



Marketing New Excipients

Clearing Regulatory Hurdles

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The authors review current regulatory policies for submitting new excipient information and present several models for the independent evaluation of new excipients.

Consider the following scenario: you are a business development manager at a chemical company where one of your researchers has presented some data on a new chemical compound that enhances the delivery of a specific class of drugs. A literature review and some initial short-term testing present no “red flags” that would affect safety. What’s the next step? Some examples of your options might be

- to embark on a 2–3 year formulation and safety testing program with your own capital
- to obtain financing from a pharmaceutical company or other business partner to conduct formulation and safety testing
- to license the compound to a pharmaceutical company that will commit to a testing program.

As with any new product, potential investors will judge the likelihood that a product will be successful before committing substantial resources, and they need specific criteria to make such a judgement. Although safety criteria are relatively clear, the regulatory environment is ambiguous at best because of the lack of regulatory procedures developed specifically for the evaluation of new excipients. As a result, many potentially promising leads may be abandoned, depriving the public of possible advances in excipient technology.

The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) has begun to address this situation through the development of an IPEC “Excipient Drug Master File Guide” that is intended to provide a standard format for submitting excipient safety and manufacturing information to regulatory agencies. The IPEC Guide has been submitted to FDA for review. Eventually, it is hoped that a regulatory framework could be established that would encourage the development of new excipients. Such a framework might include an independent evaluation process followed by regulatory review. This

article reviews the current situation regarding the regulation of new excipients and presents proposals for several models for the regulatory evaluation of new excipients.

The current situation

In general, the safety characteristics of an excipient can be considered a property of the excipient, although this must be considered in the context of its use. In the United States, no structure currently exists to evaluate the safety of new excipients. Because many excipients are also food ingredients, excipient manufacturers have tended to rely on food regulations (food additive status or generally recognized as safe [GRAS] determination) as an initial safety review and as an indication of eventual acceptability of their products. However, this option may not be appropriate for many new excipients for the following reasons:

- The GRAS and food additive approval processes were developed for food, and food risk assessment assumptions may be different from those for drugs such as general population exposure.
- These approval mechanisms are applicable only to oral dosage forms.

In the current system in the United States, an excipient would be considered acceptable if it is referenced in, and part of, an approved new drug application (NDA) for a particular function in that specific drug product (1). Acceptable excipients are published in FDA’s Inactive Ingredient Database along with the approved dosage forms and concentrations. However, this approach may also be problematic because there are no indications of an excipient’s approvability outside of a specific route of administration and concentration range listed in the database. Pharmaceutical manufacturers may be reluctant to even experiment with formulations that contain excipients that are not listed in the database.

Regulatory and legal definitions of *newness* have plagued inventors in all areas of new product development, and excipients are no exception. Strictly speaking, any excipient that is not listed in the FDA’s Inactive Ingredient Database or proposed for use in a dosage form or concentration different from those in the database can be con-

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Currently, IPEC is working to more clearly define what safety information and manufacturing data in an NDA is considered complete.

sidered *new*. Changes to specifications or manufacturing methods for an approved excipient must be included in NDAs or NDA supplements but do not indicate a *new* excipient. Minor changes to the chemical structure such as the substitution of one salt for another or the alteration of solubility characteristics are less clear and are left to the manufacturer to decide.

To add further uncertainty to the process, the format for submitting safety and manufacturing information for a new excipient in an NDA is not clearly defined. The Drug Master File (DMF) procedure is used most frequently for the confidential submission of this information in the United States and Canada but was not designed to detail safety and other information for a new chemical entity. No system exists in Europe or Japan for confidential submission of safety and manufacturing data. Therefore, even at the application stage, manufacturers and potential users of a new excipient face a “moving target” and cannot be sure whether the information will be considered complete. IPEC-Americas’ proposed Excipient Master File Guide, which is described in this article, could provide a measure of certainty to this process by specifying the data necessary for acceptance.

GRAS notification: Is it always greener?

