IPEC Europe Statement on Primary Packaging Materials (PPMs) for Pharmaceutical Excipients

Scope

Primary packaging materials include all packaging materials in contact with a pharmaceutical excipient ("excipient") as supplied by manufacturers and distributors to customers for use in the manufacture of human medicinal products[1].

The potential risks related to secondary / indirect materials such as printing inks, labels, adhesives are highlighted in this document.

Background and Regulatory Framework

Common to all requirements for primary packaging materials intended for use in human medicinal products is the general expectation that the primary packaging materials ("PPM") should be sufficiently inert so that its constituents do not migrate into the product contained therein so that neither consumer health nor the quality of the product is adversely affected. Also, in the case of PPMs for excipients, they should not affect their functional or physical-chemical characteristics.

Many excipients are not manufactured exclusively for pharmaceutical use. As a result, they can be manufactured and subject to other legislation for particular industry sectors concerning storage and transportation.

Regulations relating to PPMs for medicinal products and even APIs are not designed to represent the diversity seen in the manufacture and sourcing of excipients. However, with the increasing regulatory focus on the security of supply chains relating to medicinal products, it seems reasonable that drug product manufacturers in cooperation with their suppliers of excipients develop a rationale to ensure that the packaging materials used for excipients protect the excipient from physical, chemical or microbiological damage during storage and transport. As stated, many excipients are classified as foods, chemicals or cosmetic ingredients and therefore subject to relevant regulations. In the absence of specific packaging guidelines for pharmaceutical excipients, extrapolating guidance can provide a useful approach with appropriate risk-based considerations, to establish that excipients and their container/closure systems are fit-for-purpose when used in medicinal products. Thus, IPEC supports the principles outlined in this position paper as helping to achieve that objective.

For active pharmaceutical ingredients (API's) and finished medicinal products, binding requirements for the composition and the safety of PPMs exist or are being developed in the USA, the European Union and many other countries. Several pharmacopoeias established general chapters and monographs for primary packaging materials for medicinal products.

[1] Some medicinal products have ingredients designated as active pharmaceutical ingredients (APIs) that were not manufactured as APIs in accordance with ICH Q7 GMPs nor are they likely to be. The term "Atypical Actives" has been used to describe these starting materials which may be considered to be within the scope of the document.

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Likewise, a consistent legal framework for food contact materials has been established applicable to the primary packaging materials in contact with food products including dietary ingredients and infant foods.

In legislation for cosmetic products, no specific requirements for primary packaging materials are mentioned for cosmetic ingredients.

For chemicals, legal requirements exist for PPMs which focus mainly on safety aspects. These require manufacturers to provide packaging for their products meeting stringent requirements on suitability and damage resistance to protect people and the environment from the contents of the packaging.

Risk based approach

The absence of directly applicable regulation for excipients and their diversity in terms of material types and intended uses, supports an approach based on risk assessment.

Within the regulatory framework and other guidance established for medicinal products and excipients, there exists provisions to conduct risk assessments to determine if excipients are fit for use. These concepts can be extrapolated to determine the impact of PPMs on excipients used to package them (see for example[2]). Risk assessments for PPMs should consider the following hazards related to the migration of their constituents:

- Toxicological risks of extractable/leachable/migrating substances[3]
- Influence on product quality (organoleptic properties, functionality related characteristics, contamination with micro-organisms), including barrier characteristics against, e.g., oxygen or water vapour.
- Interaction with the packaged material

The potential impact of PPMs for excipients on the final medicinal product consumed by patients may be applied inappropriately may be either over- or underestimated by excipient users if current expectations on excipient packaging material controls are not well understood.

[2] Examples are:
- Pharmaceutical manufacturers are required, under the Falsified Medicines Directive legislation (Directive 2011/62/EC), to ensure that excipients are fit for their intended use using a formalized risk assessment to ascertain appropriate GMPs.
- Excipient manufacturers (including repackers) using the current IPEC PQG Joint GMP Guide for Pharmaceutical Excipients or the EXCiPACT™ GMP/GMP or NSF/IPEC/ANSI 363 certification standard, must conduct risk assessments to ensure appropriate controls are applied to deliver safe excipients, of appropriate quality and of consistent composition throughout their shelf life.

