time, color and taste, and irreversible sedimentation in suspensions.[5]

Excipients can play a significant role in the marketability of pharmaceutical products, influencing the possibility of accessing specific markets. Excipients are listed in patient leaflets and product labels, and their origin may have implications for marketing to certain religious communities (e.g., kosher and halal certifications) or to individuals who restrict their use of animal-derived products for ethical reasons.[6] Excipients are also important in defining aspects such as taste, smell, appearance, and texture, all of which can affect patient perception and compliance, and thus influence the marketability.

The traditional understanding of an excipient

has undergone a substantial evolution from an inert and cheap vehicle to an essential constituent of the formulation. The rapid evolution of scientific, regulatory, and economic factors, the introduction of innovative drug delivery systems, and the advances in biopharmaceutics have led to a new interest in the role and functionality of excipients.[4] However, excipient selection is still considered a largely secondary concern for pharmaceutical companies mainly focused on drug substances and drug products, as reflected by the number of regulatory guidelines concerning drug substances and drug products compared to the guidelines addressing specific points for excipients.

Regulatory and quality control of excipients is gaining importance among regulatory authorities.[7] For example, the following excipient regulatory guidelines were published or updated in 2024 and 2025:

- In 2025, the European Medicines Agency (EMA) updated the annex in the European Commission guideline on excipients in the labeling and package leaflet of medicinal products for human use.[8] Two additional updates were released in 2024.
- In 2024, the World Health Organization (WHO) issued a new guideline for the good manufacturing practices of excipients.[9]
- In 2024, the US Pharmacopeia (USP) published a position paper about the use and development of novel excipients.[10] During the same year, USP also updated its general chapter on good manufacturing practices (GMP) for bulk pharmaceutical excipients.[11]

The growing interest in excipients is also reflected in industry market trends, with the excipient market expected to grow steadily in the coming years. The market was evaluated at $9.51 billion in 2022 and is projected to reach $14.72 billion by 2033.[12]

The selection of excipients must be rigorously justified from both the technical formulation and regulatory perspectives. While an excipient may have ideal physicochemical properties for a given formulation, excipient documentation, data, or specifications that do not comply with regulatory requirements could impact drug product approval or complicate the regulatory process. Regulatory compliance is essential in excipient selection to ensure a streamlined approval process and successful product development.

The aim of the article is to provide an overview of regulatory considerations in excipient selection and management, elucidating the complex landscape companies must navigate in the development of drug products.

Main aspects of the excipient regulatory environment

Regulating excipient quality is no small task. Compared to the regulatory framework for drug substances and drug products, the regulatory framework for excipients is less developed and lacks international harmonization. Regulations for excipients are less prescriptive and detailed, whereas drug substances and drug products benefit from extensive, internationally harmonized pharmaceutical regulations.

This is partly due to the fact that more than a thousand excipients exist, and only a small number of them are manufactured solely for pharmaceutical use. Many materials used as excipients are also often used in other fields, such as the food and cosmetic industries. For some substances, the pharmaceutical industry is not even a major customer in terms of volume supplied.[13] Although the pharmaceutical industry has increased its effort and interest in GMP standards for excipient manufacturing, in some cases, the supply chain, environmental conditions, equipment, and operational techniques may still resemble those of the chemical industry more than those of the pharmaceutical industry. Excipient manufacturing sites are not routinely inspected by the pharmaceutical regulatory authorities. Although pharmaceutical companies can audit these sites, their ability to do so, particularly when sourcing widely used excipients, is often limited by contractual leverage over suppliers.

The use of a substance as an excipient, when it is concurrently employed in diverse industrial fields, frequently results in an overlap in regulatory requirements. For example, a substance primarily manufactured for the food industry is likely to comply with a specific set of sector-related regulatory standards. However, it cannot be presumed that this substance also complies with all of the potential requirements of the pharmaceutical industry.

The use of substances that do not fully comply with the pharmaceutical requirements may introduce quality, regulatory, and safety risks.[14] As an example, triethyl citrate is a substance commonly used in the food industry and as a

pharmaceutical excipient. Regulation (EU) No 231/2012[15] lays down specifications for food additives and provides a list of specifications for the use of triethyl citrate in the food industry. Pharmaceutical-grade specifications for triethyl citrate are reported in the European Pharmacopoeia (Ph. Eur.). Although the two sets of specifications align for many parameters, significant differences exist with respect to the impurity profile, for which Ph. Eur. monograph requirements are considerably more stringent. In this specific example, the use of food-grade triethyl citrate would pose regulatory and potentially patient-safety risks due to its higher impurity levels compared to pharmaceutical-grade material.

