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Regulatory Update: The IPEC Novel Excipient Safety Evaluation Procedure

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The lack of a pathway for regulatory approval of novel excipients outside a new drug application has stifled innovation in drug development.

The authors, representing the International Pharmaceutical Excipients Council, propose a new evaluation procedure, including tiered toxicology testing that may change the way pharmaceutical and biopharmaceutical manufacturers look at drug-product development.

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The US Food and Drug Administration has approved a substantially lower number of drug formulations containing new molecular entities (NMEs) in the past decade (1). In 2008, the agency approved formulations containing 21 NMEs and four biologics, slightly higher than the 2007 total of 17 NMEs and two biologics. The growth between 2007 and 2008, however, was not enough to counter the marked downward spiral of drug approvals during the past 10 years (1). Behind the trend may be tightening safety standards, the complexity of clinical trials that have escalated drug-development costs, and even perhaps a shift in emphasis as pharmaceutical companies move away from truly innovative solutions toward more complex therapeutic profiles.

An additional barrier to the development of new drug formulations is that, in some cases, active pharmaceutical ingredients (APIs) that show promising activity in animals or *in vitro* biologic systems fail to show sufficient efficacy in human clinical trials. In some cases, this discrepancy may be due to a lack of bioavailability and desired effect at the target site in the human body—properties potentially linked to the specifics of the formulation.

The choice of excipients also can be a critical factor for developing clinically efficacious drug formulations. The current regulatory environment both inside and outside the United States, however, strongly discourages development of new excipients, limiting the choices to those already approved. The International Pharmaceutical Excipients Council of the Americas (IPEC–Americas) has proposed specific regulatory changes to encourage new excipient development which, if adopted, could

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expand options for API formulation, potentially removing this formidable barrier to drug development. IPEC–Americas also developed an independent excipient review procedure, the IPEC Novel Excipient Safety Evaluation Procedure, which can serve as a temporary solution to this issue until the council’s proposals are implemented. These efforts resulted in the evaluation of at least one novel excipient, Solutol HS 15 [Polyoxyl (Macrogol) 15 hydroxystearate manufactured by BASF, Ludwigshafen, Germany). The development of procedures for independent safety evaluation and its application to Solutol HS 15 are described in subsequent sections of this article.

There is considerable activity in the development of new and innovative excipients (2, 3), including excipients for orally disintegrating tablets and controlled-release formulations. In the future, the application of nanotechnology may be evaluated for developing novel excipients for new therapeutic solutions. In many cases, these excipients will never be included in drug products under development because the regulatory risks under the current system are simply too great.

In the long term, new paradigms are needed to evaluate excipient safety. The FDA guidance on the safety evaluation of excipients details safety tests generally required to establish safety of a novel excipient, which are strikingly similar to those required for a new drug (4). However, unlike drugs, excipients are designed to be pharmacologically inactive and these tests may be excessive for safety evaluation, thereby representing a potential barrier to innovative development of new excipients.

Current regulatory status of new excipients

Under the current paradigm, even though excipient innovators are able to adapt to new procedures and are willing to invest in development and safety-evaluation costs, novel excipients are not finding their way into drug products. Understandably, drug-product manufacturers are risk-averse because of the large investments required for drug development. Despite these challenges, the expanding FDA Inactive Ingredient Database (IID) suggests that the demand for new excipients is strong. The IID lists excipients used in approved drug products, their route of administration, and their maximum dosage (i.e., maximum potency per dosage unit). A regulatory system with a strong, predictable excipient safety and efficacy evaluation could potentially lead to an explosion of new choices for drug formulators.

Under current drug approval processes, novel excipients are not independently evaluated; they are only reviewed in the context of the first drug application containing the excipient. There is no regulatory approval process specifically for a new excipient as a unique molecule. Globally, the International Conference on Harmonization (ICH) does not have specific excipient safety evaluation guidelines, but FDA guidance on excipient safety evaluation cites several ICH safety-testing guidelines (e.g., ICH S1A, S2B, S3A, S5A, S7A and M3) as reference materials for the conduct of safety tests (4).

