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A REVIEW OF CURRENT REGULATORY MECHANISM FOR PHARMACEUTICAL EXCIPIENTS IN USA

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Abstract

Pharmaceutical excipients contribute unique functionalities to formulations, thereby largely determining the drug products quality and influencing its safety and efficacy. Changes and variations of excipients in licensed products are, therefore, placed under strict regulatory control. This article presents a proposed regulatory mechanism for pharmaceutical excipients by United States of Food and Drug Administration (USFDA). In Unites States, excipients are regulated by United States of Food and Drug Administration (USFDA).

The United States of Food and Drug Administration (USFDA) is an agency of the United States Department of Health and Human Services. From a regulatory standpoint, the FDA's concern regarding excipients involves GMP, toxicity, impurity, safety, quality assurance, stability, USP-NF monograph requirements, labelling regulations and approval or review mechanism.

Key words:

Pharmaceutical Excipients, United States of Food and Drug Administration (USFDA), Good Manufacturing Practices, Regulations.

Introduction

The Food and Drug Administration (FDA) is generally recognized as one of the, if not the, premier therapeutic agent gatekeepers among nations. The Elixir of Sulphanilamide disaster, in which 107 people died as a result of the use of a toxic inactive ingredient, dramatized the need to establish drug safety before marketing and provided the impetus to pass the pending Federal Food, Drug, and Cosmetic Act of 1938.

An inactive ingredient is defined by the FDA as ‘‘any component of a drug product other than an active ingredient’’ [Title 21 Code of Federal Regulations [21CFR Part 218.3C(b)(8)]. [1] It is also known as compendial excipients. New excipients are defined as any inactive ingredients that are intentionally added to drug products to improve product delivery (e.g. enhance absorption or control release profile) but they are not intended to give therapeutic effects. [2]It is also known as non-compendial or novel excipients.

Excipients Source of Information: [3,4]

Information about excipients can be obtained from various sources. Different sources for information are shown in

Table-1: Excipients Sources of Information.

Sr. No.	Source	Information	Comments
1.	United States Pharmacopeia National Formulary (USP- NF)	include standards and monographs for excipients	Updated regularly; many available in book format or CD-ROM; can be obtained through various publishers including Informa Healthcare
2.	FDA Inactive Ingredient Guide	lists excipients used in FDA-approved drug products marketed for human use by route administration and dosage form	Published by FDA, DDIR; available through FDA Web site www.fda.gov; updated regularly
3.	Chapter 3 - Requests for Revision of the USP-NF	Available at the USP Web site www.usp.org offers guidance on various tests useful for new monograph excipients	updated regularly
4.	Handbook of Pharmaceutical Excipients	Excipient monographs containing data on uses, properties, safety, excipient interactions, standards; also a supplier’s directory	A joint publication of the American Pharmaceutical Society and the Royal Pharmaceutical Society of Great Britain
5.	Handbook of Pharmaceutical Additives	Excipients used in prescription and OTC products approved by the FDA or recommended by USP/NF, BP, and Ph. Eur., details manufacturers, composition, properties, function, and applications, toxicology and regulatory status of additives	Compiled by M. and I. Ash; Published by Gower, Aldershot, U.K, and Vermont, U.S.A

6.	Physicians' Desk Reference	Compendium of FDA approved pharmaceutical products; details formulation, pack, administration and use; identification guide	Published by Medical Economics Co., N.J., U.S.A., in participation with individual manufacturers; also PDRs for ophthalmology and nonprescription drugs; CD- ROM or hard copy or available electronically

*DDIR: Division of Drug Resources

U.S. Code of Federal Register References to Excipients: [5]

U.S. Code of Federal Register References to Excipients is shown in Table 2.

Table 2: U.S. Code of Federal Register References to Excipients

Subject	Reference	Content
General	21 CFR § 210.3(b)(8)	Definitions
	21 CFR § 201.117	Inactive ingredients
	21 CFR § 210.3(b)(3)	Definitions
Over-the-counter drug products	21 CFR § 330.1(e)	General conditions for general recognition as safe, effective, and not misbranded
	21 CFR § 328	Over-the-counter drug products intended for oral ingestion that contain alcohol
Drug Master Files	21 CFR § 314.420	Drug master files
Investigational New Drug Application	21 CFR § 312.23(a)(7)	IND content and format
New Drug Application	21 CFR § 312.31	Information amendments
	21 CFR § 314.50(d)(1)(ii)(a)	Content and format of an application
	21 CFR § 314.70	Supplements and other changes to an approved application
Abbreviated New Drug Application	21 CFR § 314.94(a)(9)	Content and format of an abbreviated application
	21 CFR § 314.127	Refusal to approve an abbreviated new drug application
	21 CFR § 314.127(a)(8)	Refusal to approve an

		abbreviated new drug application
Current Good Manufacturing Practice	21 CFR § 211.84(d)	Testing an approval or rejection of components, drug product containers and closures
	21 CFR § 211.165	Testing and release for distribution
	21 CFR § 211.180(b)	General requirements
	21 CFR § 211.80	General requirements
	21 CFR § 211.137	Expiration dating
Listing of drugs	21 CFR § 207	Registration of procedures of drugs and listing of drugs in commercial distribution
	21 CFR § 207.31(b)	Additional drug listing information
	21 CFR § 207.10(e)	Exemptions for domestic establishments
Labeling	21 CFR § 201.100(b)(5)	Prescription drugs for human use
	21 CFR § 201.20	Declaration of presence of FD&C Yellow No. 5 and/or FD&C Yellow No. 6 in certain drugs for human use
	21 CFR § 201.21	Declaration of presence of phenylalanine as a component of aspartame in over-the-counter and prescription drugs for human use
	21 CFR § 201.22	Prescription drugs containing sulfites; required warning statements