[3] The following definitions apply :
Extractables <USP 1663>; Chemical species that are be released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction under laboratory conditions including extraction solvent, technique, stoichiometry, temperature and duration.
Leachables <USP 1663>; Chemical species that migrate from a packaging/delivery system, packaging component, or packaging material of construction into an associated drug product formulation under normal conditions of use or during accelerated drug product stability studies. Leachables are typically a subset of extractables or are derived from extractables.

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The regulations mentioned above may be considered as risk management measures to address the hazards mentioned taking into account the intended use as ingredient in food, cosmetics, chemicals, pharmaceuticals, etc.

Points to consider

In the absence of regulatory guidance, excipient manufacturers should consider information which can be made available from suppliers of PPMs to enable a conclusion to be drawn that the selection of a PPM will not adversely impact the material it contains, and ultimately the medicinal product and the patient.

- Food legislation provides a basis for the evaluation of PPMs (including coatings) (in food terms; **Food Contact Materials**) with respect to migration[4] and safety for solid and liquid excipients. Both the extent of migration as well as the safety evaluation of the intake of any migrated compound is addressed in food regulations.

  As excipients are generally consumed in lower amounts than foods, for orally administered drug products, a greater safety margin may be justified.

  The supply chain for PPMs may be complex involving chemical manufacturers of polymers, producers of granulates, producers of plastic foils, assemblers of several elements. European Food Law acknowledges this situation and provides a practical solution in the form of a Declaration of Compliance. The Declaration of Compliance considers overall and substance-specific migration relevant for the contact situation together with other aspects (quality system of the PPM manufacturer).

- Reference to and meeting pharmacopoeia requirements for PPMs used in **pharmaceutical products** provide another approach for the evaluation of PPMs for excipients.

  The EMA Guideline CPMP/QWP/4359/03 on Plastic Primary Packaging Materials for medicinal products provides in its Appendixes decision trees for required documentation based on the physical state of the product and its intended use.

- Compliance with hazardous substance packaging rules are required where the carriage of **dangerous goods** is permitted if certain and specific conditions are met, notably regarding the strength and suitability of the packaging. The priority for excipients which are classified as hazardous will be to identify suitable "UN" marked packaging which ensures the integrity of the packaging in the supply chain. In some situations, it may be difficult to purchase PPMs complying with both the requirements for human consumption and the safety related requirements. In this case a documented, long history of safe use may be part of the risk assessment for the use of the PPM.

[4] **Migration** is the transfer of chemical substances from food contact materials into food. For plastic materials two types of migration limits (overall migration, specific migration) have been established in Commission Regulation (EU) No. 10/2011.

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UN Steel drums can be provided with an inner coating, which protects both the excipient from the packaging and the packaging from the excipient. It may not always be possible to identify coatings deemed as food grade or suitable for food contact. Nevertheless, if the coating is inert to the excipient there should not be a substantial risk to patient safety.

Some packaging suppliers can confirm the compatibility of the packaging with the substances stored inside via studies which examine the visual impact on the substance and the packaging. It is possible they can provide additional assurance that the packaging and its coatings are inert through historical use of the packaging materials for the excipient in question. The excipient manufacturer is responsible for determining suitability of the primary packaging material.

- Excipient suppliers should be prepared to share details of their packaging which should also detail any coatings that may be used and in contact with the excipient. Consideration should be given to risks presented by secondary / indirect materials such printing inks, adhesive and labels which may feature on the primary packaging material. Where compatibility studies have been done between the packaging and the excipient then these too could be made available. The provision of such details will allow the excipient user to perform a risk assessment to determine if the packaging is acceptable for that excipient.

- Packaging manufacturers may not be willing to obtain food compliance or to meet pharmaceutical requirements of the packs for low volume items. However, where the excipient is not defined as a hazardous material then the packaging is not subject to the relevant transport and supply legislation pharmaceutical or food grade materials is preferred.

- Non-solid bulk pharmaceutical excipients that create aggressive contact situations with PPMs (for example, hydrochloric acid, sulfuric acid) will only be used after dilution in pharmaceutical products. In this case the dilution factor may be used to correct the global and specific migration limits to be applied.

- Documentation on the risk assessment with respect to PPMs used for excipients are part of the information package that may be requested by excipient users.

- The Annex shows a decision tree that may be used as a guide to choose a suitable material and the types of documentation which the supplier could provide to users on request.

Recommendations

Excipient suppliers and excipient users should consider:

1. Evaluation of PPMs in the context of the points presented above.
2. (Suppliers) Make available on request the information outlined in Annex 1 or a rationale as to why it is not needed / required.

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3. Changes related to PPMs and their impact on excipients.