GRAS substances have been exempted from the food additive definition in the Federal Food, Drug and Cosmetic Act. The preclearance requirements for food additives are not applied to GRAS substances.

As previously discussed, the only existing mechanism for evaluating the safety

of a new excipient is through a food additive petition or GRAS notification. Food additives must undergo specific safety tests depending on the level of overall population exposure to the substance. The results of the safety testing are then submitted to FDA along with manufacturing and other information, as part of a food additive petition, which is then approved or rejected. Elements of the petition are confidential, and the time required for approval can be many years.

Four requirements must be met for a substance to be determined to be GRAS:

- Qualified experts must conclude that there is a general recognition of safety for the substance.
- The experts must be qualified with sufficient scientific training and experience.
- The experts must base their opinion on scientific procedures or the experience with the substance’s use in foods before 1958.
- The expert’s decision must be based on a substance’s specific intended use or uses.

The scientific procedures used to determine GRAS status for a substance include human, animal, analytical, and other scientific studies, either published or unpublished. GRAS substances recognized by FDA are listed in 21 *CFR* 182, 184, and 186. FDA states that additional substances are independently determined to be GRAS and are not listed in 21 *CFR* regulations.

The data and information relied on to establish a substance as GRAS must be generally available and, by definition, are not confidential. The usual procedure to establish that scientific data and information are generally available is the publication of the information in a peer-reviewed journal.

Individuals were previously permitted to petition FDA to review the GRAS status of a substance and affirm the substance as GRAS. In 1997 FDA proposed to replace this GRAS affirmation petition process with a notification procedure by which any person may notify FDA of a determination that a substance is GRAS. FDA then evaluates whether the notice provides a sufficient basis for a GRAS determination. Within 90 days of receipt of the notice, FDA may respond to the notifier with a “no objection” letter. FDA does not approve GRAS notifications.

At present, recognition of an ingredient as GRAS is the only mechanism available for the pre-NDA evaluation of a new excipient. GRAS status is no guarantee that the material will be approved as an excipient in a drug product—such approval can only take place within the context of an NDA. However, GRAS status indicates a measure of FDA review to a pharmaceutical manufacturer and may eliminate some of the uncertainty associated with use of a new excipient.

NDAs for introducing new excipients: The cart before the horse?

The current evaluation mechanism for excipients involves an approval through an NDA for a specific drug product. However, this procedure presents several issues for excipient developers including the following:

- Excipients can only be approved for a particular function in a specific drug product, route of administration, and level of use. Therefore, drug manufacturers risk the possibility that FDA will not find a new excipient suitable for use in their product, thereby rejecting the application because of the excipient. Therefore, “non-novel” excipients are perceived as lower risk than new excipients.
- In addition to required information about the drug product such as efficacy and bioavailability, additional data are required for applications that involve new excipients such as the excipient’s manufacturing and safety data. The format for submitting that data is unclear.
- In FDA’s January 2003 draft Chemistry, Manufacturing, and Controls (CMC) Guidance, excipients are divided into four categories: compendial–non-novel, non-compendial–non-novel, novel, and excipients of human or animal origin (2). Applications for drugs containing excipients in all four categories require information about excipient specifications, analytical procedures, validation of analytical procedures, and validation of specifications. Noncompendial–non-novel excipients require additional unspecified manufacturing information—applicants are encouraged to contact FDA to determine the type of information required. Novel excipients require the same CMC information as what is required for a pharmaceutical active.

An excipient review procedure would allow manufacturers to develop their products independently of any specific drug product.

- Excipient manufacturers can submit this information confidentially to FDA using a Type IV DMF, but DMF guidance documents do not specify how this information should be presented. DMFs are not approved or denied separately, which creates uncertainty for excipient and pharmaceutical manufacturers regarding the acceptability of the documentation in the DMF.