Current Good Manufacturing Practices for Excipients in USA:

Current GMP rules and regulations for excipients in USA are as following:

21 CFR § 211.84(d) [6]

Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

Sec. 211.165 Testing and release for distribution. [7]

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release.

The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

21 CFR § 211.180(b) General requirements [8]

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

Sec. 211.80 General requirements. [9]

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Sec. 211.137 Expiration dating. [10]

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in 211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labeling in accordance with the requirements of 201.17 of this chapter.

(e) Homeopathic drug products shall be exempt from the requirements of this section.

(f) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

(g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.

(h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

Toxicity Evaluation of Excipients:

Several different toxicities have been ascribed to excipients both from topical administration and systemic administration. [11]

- Regarding topical application of some excipients, dermal toxicities— such as hypersensitivity from lanolin, benzoic acid, para-amino benzoic acid (PABA), and local anesthetics; photo toxicity from cinnamon oil, Bergamot oil (used in perfumes), and 8-methoxypsoralen with Ultraviolet A light (PUVA) as therapy for psoriatic lesions; and contact dermatitis from propylene glycol, polyethylene glycol, and oleic acid—have been observed.
- Examples of systemic administration associated with some excipients include renal tubular necrosis caused by intravenous (IV) or subcutaneous (SC) administration of b-cyclodextran, respiratory toxicities in young children caused by inhalation of solutions containing benzyl alcohol, digestive problems caused by ingestion of lactose,

allergic responses caused by ingestion of sulfites, and diarrhea caused by ingestion of mannitol-containing solutions have been reported.

During that time, the FDA/CDER's Inactive Ingredients Subcommittee of the Pharmacology/Toxicology Coordinating Committee was working on an excipient guidance that was published for public comment in 2002 and finalized in 2005.

This guidance is entitled ''Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients'' [12] and is available on the FDA/CDER Web site. It was a product of the International Conference on Harmonization (ICH) M3 guidance and the IPEC Safety Committee's guideline for the testing of excipients.

The FDA's guidance recommends the acquisition of toxicology data from the following types of studies

- safety pharmacology with an emphasis on cardiovascular, respiratory, and central nervous systems,
- pharmacokinetic/absorption, distribution, metabolism, and excretion (ADME) studies,
- ICH S2B genetic toxicology battery,
- reproduction toxicology,
- appropriate duration repeat dose studies in 2 species (rodent and nonrodent mammal), and
- carcinogenicity studies, if warranted.

The excipient must be tested using the anticipated clinical route of administration. It is recommended that before any studies are begun, the appropriate FDA/CDER review division be contacted to discuss the appropriate tests. Specific guidance regarding routes of administration can be found in the FDA/ CDER Excipient Guidance and in the IPEC publication.

It was mentioned above that data from carcinogenicity studies may be necessary, ''if warranted.'' A review of the FDA/ CDER guidance indicates that one of the following approaches could be used, but it must be emphasized that any of the approaches chosen should be discussed with the FDA review division before studies are begun.

- Either two 2-year bioassays in rodents or a 2-year assay in a rodent (usually rat) and
- an alternative assay such as a neonatal or a transgenic assay in a different rodent species (usually mouse).
- However, there is a third possibility that is implied in the ICH Guidance S1A, which is ''The need for long-term rodent carcinogenicity studies of pharmaceuticals,"

If the excipient

- has no structural alerts,

- has no pharmacological activity in the ICH safety pharmacology studies and in other pharmacological assays,
- is not genotoxic,
- is not a reproductive toxicant,
- shows no severe toxicities in a 90-day or 180-day repeat dose tests in rodent and non-rodent mammalian species,
- has a very large margin of safety in the repeat dose tests, and
- perhaps has negative data from a transgenic assay, maybe carcinogenic assay/assays can be waived.

It should be understood that if a request for a waiver is accepted by the CDER review division, the excipient may be capable of producing tumors in rodents if tested in the 2-year bioassays.

Excipients Impurity

For the oral route of administration, the risk assessment should evaluate the possibility for inclusion of Class 1 and Class 2A elemental impurities in the drug product. For parenteral and inhalation routes of administration, the risk assessment should evaluate the possibility for inclusion of the Class 1, Class 2A, and Class 3 elemental impurities as shown in Table 3.