According to FDA and ICH definitions, an excipient is con-

Table I: Estimated costs of a typical toxicology program.

Toxicology study	Estimated cost (\$)
90-day repeat dose toxicity (two species)*	250,000-400,000
<i>Developmental and reproductive toxicity</i>	
Fertility/early prenatal development (Seg. I)	150,000
Developmental toxicity (Seg. II)	125,000
Postnatal development (Seg. III)	175,000
<i>Genotoxicity</i>	
Bacterial reverse mutation	8000
<i>In vitro</i> chromosomal aberration	28,000
<i>In vivo</i> micronucleus	25,000
<i>Safety pharmacology</i>	
Central nervous system	20,000
Respiratory	25,000
Cardiovascular	60,000
Carcinogenicity (two species)*	900,000-1,500,000
Absorption, distribution, metabolism, excretion (ADME)	250,000
Costs reflect 2009 estimates.	
*For repeat dose toxicity studies, the species would be rodent and non-rodent; for carcinogenicity studies, the species would be rat and mouse.	

sidered “novel” if it is used for the first time in a human drug product. Although FDA maintains the IID, none of the US nor ICH standards distinguish between new chemical entities and minor modifications of approved excipients, coprocessed mixtures of existing excipients, approved excipients proposed for a new route of administration, or excipients approved for use in foods or cosmetics. Some of these excipients may not require the full battery of tests listed in the FDA guidance on excipient safety evaluation (4). In these cases, excipient and pharmaceutical manufacturers must predict what the reviewing agency will require upon review of the drug application. If the manufacturer is wrong, the consequence could be significant delays in drug approvals or rejection of the drug application. Most drug manufacturers are wary of this process and therefore rely on excipients already used in approved drug products for their formulation needs.

In 2007, the IPEC–Americas Safety Committee proposed and developed the IPEC Novel Excipient Safety Evaluation Procedure, which is an independent excipient review procedure. This process was anticipated to reduce the cost and uncertainty related to the use of novel excipients in pharmaceutical formulations, thereby encouraging their use in drug-development programs and providing a needed boost to drug formulation innovation.

The Aclairo Pharmaceutical Development Group (Aclairo PDG, Vienna, VA) manages the Novel Excipient Evaluation Committee (NEEC), an independent expert group of IPEC charged with conducting the safety evaluations of new excipients. The committee has successfully evaluated one excipient, Solutol HS 15, and is in the process of reviewing others. Two

Table II: Estimated costs of a proposed tiered-testing toxicology program.

Toxicology study	Estimated cost (\$)
Tier 1	
<i>In vitro</i> cytotoxicity	1000
<i>In vitro</i> membrane penetration	1000*
Genotoxicity	
Bacterial reverse mutation	8000
<i>In vitro</i> chromosomal aberration	28,000
<i>In vitro</i> metabolism	50,000
<i>In vitro</i> immunotoxicity	25,000–50,000
QSAR	1000
Tier 2	
90-day toxicity (OECD 422, rat, with micronucleus)	300,000
90-day toxicity (dog)	350,000
Tier 3	
Developmental and reproductive toxicity	See Table I
Safety pharmacology	See Table I
Carcinogenicity	See Table I
*Cost is dependent on tissue system (e.g., dermal, gastrointestinal).	
QSAR is quantitative structure activity relationship. OECD is Organization for Economic Cooperation and Development.	

authors of this paper (R. Osterberg and W. Brock) serve on this expert committee.

The IPEC–Americas procedure

History. The development of a regulatory strategy for novel excipient review has been an IPEC–Americas priority since the organization’s inception in the early 1990s. At that time, the IPEC–Americas Safety Committee held a series of meetings that culminated in a publication of recommendations for excipient-safety testing based on route of administration (5). In 2002, the chairman and deputy chairman of FDA’s Center for Drug Evaluation and Research (CDER) Inactive Ingredients Subcommittee published a proposal for excipient safety review largely based on the IPEC recommendations (6). The agency proposal was finalized in 2005. The ICH M3 document on nonclinical safety studies for conducting human clinical trials is also relevant in this context (7).

