POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

CMC Reviews of Type III DMFs for Packaging Materials

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PURPOSE

- This MAPP establishes standardized policy within the Office of Pharmaceutical Quality (OPQ) for chemistry, manufacturing, and controls (CMC) review of information regarding certain packaging materials in type III drug master files (DMFs). Specifically, this MAPP addresses when a written review of a Type III DMF should be prepared and how a reviewer should determine whether the information in the DMF and the application it supports satisfies the requirements for assessing the safety assessment of certain packaging systems intended for use with drug substances and orally and parenterally administered drug products.

BACKGROUND

- Reviewing the packaging information in a new drug application, an abbreviated new drug application, a biologics license application, an investigational new drug application, or an amendment or supplement to these applications involves assessing whether each packaging component or material is suitable for its intended use. Suitability is generally assessed in terms of protection, compatibility, safety, and performance (as described in more detail in section III.C of the guidance for industry, *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation*.

- Suitability information for packaging components or materials may be submitted either in the application or a referenced DMF. However, the following information is typically provided in a type III DMF:

  - Description of the packaging component or material (e.g., high density polyethylene (HDPE) bottles, polypropylene (PP) caps) or description of a material of construction (MOC) (e.g., HDPE resin, PP resin).

  - Quantitative or qualitative statement of the composition.

  - Release specification or quality attributes for the packaging component or material.

  - Results of certain kinds of qualification testing (e.g., some of the tests described in United States Pharmacopeia (USP) General Chapter <661>).

- The following information is usually provided in the application:

  - Information that addresses a container closure system's protection, compatibility, and performance attributes.

  - Fundamental or basic physical attributes (e.g., component dimensions). (These attributes are usually addressed in the applicant's acceptance specifications.)

- Assessment of the safety of a packaging component or material is generally based on the potential or observed interaction between the MOC and the drug substance or drug product during storage and usage. Reviewers should consider the following factors when evaluating the safety of packaging components or materials:

  - Drug product's dosage form and route of administration.

  - MOCs of the packaging components and materials.

  - Likelihood that a component of the MOC will leach into the drug substance or drug product. (Unless a component in an MOC is volatile, a medium of extraction (e.g., a liquid phase) must usually be present for leaching to occur.)

  - Amount of leachable materials detected in the drug substance or drug product.

  - Toxicity of the leachable material, taking into account the dosage form, route of administration, target population, and patient exposure.

  - Usually, if water and ethanol are the only potential extraction media, the safety of the MOC can be established by referencing appropriate food additive

regulations (FARs) under 21 CFR 172-186 and the cited uses for the listed materials. Some MOCs listed in the FARs are specifically designated as being acceptable for use with fatty foods (see 21 CFR 177.1330(d)(1)). If leachable material is a cause for concern, it may be appropriate to review the applicable DMF to assess the details of its composition.

- Typically, the supplier of the packaging component or material provides the composition information, and the applicant provides the remaining safety information (including the list of leachable materials). (Refer to relevant USP monographs, as well as USP extraction tests on plastics (USP General Chapter <661>) and USP Biological Reactivity Tests (USP General Chapters <87> and <88>) on plastics).

POLICY

Written Review of Information in a Type III DMF

- Written review of the information in a type III DMF should be prepared unless the information in the application sufficiently establishes that the packaging material or component is suitable for its intended use. The table on page 5 outlines the appropriate CMC information and FAR citations that may be referenced to satisfy this requirement for information.

- Other circumstances under which a DMF might not need review (e.g., the item has been reviewed previously for a similar drug product) are outside the scope of this MAPP.

- The status of each type III DMF referenced in the application should be indicated in the CMC review of that application.