Table 3: Class of impurity [13]

Element	Class	If intentionally added	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	Yes	Yes	Yes	Yes
Pb	1	Yes	Yes	Yes	Yes
As	1	Yes	Yes	Yes	Yes
Hg	1	Yes	Yes	Yes	Yes
Co	2A	Yes	Yes	Yes	Yes
V	2A	Yes	Yes	Yes	Yes
Ni	2A	Yes	Yes	Yes	Yes
Tl	2B	Yes	No	No	No
Au	2B	Yes	No	No	No
Pd	2B	Yes	No	No	No
Ir	2B	Yes	No	No	No
Os	2B	Yes	No	No	No
Rh	2B	Yes	No	No	No

Ru	2B	Yes	No	No	No
Se	2B	Yes	No	No	No
Ag	2B	Yes	No	No	No
Pt	2B	Yes	No	No	No
Li	3	Yes	No	Yes	Yes
Sb	3	Yes	No	Yes	Yes
Ba	3	Yes	No	No	Yes
Mo	3	Yes	No	No	Yes
Cu	3	Yes	No	Yes	Yes
Sn	3	Yes	No	No	Yes
Cr	3	Yes	No	No	Yes

The Code of Federal Regulations [21 US CFR 211.84(6)(d)(2)] indicates that each excipient component shall be tested for conformity with all appropriate specifications for purity, strength, and quality. The FFD&C recognizes the USP/NF13 as official compendia. In USA. there is currently no formal guidance regarding the assessment of excipient-related impurities. Based on the FDA guidance on excipient safety, however, novel excipients, or those proposed for use by a novel route of administration, would generally require a more stringent assessment. Excipients may in fact be treated similarly to an API with submission of a DMF, if desired, and the evaluation may include the safety evaluation of impurities. Given the lack of specific guidance related to impurities, the recommendations provided in the ICH Q3 guidance may serve as an initial starting point for consideration. [11]

Safety Evaluation of Excipients: [12]

FDA has released a guidance document entitled "Nonclinical Studies for Development of Pharmaceutical Excipients," which was finalized in May 2005 (a draft version of this document first appeared in September 2002). Guidance is intended to foster and expedite the development of new excipients and to communicate agency expectations to industry. This document provides guidance concerning development of safety profiles to support use of new excipients as components of drug or biological products. This guidance describes the types of toxicity data that the Agency uses in determining whether a potential new excipient is safe for use in human pharmaceuticals. It discusses recommended safety evaluations for excipients proposed for use in OTC and generic drug products, and describes testing strategies for pharmaceuticals proposed for short-term, intermediate, and long-term use. It also describes recommended excipient toxicity testing for pulmonary, injectable, and topical pharmaceuticals.

Submission of Safety Data

A. Over-the-Counter Products

- For products marketed under OTC drug monographs, 21 CFR 330.1(e) requires: "The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity.
- Colour additives may be used only in accordance with section 721 of the act and subchapter A of this chapter." It is the manufacturer's responsibility to comply with these requirements and to have appropriate supporting data in its files.
- The provisions of § 330.1(e) do not apply to OTC products marketed under NDAs or abbreviated new drug applications (ANDAs).
- Some excipients used in NDA-approved drug products may not be safe for use in OTC products (e.g., some toxic excipients used in cancer chemotherapeutics).

B. Generic Products

- Requirements for submitting safety information on excipients in ANDAs for generic products are stated in 21 CFR 314.94(a)(9).
- Under this regulation, drug products intended for parenteral, ophthalmic, or optic use should contain the same excipients in the same concentrations as the reference listed drug product, with the exception of buffers, antioxidants, and preservatives, provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product.
- For other routes of administration (e.g., topical dermal, oral), there is no requirement that the excipients in the final formulations be the same as those in the reference listed drug product, although the applicant must demonstrate that the inactive ingredients do not affect the safety or efficacy of the proposed drug product (21 CFR 314.94(a)(9)(ii)).

C. New Drug or Biological Product Application

- It is important that a new or inadequately qualified inactive ingredient proposed for use in any product to be marketed pursuant to an NDA, biologics license application (BLA), or ANDA be supported by adequate data.

- These data can be placed in the application directly or in a drug master file (DMF). This guidance describes the nonclinical data we recommend be submitted to verify that a proposed excipient is safe in the amounts administered if relevant prior human use cannot be adequately documented.

D. Requests for Additional Safety Data

- FDA may request additional safety data if FDA determine that the proposed conditions of use are not fully supported by the available data.
- FDA may request a pharmacokinetic profile for excipients that are extensively absorbed or bio transformed. When applicable, drug-excipient interaction studies may also be requested.
- The proposed conditions of use of a new excipient (e.g., use in paediatric patients) may affect the need for toxicology data. The sponsor is encouraged to contact the appropriate review division for guidance.

E. Exceptions

Excipients that are large polymers that differ from previously characterized excipients only in molecular weight (chain length) can be adequately characterized in an abbreviated manner using less safety data, provided that the new excipient and the previously studied excipient are sufficiently similar with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other impurities.

The following recommendations are primarily intended for excipients for which adequate prior human exposure has not been documented.

A. Safety Pharmacology

All potential new excipients be appropriately evaluated for pharmacological activity using a battery of standard tests (see ICH guidance S7A). These evaluations can be performed during the course of toxicology studies or as independent safety pharmacology studies.