In August 2005, IPEC–Americas presented a proposal for an independent excipient evaluation procedure to FDA staff. FDA agreed to review the first excipient-safety evaluation expert committee submission for consistency with FDA procedures. Over the next two years, the IPEC Safety Committee convened the expert committee, developed procedures, and solicited the first submission. In September 2007, the expert committee reviewed the safety package for Solutol HS 15 and submitted their conclusions to the sponsor. In May 2008, in a letter to IPEC, FDA

concluded that, “The issues considered by the expert committee reviewers in the weight-of-evidence determination on the safety of Solutol HS 15 are the same as would be considered by a reviewing division,” indicating that the IPEC process provides a reasonable proxy for FDA review.

Review procedure. NEEC’s primary function is to evaluate compliance of excipient data with the FDA guidance on safety evaluation and to make recommendations to the excipient manufacturer if data gaps are noted in the excipient dossier. The expert committee acts independently of the IPEC–Americas Safety Committee and its members must have confidentiality agreements in place. NEEC is comprised of three experts in general toxicology and, ideally, members have experience in industrial, academic, or regulatory toxicology, including experience in toxicology laboratories. Committee members may rotate off the committee every two to three years to provide new expertise to the process. If the committee decides that an expert in one facet of toxicology is needed to help in decision-making, a request to the excipient manufacturer will be made for permission to include the expert in the deliberations. This expert must also sign a confidentiality agreement. Aclairo PDG administers this review procedure.

An excipient safety dossier in common technical document (CTD) format (to facilitate subsequent FDA review) is submitted to Aclairo PDG who sends it to the expert committee chairperson, who in turn distributes it to other committee members. Review times will depend upon the quantity of the information within or absent from the dossiers but are anticipated to take one to three months; in most cases, costs will not exceed a total of 50 hours of review plus administrative overhead. The chairperson or a designee collates the comments of the committee members and writes a draft report that will be sent to each member for concurrence or further discussion. Once agreement is reached, the final draft is sent to the excipient sponsor for review and comment. If the expert committee cannot reach agreement on one or more points in the final draft, the sponsor is told about the disagreements and the reasons for them. The sponsor may discuss the final draft with the expert committee, request clarifications or explanations and when satisfied, the final report is signed by the chairperson and sent to the sponsor who is the sole owner of the committee report. The committee report will contain at a minimum:

1. A discussion of chemical and toxicological data and human safety concerns based upon intended use of the excipient
2. Opinions on conformance with data needs according to the FDA guidance on safety evaluation for excipients
3. Identification of any data gaps
4. Points of reviewer disagreement if not resolved with the reasons identified in the final draft.

The expert committee’s review of Solutol HS 15

BASF novel excipient, Solutol HS 15, a non-ionic solubilizer, was developed to fulfill an unmet need for a safe and effective excipient for parenteral and solid oral dose formulations containing poorly soluble APIs. Chemically, Solutol HS 15 is

composed of polyglycol mono- and di-esters of 12-hydroxystearic acid and contains approximately 30% polyethylene glycol. Solutol HS 15 is listed as Macrogol 15 hydroxystearate in the *European Pharmacopoeia (PhEur)*. The excipient has been used in approved drugs in some countries, including Canada and Argentina. Even though the Solutol HS 15 drug-master file (DMF) was filed with FDA in January 1992 (DMF #9501), it has not yet been used in FDA-approved drugs because of its novel excipient nature and absence of FDA-review status.

In 2007, IPEC–Americas Safety Committee Chair Jay Goldring, recognizing the urgent industry need for an excipient that meets the requirements in formulations containing poorly soluble APIs, selected Solutol HS 15 solubilizer as the subject for the first NEEC review. The expert committee's report would then be reviewed by FDA for consistency with its own review process.