In addition, regulatory requirements may vary between countries. For example, regulators in the US, Canada, and Japan have a drug master file (DMF) system for excipients. In the EU, although a DMF system exists for drug substances, a master file system is not available for excipients.[16] However, in the EU, an excipient can be the subject of a Ph. Eur. certificate of suitability (CEP),[5] which is an accepted but voluntary option demonstrating compliance with Ph. Eur. quality standards. All of these examples indicate the complexity of excipient regulation across different regulatory environments. An overview of the main differences in excipient management across regulatory environments is reported in **Table 1**.

According to the International Council for Harmonisation (ICH) Q8 Guideline,[17] the marketing authorization application should discuss the excipients chosen and their concentration. Comprehensive excipient information is required in regulatory submission dossiers, with Module 3.2.P.4 of the electronic common technical document (eCTD) specifically dedicated to excipients.[18] The specifications and analytical procedures used to test the excipients must be provided. If specifications other than the compendial or supplier's specifications are used, this point should be discussed. Furthermore, if noncompendial

Table 1. Excipient regulatory requirements across different geographic areas

Region – Pharmacopoeia title	DMF	Database	Main requirements for labeling
United States – US Pharmacopeia-National Formulary, or USP-NF	Yes	Inactive Ingredient Database lists excipients used in FDA-approved drug products with maximum potency per route	Excipients must be reported in the summary of product characteristics. Excipient reporting on labels may vary based on the excipient's characteristics and whether the drug product is for prescribed use.
Europe – European Pharmacopoeia, or Ph. Eur.	No[a]	No centralized excipients database	All excipients must be reported on the labels. Specific standardized statements must be included for some excipients, based on the drug product's dose and route of administration. Excipients that are known allergens must be highlighted.
China – Chinese Pharmacopoeia, or ChP	Yes	A database of registered/ filed excipients is available	All excipients must be reported on the labels. Excipients that are known allergens must be highlighted.
Japan – Japanese Pharmacopoeia, or JP	Yes	No dedicated public excipients database	All excipients must be reported on the labels. Functional classification of some excipients must be stated.
Canada[b] – USP-NF, Ph. Eur., JP, or other recognized compendia are accepted	Yes	Drug Product Database includes information on excipients used in approved products	Excipients must be reported in the summary of product characteristics. Labels include only a specific category of excipients (e.g., known allergens, colorants, alcohol).

CEP, certificate of suitability; **DMF,** drug master file; **FDA,** Food and Drug Administration [US].

[a]No DMF, however, the excipient manufacturer can request a CEP. [b]Canada does not have its own pharmacopoeia.

methods are used, information about the in-house analytical methods must be provided. Additional information is needed for animal or human origin excipients.

Further to the requirements of eCTD Module 3.2.P.4, excipient-related data and discussions may be included in the regulatory sections pertaining to drug product release specifications, stability studies, impurity characterization, and drug product formulation development.[7] Discussions about compatibility between excipients and drug substance and potential interaction between excipients are highly suggested to be included in regulatory dossiers. **Table 2** lists the main information to be included in eCTD Module 3.2.P.4 for compendial and noncompendial excipients.

There is no independent pathway to obtain approval of an excipient prior to use in a drug product formulation: excipient approval is always tied to the drug product. Even in regulatory frameworks that establish DMFs for excipients, such as the US regulatory framework, these DMFs are not subject to evaluation until the excipient is

Table 2. Information to be included in electronic common technical document Module 3.2.P.4