It is useful for these data to be obtained at an early point during the safety evaluation of an excipient, since, if the excipient is found to be pharmacologically active, this information can influence subsequent development. Appropriate regulatory guidance can be given by the responsible review division.

B. Potential Excipients Intended for Short-Term Use.

The safety evaluation of potential new excipients that are intended for use in products that are limited by labelling to clinical use of 14 or fewer consecutive days per treatment episode and are infrequently used include at least the following:

1. Acute toxicology studies performed in both a rodent species and a mammalian nonrodent species by the route of administration intended for clinical use (see CDER guidance for industry Single Dose Acute Toxicity Testing for Pharmaceuticals).

It is not necessary to determine the LD50 of an excipient. It may be appropriate to omit acute toxicology studies from the safety evaluation of a new excipient under certain circumstances.

For example, if repeat-dose toxicology studies are performed in which the high dose is the limit dose (e.g., 2 g/kg or 2 percent of the diet) and little or no toxicity is observed at that dose, it can be assumed that the acute toxicity has been adequately evaluated. In some cases, a dose-escalation study is considered an acceptable alternative to a single-dose design (see ICH guidance M3).

2. It is recommended that the absorption, distribution, metabolism, and excretion of the excipient be studied following administration by the clinically relevant routes to the same species that are used in the nonclinical safety studies (see ICH guidelines S3A and S3B).

3. It is recommended that excipients be evaluated in the standard battery of genetic toxicology studies discussed in ICH guidance S2B.7

4. It is recommended that 1-month repeat-dose toxicology studies be performed in both a rodent species and a mammalian nonrodent species by the route of administration intended for clinical use. It is important that the studies include complete clinical pathology, histopathology, and toxic kinetic analysis.

5. It is recommended that the reproductive toxicology of the excipient be evaluated as discussed in ICH guidelines S5A and S5B,8 including: (1) assessment of potential to affect fertility or early embryonic development to implantation; (2) teratology in both a rodent species and a mammalian nonrodent species; and (3) effects on prenatal and postnatal development, including maternal function. The most efficient way to address these different developmental landmarks is use of a single-study rodent assay (as defined in ICH guidance S5A) to assess all phases of reproductive toxicity, in conjunction with a teratology study in a nonrodent species, provided that the available data predict the excipient has minimal toxicity.

C. Potential Excipients Intended for Intermediate Use

The nonclinical safety evaluation of potential new excipients that are intended for use in drug products that are labelled for clinical use of more than 2 weeks but less than or equal to 3 months per treatment episode include at least the following:

1. All studies with the exception of the 1-month toxicology studies. Note: If toxicity or significant biological activity is observed in short-term studies, 1-month toxicology studies may be useful for establishing dosages to be used in 3-month studies.

2. 3-month repeat-dose toxicology studies be performed in both a rodent species and a mammalian nonrodent species by the appropriate route of administration. It is important that the studies include complete clinical pathology, histopathology, and toxic kinetic analysis.

D. Potential Excipients Intended for Long-Term Use

The safety evaluation of potential new excipients that are intended for use in drug products labelled for clinical use of more than 3 months in a given patient (either as a single treatment episode or as a result of multiple courses of therapy to treat a chronic or recurrent condition) include at least the following:

1. All studies and 1-month and 3-month toxicology studies are not essential, but may provide useful dosage selection data.

2. 6-month repeat-dose toxicology study be performed in a rodent species by the appropriate route. It is important that the study include complete clinical pathology, histopathology, and toxic kinetic analysis. FDA recommend that studies that involve excipients of low toxicity in general use the limit dose as the highest dose for testing.

3. It is important that a chronic toxicology study be performed in a mammalian nonrodent species by the appropriate route. If toxicity and pharmacologic effect were absent in state-of-the-art sub chronic studies, a 6-month study may be sufficient. When toxicity is detected in shorter duration studies, or in rodents, a chronic study in nonrodents of 9 to12 months may be appropriate. The sponsor is encouraged to contact the appropriate review division for guidance.

4. If appropriate (see ICH guideline S1A), one of the following approaches may be used to evaluate carcinogenic potential:

a. Two-year carcinogenicity bioassays in two appropriate species by the relevant routes.

b. A 2-year carcinogenicity study in one rodent species plus an alternative study (e.g., appropriate use of neonatal or transgenic animals) in a different rodent species.

c. Submission of documentation providing scientific justification that carcinogenicity data are not necessary. For example, based on negative genetic toxicology data (see ICH guidance S2B for recommended assays), limited systemic exposure, absence of accumulation based on nonclinical and clinical pharmacokinetic data, negative histopathology data from chronic toxicology studies performed at the maximum feasible dose (MFD) (absence of

paraneoplastic lesions and other toxicological effects), and knowledge of other excipients in the same class, it may be reasonable to forego carcinogenicity testing. Decisions concerning the adequacy of this approach would be made on a case-by-case basis, using a weight-of-evidence approach. In other cases, adequately performed cell transformation assays or one 2-year bioassay in the rat or one transgenic assay, if negative, may be sufficient to contribute to the weight-of-evidence assessment to address the carcinogenic potential of the excipient. It is strongly encouraged that application of the approach described herein be undertaken in consultation with appropriate review division staff.