FDA has attempted to deal with some of the ambiguity related to the safety evaluation of new excipients by publishing a draft guidance entitled "Nonclinical Studies for the Development of Pharmaceutical Excipients" (3). However, this guidance only applies to the evaluation of new excipients within an NDA but could be adapted to an independent evaluation process.

The current regulatory situation creates a "catch 22" for excipient manufacturers—pharmaceutical companies are unwilling to use a new excipient until it has been used in an FDA-approved drug product, but FDA will not approve a new excipient unless its use has been documented in an approved NDA. As a result, new excipients have become another orphan of the pharmaceutical industry with no one willing to bear the costs of development and commercialization. Thus, an independent evaluation procedure is needed for new excipients.

Excipient evaluation: A proposal

To reduce the perceived risks that are associated with developing and using new excipients, regulatory parameters must be defined. To clarify these parameters for excipient and pharmaceutical companies, the following two components are necessary:

- Regulatory authorities must recognize a scientific review procedure in which an excipient is evaluated independently of any drug product.
- Manufacturers must have a consistent format for submitting information so that they know what is required.

Scientific review. An excipient review procedure would allow excipient manufacturers to develop their products independently of any specific drug product. If such a procedure were instituted, excipient manufacturers would be free to market their new product with a variety of applications without significant concerns about the possible acceptability of the excipient to FDA for the intended applications.

Several models for an excipient evaluation procedure can be taken from other industries, where each model is currently being used successfully. Such models include

- FDA evaluation, similar to what is required for pharmaceutical drug products
- third-party review, as is currently available for medical device approval
- evaluation by an independent scientific review panel such as the Cosmetic Ingredient Review (CIR) for new cosmetic ingredients or the Flavor and Extract Manufacturers Association's (FEMA) GRAS process for new flavors and fragrances
- a self-affirmation process, similar to that for GRAS food ingredients.

In the FDA evaluation model, excipient companies would file a "new excipient application" with FDA, which would include many of the same components as an NDA. As with an NDA, FDA could hold meetings with the excipient manufacturer before the application is submitted. FDA would then evaluate the application and issue an approval or rejection. Of course, a final approval to market the excipient would depend on satisfactory data in the application for the new drug that contains the excipient, and therefore this evaluation would not result in a true approval because the excipient manufacturer could not sell it for any application. However, such a procedure would sharply reduce pharmaceutical manufacturer's concern about possible delays to their NDA if their use of the excipient is within the scope of the excipient marketing approval.

The advantage of this model includes the perception of a thorough review by a trusted source. The model would give the pharmaceutical companies the most confidence that their product containing the excipient is approvable. The disadvantages are the administrative burden that the process would add to FDA, the high cost, and the uncertain time period for FDA reviews.

The third-party review model is similar to a program that is currently in place for medical devices. The FDA Modernization Act of 1997 created a pilot Accredited Persons Program to expedite review of premarket notifications (PMNs) of medical devices. In this program, FDA has accredited third parties (such as consultants) who are authorized to conduct primary review of PMNs for specific categories of medical devices. The theory was that third-party reviewers would be able to resolve most of the potential issues with a PMN more quickly than FDA, and as a result, FDA review would be less costly and easier. In fact, the pilot program was expanded in 2001 and 2002, and PMNs that were reviewed by third parties were approved by FDA an average of 29% faster than those not reviewed (4).

This model could be slightly modified for manufacturers of new excipients in the way that the third-party review would be applied to the excipient alone whereas a formal FDA review would occur for the drug product. A review by an accredited third party could be perceived as an indication of final FDA approval, which could potentially ease pharmaceutical manufacturers' concerns about using new excipients in their formulations. In addition, a preliminary review process could help decrease FDA's workload.

The independent scientific review model involves an independent group of experts who would meet periodically to evaluate data packages for new excipients. Such a group could be convened by IPEC or USP, and the results of their evaluations could be published in a format similar to the CIR's conclusions (5). In the cosmetic area, FDA considers CIR's conclusions when evaluating the safety of cosmetic ingredients but is not required to accept their conclusions (5). Advantages of independent scientific review, such as CIR, include a good indication (but not a guarantee)

of FDA acceptance of an NDA and a more predictable time frame than direct FDA approval. Disadvantages include somewhat less confidence of FDA approval in specific formulations.