eCTD section	Main information requested
3.2.P.4.1 Specifications	▪ If compendial specifications are applied, no additional information is needed ▪ If, further to the compendial tests, additional tests are performed, these should be listed together with acceptance criteria and the method used for testing ▪ For noncompendial excipients, the applied specifications should be provided, together with acceptance criteria and the method used for testing ▪ Evidence of compliance with local regulations; statements provided by the excipient's supplier may be supportive
3.2.P.4.2 Analytical methods	▪ If compendial methods are applied, method description is not needed ▪ If noncompendial tests are used, these tests should be described
3.2.P.4.3 Validation of analytical procedures	▪ Method validation data are not necessary for compendial methods, but they should be provided for in-house methods ▪ If compendial methods other than the reference compendial are used (e.g., Ph. Eur. specifications are assessed using USP methods), method equivalence studies should be reported
3.2.P.4.4 Justification of specifications	▪ Example of batch analyses should be provided, and a certificate of analyses may be needed ▪ For a compendial excipient, if compendial specifications are applied, justification is not mandatory ▪ For compendial excipients, justification should be provided for any additional tests performed further to the compendial tests ▪ For compendial excipients, justification for not performing a test foreseen by the compendial reference should be included ▪ For noncompendial excipients, a discussion on the applied specifications must be included
3.2.P.4.5 Excipients of human or animal origin	▪ If human or animal origin excipients are used, sources, safety data (e.g., TSE/BSE, viral clearance, etc.), and description of tests performed are needed, and a cross-reference to eCTD Module 3.2.A.2 may be necessary
3.2.P.4.6 Novel excipients	▪ For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to nonclinical and clinical data, should be provided, and a cross-reference to eCTD Module 3.2.A.3 may be necessary
Additional information to be included in the eCTD dossier other than in Module 3.2.P.4	▪ Discussion about the choice of excipients, their concentration, their characteristics, their compatibility with the drug substance, and the packaging materials that can influence the drug product performance and manufacturing process ▪ Discussion about the contribution of excipients to the drug product impurity profile, if any ▪ Discussion about excipients that should be monitored during drug product stability, if any

BSE, bovine spongiform encephalopathy; **eCTD,** electronic common technical document; **Ph. Eur., European** Pharmacopoeia; **TSE,** transmissible spongiform encephalopathy; **USP,** US Pharmacopeia.

incorporated into a pharmaceutical product. It should be noted that, beyond the information provided in the DMF, regulatory authorities may request additional data and clarifications on the excipient during the evaluation of the drug product. Such requests may include further analytical data, manufacturing information, or relevant nonclinical and clinical data.

An overview of the key regulatory factors to be evaluated during excipient selection is presented in the following sections, with the intent of providing a framework for regulatory decision making.

Regulatory considerations for excipient selection

Compendial and noncompendial excipients

Pharmacopoeias are a good starting point for the regulatory selection of excipients. There are multiple compendia used around the world. The most referenced are the US Pharmacopeia–National Formulary (USP-NF), the European Pharmacopoeia (Ph. Eur.), the Chinese Pharmacopeia (ChP), the Japanese Pharmacopoeia (JP), and the Japanese Pharmaceutical Excipients (JPE). Compendia establish analytical specifications, test methods, and other attributes to demonstrate the quality of the materials used in pharmaceutical products.[8] When an excipient is listed in an official pharmacopoeia, sponsors are advised to source from suppliers capable of providing pharmacopeial-grade material.

It should also be considered that different pharmacopoeias may require different tests or different acceptance criteria for the same excipient. Consequently, an excipient that conforms to the standards set by the Ph. Eur. may not necessarily meet the requirements of the ChP, or vice versa. A significant harmonization effort among pharmacopoeias is currently underway within the international Pharmacopeial Discussion Group (PDG).[19] Furthermore, the ICH Q4B guideline[20] specifically addresses the evaluation and recommendation of pharmacopeial texts for use in the ICH regions. The harmonization process is ongoing, and substantial progress has been achieved in the alignment of numerous monographs, but much work remains to be done.

Drug products might also utilize noncompendial excipients. When the excipient is not described in any pharmacopoeia, companies must check whether the supplier's specifications ensure regulatory compliance or whether additional tests should be performed upon receipt of the material, considering the intended use of the excipients in the formulation. The EMA's guideline on excipients in the dossier for applying for marketing authorization of a medicinal product[21] provides important guidance in this regard, stating that specifications for noncompendial excipients should at least include tests for the main physical characteristics, identification tests, purity tests, including limits for total and individual impurities, and assay.