E. Potential Excipients for Use in Pulmonary, Injectable, or Topical Products

1. The safety evaluation of potential new excipients that are intended for use in injectable, topical (dermal, intranasal, intraoral, ophthalmic, rectal, or vaginal), or pulmonary drug products include the following:

All studies using the appropriate route of administration. Studies that include the to-be-marketed formulation of the drug product are preferred, if this information is available at the time of excipient evaluation.

2. Sensitization study (e.g., guinea pig maximization study or murine local lymph node assay). Consult CDER guidance for industry Immunotoxicology Evaluation of Investigational New Drugs for more information.

3. For excipients intended for injectable use, the following considerations may be appropriate:

a. An in vitro haemolysis study could be performed at the intended concentration for I.V. administration (bolus and/or infusion) to determine the haemolytic potential.

b. The plasma concentrations of creatinine kinase determined at the intended excipient concentration for I.M. or S.C. administration can provide information on potential muscle damage.

c. An evaluation of protein binding in relation to local site tolerability could be done.

4. Excipients intended for topical use may need support from toxicology studies by both the intended clinical route and the oral or parenteral route if clinical pharmacokinetic studies conducted under conditions of maximum exposure show patients would experience systemic exposure to the excipient or its metabolite, particularly if limited systemic exposure were observed in nonclinical studies conducted by the clinical route of administration. The developer of a potential new excipient is invited to contact the appropriate review division to discuss whether or not this is appropriate for a specific excipient.

5. For topical dermal products and ophthalmic products, it may be appropriate to conduct an ocular irritation study.

F. Photo safety Data

Excipients be evaluated regarding the need for photo safety testing as described in the CDER guidance for industry Photo Safety Testing. Either the excipient or the complete drug product could be tested.

Quality Assurance of excipients:[1]

Section 501 [21 U.S.C. 351] of the Federal Food Drug and Cosmetic Act (FFDCA) act describes the conditions under which a drug or device may be deemed to be adulterated. One of the requirements of the act is that the drug be manufactured under current Good Manufacturing Practices (cGMP). A manufacturer will also have to submit compendial and noncompendial excipient requirements that are of critical importance to the manufacturability of a particular drug product. For example, a particular particle size distribution, viscosity grade, or hydrate may be needed for the successful and reproducible manufacturing of a safe and effective product.

Certificate of Analysis

The goal of the COA is to assure that the materials meet the expected quality criteria as per the Code of Federal Regulation (CFR) 211.84(d)(2). ‘‘Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component.’’ The COA is also discussed in the USP, see General Chapter <1078>. The COA should be attached to any excipient shipment, and is always generated by the original manufacturer of the excipient and must include the following information:

- Supplier’s name and address
- Name of Product-U.S. P/National Formulary (NF) designation
- Lot number
- Production date
- Specification and acceptance criteria of the product
- Test method used and reference to the analytical procedures
- Actual analytical results
- Supplier’s signature and date

All the acceptance criteria and test results are best expressed numerically or qualitatively (e.g., clear, colourless solution), as appropriate. The use of terms such as ‘‘conforms’’ or ‘‘meets specification’’ is discouraged.

When the specification for a raw material excipient is compendial and conforms to the monograph standard, a citation to the appropriate official compendium needs to be provided. The excipient specification is expected to be identical to

the compendial monograph and full monograph testing will be performed on each batch of excipient by the excipient's manufacturer. At a minimum, the drug product manufacturer must perform an appropriate ID test [21 CFR 211.84(d)(1)], and for materials held in inventory, full monograph testing is expected once a year. However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. When the specification for a compendial excipient differs from the compendia monograph (e.g., additional tests, different analytical methods, or different acceptance criteria) the test results will be accepted from the excipient manufacturer's COA. However, the excipient should still conform to the monograph in an official compendium if there is such a monograph; otherwise, justifications must be provided, and labelling needs to be changed to state plainly that the article does not meet the compendial requirement.

The drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals per [21 CFR Part 211.84(d)(2)]. The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate that the tests that will be performed once the reliability of the supplier's results has been established in accordance with cGMPs, prior to marketing the drug product.

Excipients of Human or Animal Origin

Excipients of human or animal origin should be identified. The genus, species, country of origin, source (e.g., pancreas), and manufacturer or supplier should be clearly indicated. Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from bovine spongiform encephalopathy countries as defined by the U.S. Department of Agriculture (9 CFR 94.11).

Approach for Excipient Vendor Qualification

For effectiveness of the quality systems and to assure continual quality of excipient to be used for drug product manufacturing, following approach may be helpful.

- Design the SOP for "Excipient Vendor Qualification" which includes following
    - Excipient vendor selection criteria
    - Procedure for evaluation of criticality of excipient for consistent output of drug product
    - Procedure for Qualifying Non-Critical Excipients
    - Procedure for Qualifying Critical Excipients
    - Onsite audit requirement and frequency of periodic audit for assurance of consistent supply

- Procedure for preparation of audit report and verification of observations made during audit
- Procedure for pre-shipment sample analysis
- Procedure for manufacturing trial batches and evaluation of stability data for preliminary screen
- Procedure for alternate vendor development
- Procedure for Trend analysis
- Criteria for Rejection of approved vendor
- Agreement with vendor

➢ Q.U.E.S.T. approach (Cafmeyer and Lewis 2009)

Q = Question phase:

What type of excipient is required for the drug product manufacturing to fulfil the drug product characteristics, safety and efficacy of the product? The defined specification for raw material required should be prepared with scientific rationale behind its proposed usage.