Decision Process to Determine Whether Information in the Application is Adequate

- The table below lists the dosage forms, routes of administration, and MOCs that this MAPP addresses and summarizes the information typically accepted to support the safety assessment of the MOCs used in the packaging component. A particular drug product and container closure configuration must satisfy all three of these criteria to be covered by this MAPP. For example, a rubber stopper used for a parenteral solution is not covered by this MAPP. Bulk drug substances are included under the heading “Dosage Form.” Notes follow the table and provide more specific information.

Dosage Form	**Route of Administration**	**Medium of Extraction**	**Container Closure**	**Component**	**MOC**	**Expected Safety Information**
Drug Substance, Powder	N/A	None	Bag	Bag	Polymer[1]	FAR Citation[2]
			Bottle	Bottle[1]	Glass	USP Glass[3]
					Polymer[1]	FAR Citation[2]
				Cap[1]	Polymer[1]	FAR Citation[2]
					Non-Polymer[4]	Composition
				Liner[5]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
				Inner Seal[5]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
Tablet, Capsule (including liquid-filled soft gelatin)	Oral	None	Bottle	Bottle[1]	Glass	USP Glass[3]
					Polymer[1]	FAR Citation[2] USP Plastics[7]
				Cap[1]	Polymer[1]	
				Liner[5]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
				Inner Seal[5]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
				Desiccant and Oxygen Scavengers[8]	Ink, Container, Sorbent	FAR Citation[2]
				Pharma-ceutical Coil[9]	Rayon or Cotton	USP Monographs for Purified Cotton and Purified Rayon
			Blister[10] Sachet	Laminate[11]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
Solution, Suspension	Oral	Aqueous Vehicle[12]	Bottle	Bottle[1]	Glass	USP Glass[3]
					Polymer[1]	FAR Citation[2] USP Plastics[7]
				Cap[1]	Polymer[1]	
				Liner[5]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
				Inner Seal[5]	Polymer[1]	FAR Citation[2]
					Adhesive[6]	FAR Citation[2]
				Dropper[14]	Glass	USP Glass[3]
					Polymer[1]	FAR Citation[2]
Solution for Injection	Parenteral	Aqueous Vehicle[12]	Ampoule, Vial, Syringe[13]	Ampoule, Vial, Syringe[13] Barrel	Glass	USP Glass[3]
Powder for Injection		None				

NOTES

1. Polymers: Bags used for drug substances and bottles and caps used for both drug substances and drug products are usually manufactured with polyethylene or polypropylene resins, whose constituents are FAR listed (see note 2). If the drug substance or drug product contains a residual solvent that may act as a medium of extraction, then potential extractables should be taken into consideration.

2. FAR Citation: Food additive regulations (21 CFR 172-186); many contain approved uses and limits for particular additives.

3. USP Glass: USP General Chapter <660> Containers – Glass.

4. Non-Polymer Caps: A drug substance or drug product may be packaged in bottles with metal caps. The cap is not considered to interact with the contents and requires no qualification information.

5. Liners and Inner Seals: These are usually laminates (see note 11).

6. Adhesives: These are a class of polymers (usually polymethacrylates) and may be part of a laminate (see note 11) or applied separately.

7. USP Plastics: USP General Chapter <661>, Containers – Plastics.

8. Sorbents: These are desiccants and oxygen absorbers. Typically they are packaged in paper or plastic containers that are reviewed for safety only. Issues of performance in terms of oxygen or moisture absorption are generally included in the review of the application that the DMF supports. Sorbent containers may also be printed with ink. The MOCs for the desiccant, oxygen absorber, container, and printing ink should comply with the cited FARs if they are in contact with the drug substance or product.

9. Pharmaceutical Coil: If this material has been bleached, it should be shown to be free of residual bleaching agents (usually peroxides). The coil's moisture content may be an issue if the drug product is moisture sensitive.

10. Blister: A blister is composed of two films (usually laminates) that are sealed together to contain the drug product. The two films may be the same or different.