As defined in the IPEC–Americas procedure in the previous section of this article, BASF entered into an agreement with Aclairo PDG to develop an independent safety evaluation of Solutol HS 15. To accomplish this, BASF prepared a package of information containing safety and chemistry information. The package included the following items:

- Technical information containing a summary of chemistry, manufacturing, and controls (CMC) information
- BASF's safety expert report on Solutol HS 15
- Reports of all acute, subchronic, reproductive, and genotoxicity studies conducted by BASF for Solutol HS 15 under different routes of administration
- Safety evaluation assessment report for Solutol HS 15 conducted by the European Medicines Agency
- Safety expert report of a related BASF solubilizer excipient Cremophor (Polyoxyl 35 Castor Oil: *NF* Polyoxyl 40 Hydrogenated Castor Oil *NF*)
- FDA IID information for use of Cremophor in 15 FDA-approved drugs
- List of other excipients with related chemistry derived from the FDA IID.

The package also included a cover letter requesting that Aclairo PDG evaluate the information submitted and provide an independent safety evaluation for Solutol HS 15.

The independent safety evaluation procedures were coordinated and led by Dr. Osterberg. Aclairo conducted an independent safety assessment using two other distinguished toxicologists. The six-month evaluation implemented all the steps of the review process described above. At the conclusion of the process, the expert committee issued an independent safety evaluation of Solutol HS 15 to BASF.

Following this process, BASF submitted a package to the IPEC–Americas Safety Committee Chair. This package included a cover letter from BASF that requested review and consideration for submission to FDA under the IPEC Novel Excipient Safety Evaluation Procedure, a safety expert report from Aclairo PDG and all the documents submitted to Aclairo PDG outlined in the previous paragraphs in this section. The BASF submission was forwarded to FDA by the IPEC–Americas Safety Committee. FDA provided its

review letter of Solutol HS 15 to the committee which then informed BASF of the agency's findings.

After receiving feedback, BASF approached the United States Pharmacopoeia (USP) for consideration of an official monograph for Solutol HS 15 on the following grounds: FDA review of this excipient, monograph status in *PhEur*, and use in approved drugs in some countries outside the US. USP informed BASF that, as required by their procedure for development of official monographs, they consulted the compendial group at FDA. USP then requested that BASF submit materials for monograph development. Efforts by BASF and USP led to the publication of Polyoxyl 15 Hydroxystearate (Solutol HS) *NF* monograph in the January/February 2009 issue of the *USP Pharmacopeial Forum*.

Excipient safety evaluation: a new paradigm

Excipients received a great deal of notoriety in the early 1930s. At that time, a chemist at the Massengill Company used diethylene glycol (DEG) as a sweetening agent for elixir of sulfanilamide as the "teaspoon of sugar to help the medicine go down" because the elixir was somewhat sour for use in children. A principle in toxicology introduced by Paracelsus about 500 years ago was "*Omnia venenum sunt, nec sine veneno quicquam existit; dosis sola facit ut venenum non sit,*" which, literally translated, states that "all substances are poisons; there is none which is not a poison." This concept continues to be a basic tenet in the field of toxicology. The Massengill Company at the time had not completely investigated the potential toxicity of DEG. Hence, many children fell ill to the kidney toxicity associated with this compound, and many of those children unfortunately died (8).

Based on this tragic incident, the 1938 amendment to the Food, Drug, and Cosmetic Act was promulgated, essentially requiring that the safety of a drug be demonstrated before marketing. In spite of this regulation in the US and the incident that occurred in the 1930s, additional incidents of DEG contamination occurred internationally in the 1980s and 1990s. An important consideration with regard to these incidents, however, is that the safety of the drug substance was not in question, but rather the safety of the excipient had not been demonstrated before use in the drug-product formulation.

Indeed, the regulatory environment for the approval of excipients has not kept pace with the innovations observed in the pharmaceutical industry. Except as associated with the submission of an NDA for a new pharmaceutical that contains an innovative excipient, there is no regulatory process for the independent approval of the excipient.