While the use of excipients described in a pharmacopoeia confers several advantages, it is important to note that regulatory compliance should not be limited to verifying pharmacopeial requirements. A more comprehensive assessment is necessary to ensure full regulatory compliance and suitability for the intended formulation. Often, the specifications and analytical methods reported in the pharmacopeial monographs are not enough: given the excipient's function, its characterization may go beyond simple tests for identity, purity, and assay as usually prescribed in the pharmacopoeia monographs and extend to testing the material's technological functionality.[4]

For example, magnesium stearate is widely used as a lubricant in many formulations.[4] In such cases, collecting data on particle size and specific surface area may be necessary to fully understand its lubricant performance and to support the development of a high-quality formulation. In other instances, additional tests may be required to obtain information on specific impurities, such as nitrosamines or elemental impurities, or to collect relevant nonclinical and clinical data, the latter being particularly important for novel excipients.

Functionality tests for an excipient relate to any desirable properties, such as flow and compression, that facilitate the manufacturing process and thereby enhance the quality and performance of the drug product. Examples of functionality tests are the particle size distribution test for magnesium stearate and the bulk density test for lactose monohydrate. The requirement for any functionality tests and related acceptance criteria in a general excipient monograph is typically limited, as they tend to be dosage form-related.[4] Ph. Eur. indicates that monographs on excipients may include a section on functionality-related characteristics, but it is not mandatory. The USP-NF uses the term *performance tests* for excipient functionality. The USP-NF informational chapter on excipient performance provides an overview of the key functional categories of excipients identified

in USP-NF, along with tests that relate to excipient performance.

Function of the excipients

Careful consideration of the function of the excipient in the dosage form and the critical attributes that relate to the excipient's performance will determine the need for additional tests on the excipient.[22]

For excipients with specific functional roles in the formulations, such as antioxidants, penetration enhancers, disintegrants, and release-controlling agents, demonstrating maintained functionality throughout the product's shelf life is required by ICH Q8 guidelines.[17] The EMA's guideline on excipients in the dossier for applying for a marketing authorization of a medicinal product[21] provides specific requirements for distinct excipient categories. According to this guideline, the drug product release specifications must include identification and content determination tests for each antioxidant and antimicrobial preservative present in the formulation. Additionally, shelf-life specifications must establish limits for antimicrobial preservatives when present.[21]

Flavoring agents (e.g., fumaric acid, vanillin) are another common excipient category. Most of the flavoring agents are complex, chemically synthesized substances. Because of the complexity of their composition, it is necessary to describe the general qualitative composition, mentioning the main constituents with an appropriate process to identify them.[21,23]

Also, excipients added to formulations as colorants (e.g., iron oxides, titanium dioxide, beta-carotene) need specific regulatory considerations. In the EMA regulatory environment, excipients with coloring function must comply with the specifications of the Annex of Directive 95/45/EC,[24] further to the more general requirements for colorants in foodstuffs (Directive 78/25/EEC,[25] as amended and Directive 94/36/EC[26]). In the US, excipients with coloring function must comply with the requirements of 21 CFR Part 70-82.[27]

Established and novel excipients

Another significant regulatory consideration concerns the criteria for permissible excipients. In principle, a substance may be acceptable for use as an excipient if it complies with the regulatory definition of excipient, is included in an official pharmacopoeia, or has been previously utilized in an authorized pharmaceutical product. The fulfillment of these criteria typically provides a basis for the regulatory acceptance of a substance as an excipient.

In the US, precedence of use is demonstrated by excipients being listed in the Food and Drug Administration (FDA) Inactive Ingredient Database.[28] In this database, excipients are listed by name, route of administration, dosage form, and the maximum amount of excipient contained in approved medicinal products of that listed route of administration and dosage form.[16] In Japan, the precedence of use can be assessed by referring to the Japanese Pharmaceutical Excipients Dictionary. The dictionary is a compilation of all excipients for which there is a precedent of use in medicinal products in Japan. It includes monographs from the JP or JPE as well as all nonmonograph excipients that have been previously used.[16]

Excipients used for the first time in medicinal products or by new routes of administration are classified as novel excipients. Even if an excipient has been extensively used in other approved, nonpharmaceutical applications, such as food or cosmetic products, it is still considered novel when used in drug products subject to regulatory approval. Regulators regard novel excipients as new substances, and whenever a new excipient is used in a formulation, it must be subjected to full evaluation, similar to the one required for a new active substance.[3]

Onpattro is an example of a drug product containing novel excipients approved by the EMA.[29] As outlined in the public assessment report, the data provided for the novel excipients included full structural and impurity characterization, a comprehensive genotoxic impurity assessment, together with the novel excipient specifications and relevant justifications, description of the analytical method used to release the novel excipient, stability and photostability testing, forced degradation studies, and nonclinical data discussion. Similar information has also been provided for Kostaive,[30] a drug product containing one novel excipient approved by the EMA in 2025.