Additional Information (If applicable)

During the development of this position, data were collected with respect to legal, food, pharmacopoeia and chemical requirements. These documents are available from the IPEC Europe Secretariat.
These documents also contain the appropriate References.

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Annex 1
Information for excipient users to perform a risk assessment

Excipient suppliers should provide information on PPMs to excipient users on request to enable them to perform a risk assessment.

The information about packaging materials, with which the excipient may have contact, may include:

1. A description of the PPM including the container closure system and secondary / indirect materials (inks, adhesives etc.) in cases where the container closure system may be considered a primary packaging material. Typically, the specification of PPM would contain this information.
2. Information on the composition of the PPM (including the container closure system if appropriate).
3. A compliance confirmation for the PPM. This may take several forms:
   - A confirmation that the packaging materials meets the requirements of compendial standards with reference to the current requirements such as listed in the European Pharmacopeia (Ph. Eur.), or United States Pharmacopeia (USP), and/or
   - A declaration that the packaging materials follow food contact material regulation, i.e. for the EU the requirements of the framework regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food and other EU regulation having regard to this regulation, including regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, if applicable, or for the US, the requirements for Indirect Food Additives following 21 CFR 174-186.
4. Data on the historic safe use of the PPM-excipient combination.
5. Data on the compatibility of the PPM to contain, store and transport dangerous products.
6. Data on migration (leachables and extractables) for the PPM–excipient combination if available. This data may only be considered if a confirmation as described under 3. cannot be provided and the risk assessment for the specific intended use calls for these measures.

The excipient user should consider the information above in the context of a risk assessment conducted for the specific medicinal product. Additional information may be required.

For solid excipients the information under 1, 2 and 3 are usually sufficient to finalize the risk assessment. For liquid excipients, excipients that are dangerous goods and aggressive materials, a case-by-case risk assessment would have to be performed.

The decision tree below describes the steps which may be considered when determining information needs to perform a risk assessment.

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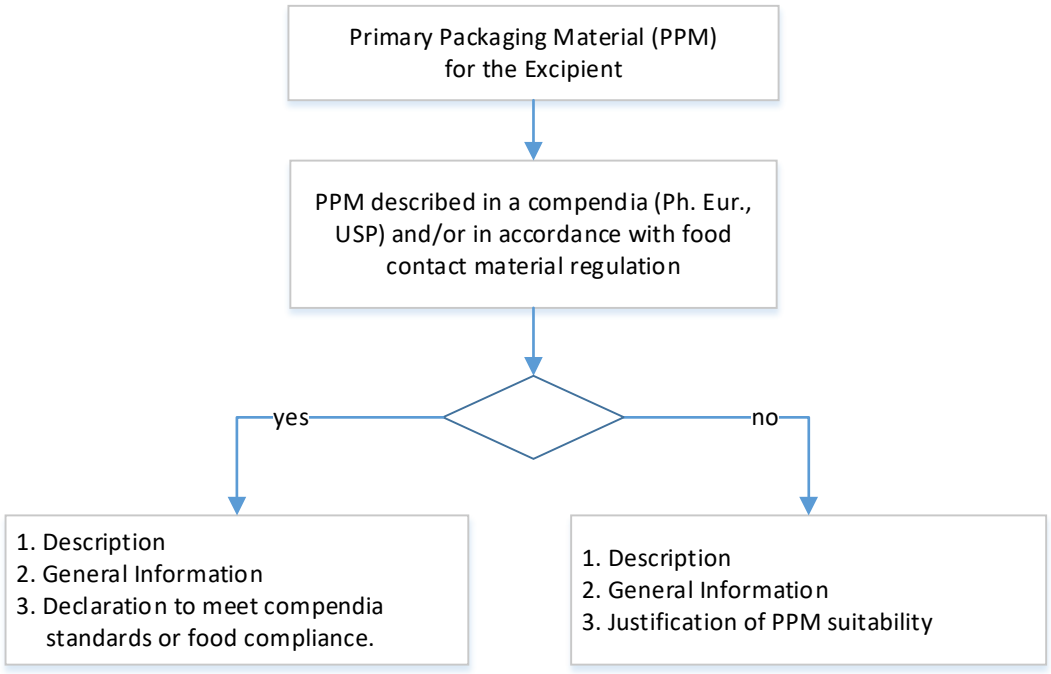

Figure 1: Decision tree for excipients suppliers on which information to provide excipient users

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