Another example of the independent scientific review model is one that was developed by FEMA for ingredients of new flavors intended for food use. In the FEMA GRAS process, a panel of experts from outside the industry review safety data to determine whether each flavor ingredient is GRAS using the specified conditions of intended use. If specific safety criteria is fulfilled, the ingredient is declared FEMA GRAS. This process is similar to the CIR process in that the panel's conclusions are published and provided to FDA.

The self-affirmation model includes components that are similar to the current GRAS program. For example, a manufacturer might obtain the opinion of experts and provide that opinion to potential customers in the absence of formal FDA approval. For this process to be useful, the experts should be recognized within the industry, and the process should be acknowledged by FDA as providing potentially useful information. However, unlike the current food GRAS procedure, the data used in this process must remain confidential. The advantage of this system is flexibility and the timing, which is entirely within the manufacturer's control. A major disadvantage is that it gives manufacturers the lowest assurance of final FDA acceptance in their formulations.

Excipient DMF. To address uncertainties related to data submission in support of an NDA, IPEC has developed and submitted to global regulatory authorities a proposed Excipient Master File Guide. In this proposal, formal and data requirements for the master file would be standardized, coordinated, and harmonized with the electronic ICH common technical document (CTD) for presenting CMC and safety information. Details of this procedure have been described in a previous issue of *Pharmaceutical Technology* (6).

Similar to a DMF, an excipient master file would not be required by law or FDA regulations, but would be submitted solely at the discretion of the holder. The file would not be approved or disapproved, and FDA would maintain the master file

as a confidential document. Excipient DMFs would be used to support an investigational new drug application (IND), NDA, abbreviated new drug application (ANDA), biological license application (BLA), veterinary drug application, another DMF, or an export application. The use of the excipient master file would be restricted to the following types of excipients:

- existing excipients that are not fully described by official monographs (e.g., mixtures of excipients, coprocessed excipients, etc.)
- new (novel) excipients
- new route of application or administration for existing excipients
- biopharmaceutical excipients.

In the IPEC proposal, the excipient master file would be in the CTD format and would include

- a description and characterization of the excipient
- facilities, manufacturing, and process controls descriptions
- a batch analysis and certificate of analysis
- specifications
- a nonclinical safety assessment.

IPEC-Americas' Excipient Master File Guide incorporates elements from several regulatory guidance documents, including FDA's "Nonclinical Studies for the Development of Pharmaceutical Excipients," and ICH's "M4Q: The CTD—Quality" and "M4S: The CTD—Safety."

A major advantage of the master file is that excipient manufacturers and users would know exactly what information was needed for submission, which would eliminate some of the uncertainty under the current system. In addition, the process of submitting information globally would be accelerated using this system because a confidentiality agreement will not be needed between the DMF holder and the drug application sponsor. The initial focus of the IPEC guide is to assist in the improvement of the DMF system in the United States. However, the hope is to eventually develop a global guide. In the United States, a Type IV DMF is used for submitting excipient information to FDA.

Conclusions

A system for the independent review of excipients and the submission of required

data to regulatory authorities is needed to encourage the development of new excipients. Several independent review models are used in other industries such as food, cosmetics, and medical devices and could be adapted to the area of excipients. IPEC is currently consulting with its members to determine which system might be most useful. IPEC will then present the organization's conclusions to FDA to determine whether it might consider the results of such a review.

In addition, IPEC-Americas, along with its counterparts in Europe and Japan, intends to work with global regulatory authorities to gain acceptance of an excipient master file procedure to assist excipient manufacturers with data submission. IPEC has proposed specific data requirements in its Excipient Master File Guide. A standardized master file format specific to excipients would eliminate the moving target faced by both excipient manufacturers and their pharmaceutical customers.

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