Such information is not necessary for non-novel excipients. Generating this information requires considerable effort from companies, which is one reason new excipients are not common. Additionally, most manufacturers can more easily focus on improving the quality, properties, and

purity of existing, approved excipients rather than on novel excipients.[3]

The origin of excipients is another aspect that requires regulatory evaluation, particularly for excipients of human or animal origin, such as those derived from blood, tissues, or cells. Common animal-derived excipients found in medications include gelatin made from the bones of cattle or pigs to produce capsule shells or as a coating agent, lactose from bovine milk as a diluent for tablets, and lanolin from sheep skin or wool as a lubricant.[31] EMA and FDA guidelines require viral safety and transmitting animal spongiform encephalopathy clearance of these excipients to be clearly documented.[21,23,32,33]

Impact of impurity carry-over from excipients

In general, excipients are used in the form in which they were purchased, without further refining or purification. Consequently, impurities present in the excipient may be carried over to the finished pharmaceutical product. Testing and control of the impurities in excipients is receiving increased attention from both industry and health authorities.[34] The use of excipients compliant with the main pharmacopeias is highly advisable and helps reduce the risk of impurities introduced by excipients.[35] The composition and impurity profile of excipients are often determined by their source and by the relevant manufacturing process.

An increasing attention towards GMP standards application for excipient manufacturing has been observed in recent years, by both regulatory authorities and excipient manufacturers. The International Pharmaceutical Excipients Council (IPEC), an international industry association formed by excipient manufacturers, distributors, and users, published a dedicated guideline for GMP manufacturing of excipients, providing insight into the application of GMP principles to excipients.[36] IPEC published this guideline, understanding that increased attention from both pharmaceutical companies and regulatory authorities is needed on the GMP application to excipient manufacturing.

The IPEC guideline covers the quality management system, including the GMP necessary throughout manufacturing, based on risk assessments, for both batch and continuous processes. A similar guidance was also issued by the World Health Organization.[9] Notably, in the European Economic Area, manufacturing authorization holders are responsible for ensuring appropriate GMP application in excipient manufacturing, performing a dedicated risk assessment for each excipient.[37]

In any case, additional evaluation of specific classes of impurities, such as elemental impurities, nitrosamines, and residual solvents, is often needed. Excipients are the greatest contributors of elemental impurities in the drug product formulation.[38] Almost all excipients contain some levels of elemental impurities, although these levels do not often impact the ability of the drug product to meet the permitted daily exposure limits of the ICH Q3D guideline.[39] Mined excipients, such as talc, and excipients that use metal catalysts during manufacturing may pose a risk of elemental impurity contamination.

A drug contamination incident reported in March 2012 involved the discovery that 77 million medicinal gelatin capsules were made from industrial-grade gelatin that contained chromium, a carcinogenic heavy metal.[40] In most cases, excipient suppliers test their products for elemental impurities and can provide very accurate information. Additional options include consulting public databases, which often contain useful information,[38,41] or testing samples of the excipients.

Excipient manufacturing pathways must be studied to identify excipients that may contribute to nitrosamine formation in the final drug product.[38] Nitrosating impurities (nitrites and nitrates) can be present in regularly used excipients, such as polyvinyl pyrrolidone, pregelatinized starch, sodium starch glycolate, cross-polyvinyl pyrrolidone, lactose, and croscarmellose sodium; therefore, a risk factor in nitrosamine generation exists in excipients containing amine-containing components.[42] Another important piece of information retrievable from the manufacturing pathways of the excipients is the use of residual solvents. This allows an evaluation of the impurity carry-over from this source.

Final considerations

All the factors in excipient selection should be evaluated through a comprehensive regulatory assessment to identify the best regulatory approach for each excipient. Maintaining up-to-date regulatory assessments enhances regulatory oversight and helps identify the most effective excipient management strategies.[43] **Table 3** (p. 56) reports a list of main regulatory documents and information that can be requested from the supplier to ease the regulatory assessment.