U = Understanding phase:

The specific requirement related to particle size, special functionality. Based on the preliminary trials taken at laboratory scale and outcome of compatibility, stability and development activity, the requirement of excipient can be finalized.

Scientific rationale shall be available in form of the laboratory trials or through published literature.

E = Evaluation phase: Identification of the best potential vendor Based on the requirement, the potential vendor can be identified.

S = Site audit phase: Onsite and offsite verifications Based on the criticality of excipient, the onsite audit shall be carried out.

T = Track phase: Monitor and requalify

The vendor's performance must be monitored on a continuous basis. The monitoring process involves a review of any problems associated with the good or service supplied by the vendor. A schedule is determined so that each qualified vendor is requalified on a periodic basis.

Excipient Supplier Qualification [14]

Regulators worldwide recognize this challenge and now allow pharmaceutical companies to rely on third-party audits and certification that can reduce the audit burden for all concerned. Currently, the main comprehensive programs

available to pharmaceutical manufacturers for the purpose of auditing excipient suppliers and ensuring drug efficacy and patient safety are Rx–360, EXCiPACT™ and IPEA. NSF International is also in the process of drafting the ANSI NSF- 363 standard, as a basis for a quality management system for the manufacture of pharmaceutical excipients.

Stability Testing of Excipients [15]

- Data on stability and storage need to be included in the application for a marketing authorization to support the information included in the section of the Summary of Product Characteristics on shelf life and precautions for storage
- When a product contains a novel pharmaceutical excipient, full data may be required as for a new active ingredient.
- For novel excipients,
  - a summary of the results and an analysis of the data;
  - the variability of the stability profiles of different batches of drug substance;
  - the most appropriate storage conditions;
  - the proposed duration of storage before retesting;
  - the significance of the degradation products that can form on storage with cross references to the relevant information in the pharmacotoxicological Expert Report; and
  - the reasonableness of the specification proposed in relation to the available batch analysis, the analytical methods used and their validation, and the available stability data.

USP-NF Monograph Requirements:[16]

A Request for Revision for an NF excipient monograph justifies the specification, which will include universal tests and may include specific tests as needed. A Sponsor should propose specific tests only when they have impact on the quality of the excipient for release and/or compendial testing and/or when needed to allow the differentiation of the available commercial physical grades of the excipient.

A NF monograph is stability indicating when taken as a whole. It contains either a stability-indicating assay procedure or a specific, accurate non–stability-indicating assay procedure and an accompanying stability-indicating impurity procedure.

Name

The name is designated using the United States Adopted Name (USAN), if available. Otherwise, the title is the common name used in the industry, which is not necessarily the USAN.

Definition

The Definition indicates the acceptance criteria for the assay, reflective of content/purity, with exceptions as needed. Where necessary the Request for Revision should include a text for additives used. For some poorly characterized excipients, the Request for Revision may suggest the physical form, source, extent of polymerization, and/or extent of derivatization as a means of defining the excipient.

Other Requirements

Packaging and Storage

Appropriate Packaging and Storage statements are defined in the General Notices and Requirements section under Guidelines for Packaging and Storage Statements in USP–NF Monographs. Requests for Revision that differ from these statements should be justified. Packaging requirements may include light-resistant, well-closed, tight, or hermetic containers. Each of these containers is defined in the General Notices and Requirements of USP−NF, as are storage conditions. The proper packaging and storage conditions are derived from stability studies. Thus, the stability data should be included in the data package submitted with the Request for Revision to support the proposed Packaging and Storage requirements.

Labeling

The Request for Revision should include text for both labels and labeling as defined in General Notices. The labeling for an excipient is frequently a Certificate of Analysis (COA). The Request for Revision should include a COA from a representative lot of material. Where needed, the Request for Revision should include additional labeling statements, e.g., additives, viscosity, or a functionality statement where appropriate. The Request for Revision should also include the name and quantity of the specific additive(s) being used. Labeling may be used to differentiate the specification for a specific grade or composition of the excipient, e.g., the relative amounts of monomers in a polymeric excipient.

Reference Standards

This section lists all the official Reference Standards needed in order to conduct the monograph tests (see General Notices and in General Chapter USP Reference Standards <11>. A list of available official Reference Standards is provided in PF and in USP catalogues.

Universal Tests

Description

Structure

The structure of the excipient is included for reference, but where the structure is undefined or loosely defined, as in polymers, the expected monomer arrangement and ratios are described.

Molecular Formula

The molecular formula describes the salt and hydration where appropriate.

Molecular Weight

The molecular weight should be calculated from the atomic weights table provided under Reference Tables in the current USP−NF. Where the material is a macromolecule or polymer, the range of acceptable molecular weights are given where appropriate and possible.

CAS Number

A Chemical Abstracts registry (CAS) is included, where available.

