Solutol HS15 as a Novel Excipient

The authors present an update to the Wyeth/BASF experience with the IPEC Novel Excipient Safety Evaluation Procedure.

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Historically, the development of novel excipients has been hampered by the global regulatory review system, including but not limited to the United States. A novel excipient is not reviewed by the US Food and Drug Administration until it is formulated by a pharmaceutical manufacturer in a finished drug product and submitted to the agency as part of a new drug or abbreviated new drug application (NDA, ANDA). Because the approval of a novel excipient for human use incurs an additional safety risk, it is not surprising that pharmaceutical drug manufacturers have been reluctant to use novel excipients until they are reviewed by FDA and listed in the FDA inactive ingredient database (IIG) (1). As a consequence, the acceptance and use of novel excipients for drug formulations has been a significant challenge within the industry.

Only a few drug manufacturers have formulated drug products containing novel excipients in recent years. Some examples of brand drugs include: GlaxoSmithKline's (London) use of Vit E TPGS (d-α-Tocopheryl Polyethylene Glycol 1000 Succinate) in Agenerase (Amprenavir); Pfizer's (New York) use of Sulfobutyl Ether β-Cyclodextrin in VFEND (Voriconazole); Bristol Myers Squibb's (BMS, New York) use of Cremophor EL (Polyoxyl 35 Castor oil *NF*) in Taxol (paclitaxel); and Abbott's (Chicago) Norvir (Ritonavir) and Kaletra (Lopinavir; Ritonavir)(2–4).

In May 2005, FDA published a guidance document to help clarify the safety data requirements, including nonclinical studies, for novel excipients (5). These noncritical studies mirror those required for preclinical evaluation of new molecular entities (NMES). Although the definitions of these studies have significantly helped in developing novel excipient innovation and regulatory strategies, they have proven to require a significant financial investment for excipient manufacturers. As a result, the guidance has failed to pave the way for innovation and may have further discouraged excipient manufacturers interested in developing novel excipients.

The situation is similar in Europe. A draft note for guidance on excipients was issued in 2003 by the European Medicine Agency's (EMA) Committee for Proprietary Medicinal Products (6). Similar to the FDA guidance, the European note also contained a long list of required preclinical studies for novel excipients. Furthermore, the International Conference on Harmonization's (ICH) common technical document (CTD) stipulates for noncompendial excipients (i.e., novel excipients) a complete workup of chemistry, toxicology, specification, and analytical methods. Validation of these methods must begin with the clinical trial application.

It is not surprising, therefore, that pharmaceutical drug manufacturers have been reluctant to introduce a noncompendial excipient in their regulatory applications. Yet, when adequate safety information is provided to the authorities, it is the experience of the authors that FDA has accepted novel excipients through their regulatory approvals of products that contain the novel excipients.

The development of combination excipients, which comprise several approved excipients and encompass a multitude of functionalities, also has gained popularity among excipient manufacturers based on positive experiences with regulatory approvals. Examples of such excipients include: ProSolv (JRS Pharma, Germany) containing silicified microcrystalline cellulose; Ludiflash (BASF) containing mannitol, crospovidone and polyvinyl acetate; Ludipress (BASF) containing lactose, povidone, and crospovidone; and polyvinyl acetate and povidone-based Kollicoat SR 30D and Kollidon SR (BASF).

The irony of the current regulatory environment is that new excipients are a crucial means to advancing new therapies. NMEs may need novel excipients. For example, compound-enabling excipients are varied (e.g., an antioxidant for an oxygen-labile compound or lactose as a carrier for dry-powder inhalation for lung delivery). Most notable among compound enabling excipients is a class of solubilizers that enable the oral delivery of insoluble compounds for improved oral bioavailability. They also can help with intravenous delivery of insoluble compounds in solution or dispersion formulations using excipients that are safe for injection into the bloodstream (7). Such excipients are often used in the preclinical setting to deliver a drug into animals at a dose 10 to 100 times that of a therapeutic dose in order to assess a compound's safety and delineate its target organ toxicity (8, 9). However, if the preclinical evaluation is successful, questions arise regarding the continued use of such a novel excipient in human clinical trials because of the perceived regulatory barriers.

In some cases, even when a regulatory authority allows an investigational new drug (IND) to contain a novel excipient during early Phase I or Phase II clinical trials, questions remain about the excipient's use in Phase III trials because of the anticipated high cost and risk in NDA filing. It is this experience of the authors that encouraged the exploration of an alternative pathway offered by the International Pharmaceutical Excipient Council (IPEC), a trade association of excipient manufacturers and users. IPEC developed a novel excipient safety evaluation procedure in 2007 to allow for a more informed decision on the part of regulators regarding a novel excipient's safety profile.