Table 3. Useful information sources for exciient regulatory assessment

Document	Regulatory information that can be retrieved
Specifications	▪ Assess compliance with pharmacopoeia (in case of compendial excipients) ▪ Evaluate if specifications meet the regulatory requirements (in case of noncompendial excipients) ▪ Evaluate analytical methods used for excipient testing ▪ Evaluate overall purity/impurity levels ▪ Evaluate if additional tests at receipt are required
Source	▪ Confirm/exclude animal or human origin of the excipient
Manufacturing process flowchart	▪ Evaluate potential impurities related to the manufacturing process, such as residual solvents ▪ Evaluate if additional tests at receipt are required
Elemental impurities analyses/assessments	▪ Useful to fulfill ICH Q3D requirements ▪ Evaluate if additional tests at receipt are required
Nitrosamine analyses/ assessments	▪ Useful to fulfill nitrosamine's regulatory requirements ▪ Evaluate if additional tests at receipt are required
DMF availability/CEP availability	▪ Important for registration in specific markets ▪ May ease the DP approval process
TSE/BSE information/ viral clearance studies	▪ Necessary in case of human or animal origin excipient
Allergens/hypersensitive information	▪ Safety statements or information to be included in DP patient leaflet
Kosher/halal status	▪ Useful for registration in specific markets

BSE, bovine spongiform encephalopathy; **CEP**, certificate of suitability; **DMF**, drug master file; **DP**, drug product; **ICH**, International Council for Harmonisation; **TSE**, transmissible spongiform encephalopathy.

Conclusion

Excipients constitute the predominant quantitative component in pharmaceutical formulations, carrying out several functions that directly influence formulation parameters, manufacturing processes, stability behavior, and the quality attributes of the drug product. Excipient selection involves technical and regulatory considerations. The regulatory framework of excipients has evolved considerably, in parallel with their redefinition from inert substances to functional constituents of pharmaceutical formulations. The current regulatory landscape for selection and management of excipients is complex, necessitating a comprehensive understanding and compliance with several guidelines and requirements. Unlike medicinal products, pharmaceutical excipients do not require regulatory approval before being placed on the market; however, inadequate regulatory evaluation of excipients may delay or prevent pharmaceutical products from reaching the desired market. Therefore, companies should not underestimate the regulatory requirements when considering excipients.

Abbreviations

CEP, certificate of suitability; **ChP,** Chinese Pharmacopeia; **DMF,** drug master file; **eCTD,** electronic common technical document; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **GMP,** good manufacturing practice; **ICH,** International Council for Harmonisation; **IPEC,** International Pharmaceutical Excipients Council; **JP,** Japanese Pharmacopoeia; **JPE,** Japanese Pharmaceutical Excipients; **Ph. Eur.,** European Pharmacopeia; **USP-NF,** United States Pharmacopeia–National Formulary.

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References

All references were last checked and verified on 17 February 2026.