Chemical Names

Although complete IUPAC names are usually the most definitive descriptors of a molecule, the chemical industry will more often use common names to describe a given compound. Therefore, NF will generally include two chemical names, which usually do not comply with the IUPAC naming conventions. Two names are used to more definitively identify the chemical structure.

Physical Form

A Request for Revision for an excipient should include a description of the physical form, including a brief description of the gross physical characteristics. This usually includes gross physical form (powder, oil, solution, etc.), crystal structure (crystalline, amorphous, or a mixture, thereof, etc.), polymorphic form, and color (white, off-white, yellow, etc.).

Solubility

The solubility or miscibility of an excipient in a given solvent is determined using the following table from the Description and Solubility section of USP−NF (see Reference Tables). Generally, the Request for Revision should assess the solubility of an excipient in three to five solvents, which typically includes water, methanol, dehydrated alcohol, acetone, and ether. Other solvents may be substituted or added where appropriate.

Identification

The purpose of identification tests in USP–NF monographs is to uniquely identify an article. One absolute procedure is generally the preferred approach for compendial identification. Thus, an infrared spectroscopy (IR) or similar spectroscopic identification tests are preferred over wet chemistry or colorimetric tests, because the spectroscopic procedures provide a conclusive identification.

Impurities

The Impurity test of an excipient monograph is intended to limit all specified impurities, with a further limit of 0.10 percent for all unspecified impurities. USP excipient monographs will include only procedures that control actual, not theoretical, impurities. When different routes of synthesis yield different impurity profiles, different Impurity test procedures may be needed.

Assay

The purpose of the Assay test is to quantify the excipient content. Wherever possible, a stability-indicating procedure should be used for the Assay test. Generally, chromatographic procedures are stability indicating, and titration procedures are not. When a non–stability-indicating assay is proposed, then a separate stability-indicating impurity procedure should be provided.

The acceptance criteria for the Assay test should be directly related to the precision or related standard deviation (RSD) of the analytical procedure. For example, an Assay test result with a 1 percent RSD should have an acceptance criterion no narrower than 97.0 percent to 103.0 percent (3) to account for statistically acceptable variability in the data.

Validation data should be based on recommendations in General Chapter Validation of Compendial Procedures <1225>. Data and representative analyses should be included for at least three batches of the drug substance.

Formulas

In a Request for Revision, the formulas should be presented in such a way that all terms, including numerical terms and their units are defined. The Sponsor should not condense several terms into a single multiplier. Where it is necessary to use a single multiplier, its origin should be clearly explained in the submission. For formulas for the calculation of impurities/related substances, an appropriate concentration term of the drug substance or another component with respect to which an impurity is measured, rather than the dilution factor(s), should be included. This reduces the need for an unexplained multiplier in the formulas.

Reference Standard Material

Most USP tests require comparison to one or more official USP Reference Standards (RS). USP monographs and General Chapters, therefore, include not only the Test procedures, but also refer to RS for these procedures, if needed. Further information is provided in General Chapter Reference Standards <11>. A Request for Revision should define the need for an RS, which should be accompanied by a sufficient quantity of candidate material, together with characterization data, stability data, storage conditions, and other relevant data. Sponsors can determine the amount of material and timing of material receipt working with appropriate USP staff. USP will evaluate the Request for Revision to determine if more or fewer RS are needed. Based upon this review, USP subsequently tests collaboratively, labels, and packages candidate material(s). Test results are reviewed by the RS Committee of the Council of Experts. If approved the material becomes official USP RS.

Labelling Requirements for Excipients:

If the drug is for other than oral use, the names of all inactive ingredients, except that: [17]

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in subchapter A of this chapter.

Subchapter A: [18]

Sec. 201.20 Declaration of presence of FD&C Yellow No. 5 and/or FD&C Yellow No. 6 in certain drugs for human use.

(a) The label for over-the-counter and prescription drug products intended for human use administered orally, nasally, rectally, or vaginally, or for use in the area of the eye, containing FD&C Yellow No. 5 as a color additive using the names FD&C Yellow No. 5 and tartrazine.

The labeling for over-the-counter and prescription drug products shall bear a statement such as "Contains FD&C Yellow No. 5 (tartrazine) as a color additive" or "Contains color additives including FD&C Yellow No. 5 (tartrazine)".

(b) For prescription drugs for human use containing FD&C Yellow No. 5 that are administered orally, nasally, vaginally, or rectally, or for use in the area of the eye, the labeling required by 201.100(d) shall bear the warning statement "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine)

sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity." This warning statement shall appear in the "Precautions" section of the labeling.

(c) The label for over-the-counter drug products intended for human use administered orally, nasally, rectally, or vaginally containing FD&C Yellow No. 6 shall specifically declare the presence of FD&C Yellow No. 6 by listing the color additive using the name FD&C Yellow No. 6. The labeling for over-the-counter and prescription drug products containing FD&C Yellow No. 6 shall declare the presence of FD&C Yellow No. 6.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named. If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection it need not be named.