11. Laminates: These consist of layers of polymer, paper, foil, and/or adhesive. One or more of the layers usually forms a "functional barrier" (see note 15) between the contents and the exterior (atmospheric air or other components). All materials between the functional barrier and container contents are expected to comply with appropriate FARs. Films made of polyvinyl chloride (PVC) should have a residual vinyl chloride monomer content of <5 parts per billion.

12. Aqueous: Water is the primary vehicle. It may contain co-solvents and other excipients that may affect the extraction properties (e.g., significant amounts of an alcohol or surfactant). The CMC reviewer will evaluate the potential for extraction by the medium and review the composition of the MOC in the DMF, if necessary.

13. Ampoule, Vial, Syringe: If pre-sterilized or pre-treated (e.g., with silicone), then processing for sterilization or coating may require review.

14. Dropper: A CMC reviewer will evaluate other MOCs used for a dropper assembly (e.g., ink, rubber bulb) on a case-by-case basis.

15. Functional Barrier: FDA's Center for Food Safety and Applied Nutrition (CFSAN) has accepted the concept of "functional barrier" as a subset of the "no migration" exclusion in the definition of food additive (21 CFR 170.3(e)). An exception to the requirement for assessing the migration of materials used in food packaging is made when there is a determination that the material is not reasonably expected to migrate to the food above the "threshold of regulation" (21 CFR 170.39), or at least not above a safe limit based on the toxicity of the material in question. If the food contact materials are determined to form a layer that prevents the migration of materials from the outer layers, then a functional barrier is presumed to exist and materials outside the functional barrier are presumed to be unable to migrate into the food. Safety of the materials in the outer layers requires less scrutiny.

    No formal definition for functional barrier exists in the Federal Food, Drug, and Cosmetic Act or in FDA regulations. The concept, however, is addressed in CFSAN guidances regarding recycled plastics and premarket submission for food contact substances (see REFERENCES). The term is also cited with reference to packaging for human foods in 21 CFR 109.30(c), 175.300(a), 176.160(b)(2), and 177.1390(a). An example of a functional barrier is metal foil or a polymeric material of sufficient thickness and impermeability. An example of an exterior layer material is printing ink or adhesive.

RESPONSIBILITIES AND PROCEDURES

Primary CMC Reviewer

- Determines whether the information in the application is adequate to establish that the packaging component or material is suitable for its intended use.

- If the information is adequate, documents the conclusion and provides a justification in the review of the application. A DMF review is not necessary.

- If the information is not adequate, requests additional information from the applicant through appropriate channels.

- If the applicant does not respond or the information in the response is not adequate, determines whether the DMF has been previously reviewed and whether the previous review is applicable to the current drug product.

  - If the previous review is applicable to the current drug product, documents the conclusion from the previous DMF review and provides a justification in the review of the application that the DMF supports. A DMF review is not necessary.

  - If the previous review is not applicable to the current drug product, prepares a DMF review.

    - If the information in the DMF is adequate, documents the conclusion in the review of the application, as well as in the DMF review.

    - If the information in the DMF is not adequate:

      - Prepares a draft letter to the DMF holder to communicate comments.

      - Documents the conclusion in the application review, as well as in the DMF review.

Secondary CMC Reviewer

- Signs off on the DMF review.
- Signs off on the CMC review of the application.

REFERENCES

- 21 CFR 314.420, Drug Master Files.

- Guidance for industry, *Guideline for Drug Master Files*.

- Guidance for industry, *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, And Controls Documentation*.

- 21 CFR 172-186 [direct additives, indirect additives, and GRAS materials].

- Guidance for industry, *Use of Recycled Plastics in Food Packaging: Chemistry Considerations*.

- Guidance for industry, *Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations*.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
3/22/2010	Original	
8/12/2011	Rev. 1	Under "***NOTES***," changed: #3. "<661>, Chemical Resistance – Glass Containers" to "<660> Containers – Glass"; and #7. "Physiochemical Tests – Plastics; Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles; and Polypropylene Containers" to "Containers – Plastics".