1. European Medicines Agency. Glossary of regulatory terms – Excipient. Accessed 11 September 2025. https://www.ema.europa.eu/en/glossary-terms/excipient
2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Published 6 November 2001. Accessed on 11 September 2025. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20250101
3. Kozarewicz P, Loftsson, T. Novel excipients – Regulatory challenges and perspectives – The EU insight. Int J Pharm. Published 30 July 2018. Accessed 22 April 2025. https://www.sciencedirect.com/science/article/abs/pii/S0378517318303570?via%3Dihub
4. Pifferi G, et al. Quality and functionality of excipients. Farmaco. Published January 1999. Accessed 10 March 2025. https://www.sciencedirect.com/science/article/abs/pii/S0014827X98001013?via%3Dihub
5. Robertson MI. Regulatory issues with excipients. Int J Pharm. Published 5 October 1999. Accessed 10 March 2025. https://www.sciencedirect.com/science/article/abs/pii/S0378517399001106?via%3Dihub
6. Queensland Health. Pharmaceuticals of animal origin – V3.0 November 2020. Last updated November 2020. Accessed 22 April 2025. Medicines/pharmaceuticals of animal origin
7. Mali A, et al. Bridging the gap: A comparative investigation of pharmaceutical excipient regulations. Ther Innov Regul Sci. Published 6 December 2023. Accessed 11 September 2025. https://link.springer.com/article/10.1007/s43441-023-00597-z
8. European Commission. Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) - Revision 5. Adopted 5 December 2025. Accessed 22 January 2026. https://www.ema.europa.eu/en/documents/scientific-guideline/all-languages-annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human-use-sante-2017-11668-revision-5_en.xlsx
9. World Health Organization. TRS 1052 – Annex 2 – WHO good manufacturing practices for excipients used in pharmaceutical products [guidance]. Adopted 26 April 2024. Accessed 11 September 2025. https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1052_annex2.pdf?sfvrsn=4729bcf0_6&download=true
10. United States Pharmacopeia. Fostering the use of novel excipients in drug products [position paper]. Not dated. Published online 2024. Accessed on 22 January 2026. https://www.usp.org/sites/default/files/usp/document/public-policy/USP%20Global%20Policy%20Position_NovelExcipients_Paper_2024.pdf
11. United States Pharmacopoeia. <1078> Good Manufacturing Practices For Bulk Pharmaceutical Excipients. Dated 2024. Accessed 20 January 2026. https://doi.usp.org/USPNF/USPNF_M99797_01_01.html
12. Auerbach M. The future of pharmaceutical excipients: A $14 billion market driven by global demand. American Pharmaceutical Review. Dated 19 March 2025. Accessed 22 January 2026. https://www.americanpharmaceuticalreview.com/Featured-Articles/618347-The-Future-of-Pharmaceutical-Excipients-A-14-Billion-Market-Driven-by-Global-Demand/
13. Elder DP, et al. Pharmaceutical excipients – Quality, regulatory and biopharmaceutical considerations. (2015). Dated 25 May 2016. Accessed 20 January 2026. https://www.sciencedirect.com/science/article/abs/pii/S0928098715300920
14. Wiggins JM, Albanese JA. A case study in pharmacopoeia compliance: Excipients and raw materials. Pharmaceutical Technology. Published March 2020. Accessed 22 January 2026. https://alfresco-static-files.s3.amazonaws.com/alfresco_images/pharma/2020/04/10/43f721b1-36d2-4934-8183-57e15eabb3d3/PTebook0320_PharmacopeiaCompendia_Part11_ONLINE%20CaseStudy.pdf
15. Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA relevance. Dated 9 March 2012. Accessed 20 January 2026. https://eur-lex.europa.eu/legal-content/EN/AUTO/?uri=CELEX:02012R0231-20251027
16. The International Pharmaceutical Excipients Council. Qualification of excipients for use in pharmaceuticals – Guide & checklist. Published 2020. Accessed 10 March 2025. https://ipec-federation.org/wp-content/uploads/2021/03/20201026-EQ-Guide-Revision_FINAL.pdf
17. International Council for Harmonisation. Pharmaceutical development – Q8(R2). Adopted 1 August 2009. Accessed 10 March 2025. https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf
18. International Council for Harmonisation. Organisation of the common technical document for the registration of pharmaceuticals for human use – M4(R4). Adopted 15 June 2016. Accessed 11 September 2025. https://database.ich.org/sites/default/files/M4Q_R1_Guideline.pdf
19. Cogliandro E. Ph. Eur. and other pharmacopoeias – The ICH harmonization process of compendial texts. Agenzia Italiana del Farmaco. Dated 17 November 2023. Accessed 11 September 2025. https://www.aifa.gov.it/documents/20142/1812131/2023-11-17_Eugenia-Cogliandro_Pavia.pdf
20. International Council for Harmonisation. Evaluation and