Sec. 201.21 Declaration of presence of phenylalanine as a component of aspartame in over-the-counter and prescription drugs for human use. [19]

(a) Aspartame is the methylester of a dipeptide composed of two amino acids, phenylalanine and aspartic acid. When these two amino acids are so combined to form aspartame (1-methyl N -L-[alpha]-aspartyl-L-phenylalanine), they produce an intensely sweet-tasting substance, approximately 180 times as sweet as sucrose. The Food and Drug Administration has determined that aspartame when used at a level no higher than reasonably required to perform its intended technical function is safe for use as an inactive ingredient in human drug products, provided persons with phenylketonuria, who must restrict carefully their phenylalanine intake, are alerted to the presence of phenylalanine in the drug product and the amount of the ingredient in each dosage unit.

(b) The label and labeling of all over-the-counter human drug products containing aspartame as an inactive ingredient shall bear a statement to the following effect: Phenylketonurics: Contains Phenylalanine (_) mg Per (Dosage Unit).

(c) The package labeling and other labeling providing professional use information concerning prescription drugs for human use containing aspartame as an inactive ingredient shall bear a statement to the following effect under the "Precautions" section of the labeling: Phenylketonurics: Contains Phenylalanine (_) mg Per (Dosage Unit).

Sec. 201.22 Prescription drugs containing sulfites; required warning statements. [20]

(a) Sulfites are chemical substances that are added to certain drug products to inhibit the oxidation of the active drug ingredient. Oxidation of the active drug ingredient may result in instability and a loss of potency of the drug product. Examples of specific sulfites used to inhibit this oxidation process include sodium bisulfite, sodium met bisulfite,

sodium sulfite, potassium bisulfite, and potassium met bisulfite. Recent studies have demonstrated that sulfites may cause allergic-type reactions in certain susceptible persons, especially asthmatics. The labeling for any prescription drug product to which sulfites have been added as an inactive ingredient, regardless of the amount added, must bear the warning specified in paragraph (b) or (c) of this section.

(b) The labeling requirements for prescription drugs for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations, shall bear the warning statement "Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people." This statement shall appear in the "Warnings" section of the labeling.

(c) The labeling requirements for sulfite-containing epinephrine for injection for use in allergic emergency situations shall bear the warning statement "Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations." This statement shall appear in the "Warnings" section of the labeling.

Approval or Review of Excipients through Drug Product Application: [5]

Under Section 505(b)(1) of the FD&C Act, a person filing a drug application shall submit to the FDA a full list of the articles used as components of a drug product, and samples of the articles used as components as the FDA may require. In the United States, there is no separate and independent review and approval system for excipients. The FDA assesses and permits use of excipients as part of a New Drug Application (NDA). Under US law, a new pharma excipient, unlike an active drug, has no regulatory status unless it can be qualified through one or more of the approval mechanisms available for components used in finished drug dosage forms.

The FDA reviews the status of an excipient in food as information to support its use in drug products. Factors relative to the use of an excipient, such as dosing regimen and route of administration, are also reviewed.

Information on existing or new excipients can be described and provided to the FDA in an NDA directly. Alternatively, the manufacturers of excipients may prepare and submit type IV Drug Master Files (DMF) to support the use of an excipient in one or more NDAs. The DMFs are discussed in FDA's regulations under 21 CFR § 314.420 and the FDA-issued Guidance for Drug Master Files. When authorized by the DMF submitter (i.e., the excipient manufacturer) and cross-referenced by an NDA submitter, the FDA reviews the DMF to make determinations on the safety, manufacture, and quality of the excipient use in the new drug that is the subject of the then pending NDA. The DMF becomes active when reviewed in conjunction with thereview and approval of an NDA.

Pharmaceutical excipients have no official regulatory status independent of the finished dosage form in which they are used. As a result, the mechanism for regulation of these ingredients is uncertain and variable. For excipients found in OTC drug products regulated under the FDA's OTC monograph system, the agency operates under a set of proposed rules (still pending) that provide the general considerations for acceptable excipients and their functions. For prescription drugs (as well as any OTC drugs approved pursuant to a new drug application), excipients are reviewed as a part of the drug application, and not given any independent review. While in theory the FDA examines every ingredient in a new drug application, in practice, excipients long used in drugs or as food ingredients are given only cursory review. The FDA looks to several sources to identify these previously reviewed excipients, including food additive or food GRAS status, favourable review by JECFA, inclusion in the USP/NF, or prior review in other new drug applications. These previously used/acceptable excipients are identified in the FDA's Inactive Ingredient Guide. Inclusion of an ingredient in this guide provides the FDA a reasonable assurance that an ingredient, used within the scope of the usage provided in the guide, will be acceptable. [1]

Conclusion:

The regulations and guidance for pharmaceutical excipients given by the United States were reviewed. With the increasing use of excipients with enhanced potential for pharmacologicaland toxicological activity, exposure assessments will need to be more sophisticated than is now usually appropriate. Requirements and strategies for safety evaluation of new topical excipients as individual agents, separate from topical or transdermal formulations, have notbeen clearly delineated by regulatory agencies. Theinitiative by IPEC to outline safety testing for excipients, separate from a clearlydefined drug product, provides modified strategies that the toxicologist can consult in planning a safety program for excipients. The development of an independent approval system for new excipients would encourage and advance the use of new excipient technology in drug products.

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