During the past two decades, regulatory allowance of an excipient occurred only through the use of the material in a drug-product formulation. Hence, with approval of the drug product came acceptance of the excipient (excipients are not approved but their use is allowed). That excipient could be used subsequently in other drug products up to the concentration and duration used in the previously approved drug formulation. Moreover, the excipient could be used in a new drug product for a different route of administration only if toxicology

data generated *via* that route was accepted by FDA. P. Baldrick proposed that a guidance was urgently needed for excipients, and further suggested that this would be a useful topic for ICH consideration (9). This suggestion was not a new concept as several years before, Steinberg et al. proposed a testing scheme for the evaluation of new excipients and that testing scheme was ostensibly similar to that used in the evaluation of a new drug substance (5). In that paper, the authors described a nonclinical program for excipients based on the oral route of administration because most drugs are approved for oral use.

Baldrick's paper was followed by several publications, each further indicating the need for a regulatory process for excipients as well as a proposal for how to manage new excipients. In 2003, G. Pifferi and P. Restani suggested that new excipients be evaluated much in the same way as food additives (i.e., by the International Toxicological Committees such as the Joint Expert Committee on Food Additives, a committee of the World Health Organization) (10). The authors demonstrated that there are a large number of substances that can be used as excipients with a very diverse chemical profile, sources, technological functions, and so forth. The Pifferi/Restani paper of 2003 followed a 1999 paper describing the need for standards of characterization and quality review, just one more aspect needed for a regulatory framework for excipients (11).

Also in 2003, at the American College of Toxicology annual meeting, a symposium on issues associated with food and excipient safety was presented (12). M. Steinberg and I. Silverstein reviewed several concepts for addressing the regulatory status of new excipients but clearly noted that there was no regulatory process in the US compared with what had been established in Europe and Japan (13). Osterberg and N.A. See subsequently described the testing paradigm of what had been recently published draft guidance from FDA on excipient testing. In that guidance, which was subsequently approved (14), the various toxicity studies needed for a new excipient are outlined.

Overall, the guidance is similar to what Steinberg et al. had proposed several years earlier in 1996 (5), although the provision for safety pharmacology studies was included in the FDA guidance. Regardless, a provision for a stand-alone regulatory process remained elusive. As described above, IPEC–Americas established an expert working group to review the safety of new excipients based on testing, and proposed to FDA that the studies represent good science and excipients should be allowed in drug products without going through a regulatory process in conjunction with a drug approval. Because of the absence of a regulatory process, the innovation of new excipients has been restricted. Moreover, because of the costs associated with a standard toxicity program for a new excipient, innovation and development have been limited (see Table I).

The IPEC program described is a typical toxicology program with costs based on 2009 pricing of studies within the contract research organization (CRO) industry. Moreover, the costs reflect a basic study design and do not include toxicokinetic assessment which could add about 5–10% of the

total cost. In addition, to initiate the 90-day studies, shorter-term repeat-dose studies would be needed to assist in setting dose levels. The added costs for these studies could approach \$200,000. Finally, the costs associated with this program do not include discovery, development, and manufacturing costs for the new excipient.

The undertaking of a toxicology program represents a risk to a business, but in the current regulatory environment, such a program is needed. There remains an option to the excipient development process that does not require such an outlay of resources early in the development phase. Lessons learned from the drug discovery and development process may be helpful in toxicological screening of excipients for use with active pharmaceutical substances.

Toxicology program considerations. In the developmental toxicology program, *in vitro* assays are used to screen for potential toxicity before undertaking more expensive toxicity tests. In this process, a compound that causes an undesirable toxicity can be eliminated from consideration. This “discovery” program leads to less cost and allows for a more rapid screening of multiple compounds to select those that represent potential utility as an excipient. In addition, the discovery program can be developed into different tiers of testing (i.e., as the compound is developed, additional testing is undertaken to further determine the potential safety of the compound).

In the first tier, a compound is subjected to different *in vitro* assays to determine the potential genotoxicity, cytotoxicity, and metabolism and the ability of the compound to be absorbed across biological membranes. At the outset, however, it is recommended that a quantitative structure-activity relationship (QSAR) model be developed. A QSAR model enables the prediction of various toxicities based on structural similarity to existing chemicals. Hence, compounds can be easily limited from consideration if structural alerts for certain endpoints are revealed (e.g., carcinogenicity). There are several QSAR models that have been developed over the years, each with its own advantages and disadvantages. The model overall is useful for predicting potential toxicity for potentially allowing the use of short-term bridging studies that could be used to determine the toxicity of the new excipient compared with an excipient that has a more robust database.