recommendation of pharmacopoeial texts for use in the ICH regions – Q4B. Adopted 1 November 2007. Accessed 23 April 2025. https://database.ich.org/sites/default/files/Q4B%20Guideline.pdf
21. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. Adopted 19 June 2007. Accessed on 11 September 2025. guideline-excipients-dossier-application-marketing-authorisation-medicinal-product-revision-2_en.pdf
22. Zheng, JY. Function, quality, and regulations of pharmaceutical excipients for oral solid dosage forms. In: Formulation and analytical development for low-dose oral drug products. Wiley; 2009. Verified 23 April 2025.
23. Food and Drug Administration. Drug master files – Guidance for industry [draft guidance]. Published October 2019. Accessed 10 September 2025. https://www.fda.gov/media/131861/download
24. Official Journal of European Communities. Commission Directive 95/45/EC of 26 July 1995 laying down specific purity criteria concerning colours for use in foodstuffs. Accessed 10 September 2025. eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31995L0045
25. Official Journal of European Communities. Council Directive 78/25/EEC of 12 December 1977 on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products. Accessed 10 September 2025 eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31978L0025
26. Official Journal of European Communities, European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs. Published 30 June 1994. Accessed on 10 September 2025 eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31994L0036
27. 21 CFR Part 70, Color additives. Current as of 4 September 2025. Accessed 10 September 2025. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-70
28. Food and Drug Administration. Inactive ingredient search for approved drug products. Last updated 22 October 2025. Accessed 11 September 2025. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
29. European Medicines Agency. EMA/554262/2018 – Assessment Report – Onpattro [public assessment report]. Dated 26 July 2018. Accessed 22 January 2026. https://www.ema.europa.eu/en/documents/assessment-report/onpattro-epar-public-assessment-report_en.pdf
30. European Medicines Agency. EMA/18711/2025 – Assessment Report – Kostaive [public assessment report]. Dated 12 December 2024. Accessed on 22 January 2026. https://www.ema.europa.eu/en/documents/assessment-report/kostaive-epar-public-assessment-report_en.pdf
31. Hospital Canselor Tuanku Muhriz [Malaysia]. Medicines with animal origin. Version 1r. Dated July 2022. Accessed on 22 April 2025. https://hctm.ukm.my/farmasi/wp-content/uploads/2023/11/MEDICINES-WITH-ANIMAL-ORIGIN-HCTM-Ver-1r.pdf
32. Sabalingam S, Jayasuriya, WJAB. Pharmaceutical excipients of marine and animal origin: A review. Published 25 December 2019. Accessed 22 April 2025. https://www.researchgate.net/publication/338199015_Pharmaceutical_Excipients_of_Marine_and_Animal_origin_A_Review
33. Official Journal of the European Union. Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products [notice]. Published 29 June 2011. Accessed 11 September 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/minimising-risk-transmitting-animal-spongiform-encephalopathy-agents-human-and-veterinary-medicinal-products_en.pdf
34. Zhang K, et al. Reactive impurities in large and small molecule pharmaceutical excipients – A review. Trends Analyt Chem. Published April 2018. Accessed 24 April 2024. https://www.sciencedirect.com/science/article/abs/pii/S0165993617303497?via%3Dihub
35. Ceragioli Y. Impurities management in drug product: A simulated case study. Regulatory Focus. Published 7 February 2024. https://www.raps.org/login?returnurl=%2Fnews-and-articles%2Fnews-articles%2F2024%2F2%2Fimpurities-management-in-drug-products-a-simulated
36. The International Pharmaceutical Excipients Council. The joint good manufacturing practices guide for pharmaceutical excipients. Version 5. Published 2022. Accessed 11 September 2025 https://www.ipec-europe.org/ajax_calls/request-resource.php?id=22
37. Official Journal of the European Union. Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use. Published 19 March 2015. Accessed 11 September 2025. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XC0321(02)
38. Ceragioli Y. Impurities in drug substances and drug products: A regulatory CMC perspective. Regulatory Focus. Published online 22 December 2023. Accessed 11 September 2025. https://www.raps.org/News-and-Articles/News-Articles/2023/12/Impurities-in-drug-substances-and-drug-products-A
39. International Council for Harmonisation. Guideline for elemental impurities – Q3D. Adopted 22 March 2019. Accessed 19 June 2025. https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf
40. Saluja V, Sekhon, B. The regulation of pharmaceutical excipients. Journal of Excipients and Food Chemicals. Published 22 August 2013. Accessed 22 April 2025. https://www.researchgate.net/publication/263844652_The_regulation_of_Pharmaceutical_Excipients
41. Alsante KM, et al. Recent trends in product development and regulatory issues on impurities in active pharmaceutical ingredient (API) and drug products. Part 1: Predicting degradation related impurities and impurity considerations for pharmaceutical dosage forms. AAPS PharmSciTech. Published 27 November 2013. Accessed 22 April 2025. https://link.springer.com/article/10.1208/s12249-013-0047-x
42. Charoo NA, et al. Risk-based approach for defining retest dates for active pharmaceutical ingredients and excipients. Pharmaceuticals (Basel). Published 7 July 2024. Accessed 22 April 2025. https://www.mdpi.com/1424-8247/17/7/903
43. Ceragioli Y. Impurities in drug substances and drug products: A risk-based approach. Regulatory Focus. Published 22 December 2023. Accessed 11 September 2025. https://www.raps.org/news-and-articles/news-articles/2023/12/impurities-in-drug-substances-and-drug-product-(1)