Following QSAR, it is recommended that the compound be subjected to *in vitro* genotoxicity and cytotoxicity assays. These studies are comparably inexpensive to the longer-term *in vivo* toxicity studies. A cytotoxicity assay is valuable to determine the potential for the compound to cause cell disruption, and such a study is particularly useful if the compound would be administered intravenously. In addition to these *in vitro* studies, an *in vitro* metabolism study can be done as a screening assay to determine the extent of metabolism and whether potential reactive metabolites would be formed. Finally, membrane penetration studies would be conducted. Ideally, the excipient would not be absorbed across biological membranes, but may enhance the penetration of API. Immunotoxicity studies would be done only if there is an important structural alert or

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the compound is from a class of excipients that may be known to induce an immunotoxic effect.

If the data developed in this first phase of the program reveals limited or no concern for toxicity, then the compound is tested in repeat-dose toxicity studies with the idea that these additional tests will be compliant with FDA guidance for excipient testing. In the second phase, data could be developed that would allow the sponsor to “bridge” to existing, structurally related compounds. In this case, for example, a repeat-dose toxicity study would be conducted with a new pegylated substance based on the extensive toxicity data that exists for PEG-400. In this manner, the sponsor would not necessarily need to conduct studies if the data demonstrate a similar toxicity profile. In addition, in the repeat-dose study, groups of animals (rats) could be included to examine for potential reproductive and developmental toxicity following the Organization for Economic Cooperation and Development’s Guideline 422. Finally, as part of the subchronic study, a micronucleus assay can be incorporated rather than conducting a separate study.

One issue that arises as part of this second phase is conducting the studies in a rodent and non-rodent species. Indeed, it would be recommended that a separate study in, for example, the dog, be conducted. If long-term toxicity studies in the non-rodent species have not been conducted with the structural analog, then the sponsor will need to conduct at least a 90-day study.

Based on the results of the second phase of the program, the sponsor would then conduct studies in a third and final phase of the program. In this final stage of excipient development, many of the studies outlined in FDA’s excipient testing guidance would be conducted (e.g., safety pharmacology). More thorough metabolism studies also would be conducted in this phase. These studies can be complex depending on the compound. For polymeric materials, these studies may not be possible although a consideration for undertaking metabolism studies with the monomer or oligomers of the polymer would provide useful data on absorption and distribution. Based on the outcome of testing in phase two, definitive developmental and reproductive toxicity studies may be warranted. For developmental studies, a second species (e.g., rabbit) would be necessary.

Undertaking a toxicology program in accordance with FDA’s excipient guidance leads to significant costs (see Table I) compared with the costs associated with alternative paradigm (see Table II). Because of the absence of a regulatory process,

the timing to gain FDA acceptance can be very prolonged, particularly if the sponsor of a drug product uses a new excipient in the formulation and in nonclinical testing of the drug product. Although the process described here is no panacea for approval, this tiered process will permit the excipient sponsor to plan a program in conjunction with the drug product sponsor and thereby avoid toxicological surprises.

Conclusion

The program outlined herein considers typical excipients. With the advent of biotechnology derived pharmaceuticals, new excipients for biotechnology drugs becomes a program development issue. How these new excipients would be examined in toxicology programs is yet to be determined. Moreover, with increasing emphasis on nanotechnology, these materials potentially represent new processes for drug delivery. Safety assessment of nanotechnology products is in its infancy, and how these materials will be evaluated remains to be determined as well. Finally, the outline of this tiered approach has not been a consideration by FDA, although a tiered-testing rationale is part of several regulatory guidance documents (e.g., metabolite testing, ICH Q3b impurity qualification). Hence, how the regulatory agency and, more importantly, API sponsors, will accept such an approach remains to be seen. Regardless, excipient sponsors should consider such an approach because it will limit cost and could advance a new excipient in a timelier manner.

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