History of Solutol HS15

In the 1990s, the use of then novel excipients, polyoxyl 35 castor oil *NF* (Cremophor

EL, BASF) and polyoxyl 40 hydrogenated castor oil *NF* (Cremophor RH 40, BASF) for solubilization and consequent bioavailability of poorly soluble active pharmaceutical ingredients (APIs) for improved efficacy, enabled drug development for cancer (e.g., BMS' Taxol [paclitaxel]) and AIDS (e.g., Abbott's Norvir, Kaletra). However, Cremophor produced slightly elevated histamine levels in dog studies. To help overcome this challenge, a new product was developed in 1992 whereby castor oil was replaced with 12- hydroxystearic acid and reacted with polyethylene glycol 30 resulting in a new excipient called Solutol HS15 (polyglycol mono- and di-esters of 12-hydroxystearic acid with about 30% polyethylene glycol, BASF). Solutol HS15 has been shown to be safe in various animal toxicity models with reduced histamine levels compared with Cremophor. Solutol HS15 has been approved in Canada and Argentina in marketed injectable-drug products. In the US, a drug master file for Solutol HS15 was filed with FDA in January 1992. However, it has not been used in any commercial product and thus is not listed in the FDA IIG. In the US, Solutol HS15 is therefore still classified as a novel excipient.

Solutol as a compound-enabling excipient. The drug-development group at Wyeth, now part of Pfizer, found Solutol HS15 to be an excellent solubilizerfor liquid-filled capsules for a series of NMEs with a new mechanism of action (10). Wyeth also found that Solutol HS15, in combination with other solubilizers, provided excellent solubility for their poorly soluble NME candidates with water solubility below high-performance liquid chromatography (HPLC) detection limits of 20 ng/mL. This developmental drug by itself is not orally bioavailable and the oral potency was affected using solution formulation containing phospholipids. Preclinical studies utilize a phospholipids formulation, which affords a slower absorption profile with delayed Cmax (maximum plasma concentration). A great bioavailability improvement with a fast absorption rate was seen with the formulation containing Solutol HS15 compared with other formulations during formulation screening studies in animals. Wyeth used the Solutol HS15 formulation in its first-in-human formulation and subsequently completed two Phase I clinical studies on one API—an ascending single dose study (SAD) conducted in healthy subjects and an ascending multiple dose study (MAD) conducted in healthy subjects. In a Phase II proof-of-concept (POC) study with 6 weeks dosing, an endoscopic examination (7 days gastrointestinal safety study) was performed after 5 capsules of the placebo and active were dosed. No adverse events were reported in the 12 patients dosed. Overall, the adverse-event profile showed that a single oral dose of up to 10 capsules of the Wyeth formulation containing 150 mg Solutol HS15/Capsule is generally safe and well tolerated.

Safety evaluation

IPEC–Americas has explored for years better ways to enable novel excipients to enter the market. After extensive internal discussions with the manufacturers and user members of IPEC–Americas, and with FDA, IPEC–Americas presented a proposal in August 2005 for an independent evaluation of novel excipients and FDA review following an independent expert evaluation. FDA agreed to review the first excipient-safety evaluation performed by a panel of experts for consistency with FDA safety-evaluation procedures. Between 2005 and 2007, the IPEC Safety Committee convened a panel which developed the IPEC Novel Excipient Safety Evaluation Procedure, as previously mentioned, and solicited the first submission for a novel excipient for the expert evaluation and review by FDA (10).

FDA review

Solutol HS15 is presented as the first case study to illustrate an excipient supplier (BASF)/user (Wyeth) collaborative effort to facilitate a safety review by FDA under the IPEC safety evaluation program. In 2007, the IPEC–Americas Safety Committee Chair approached Wyeth R&D who then contracted BASF to consider Solutol HS15 solubilizer for review by FDA.

With promising results from Phase I and II human clinical trials of a solid oral dosage formulation containing Solutol HS15 described above, Wyeth was considering ways to obtain an FDA safety review of of Solutol HS15 before embarking on a large-scale Phase III human clinical trial. In that context, Wyeth decided to provide Phase I and II Solutol HS15 related information to the agency as a part of the IPEC safety evaluation program. With Wyeth's encouragement, BASF's management volunteered to submit Solutol HS15 to the IPEC Novel Excipient Safety Evaluation Procedure.

As defined in the IPEC Novel Excipient Safety Evaluation Procedure, BASF entered into a confidentiality agreement with Aclairo Pharmaceutical Development Group (PDG) to develop an independent expert safety evaluation of Solutol HS15, led by Robert Osterberg, PhD, a distinguished scientist in pharmacology/toxicology. BASF submitted a package of information about Solutol HS15 to PDG containing the following safety and chemistry information: technical data containing a summary of chemistry, manufacturing, and controls (CMC); the company's safety expert report on Solutol HS15; reports of all acute, subchronic, reproductive, and genotoxicity studies; a safety evaluation assessment report that had been conducted by EMA; a safety expert report of a related BASF solubilizer excipient (Cremophor); the FDA IIG information regarding use of Cremophor in 15 FDA-approved drugs; and a list of other excipients with related chemistries derived from the FDA IIG. The package also included a cover letter requesting that PDG evaluate the information submitted and provide an independent safety evaluation for Solutol HS15 to BASF.

Under a separate confidentiality agreement with PDG, Wyeth submitted Phase I and Phase II human clinical trial solid oral-drug information relevant to Solutol HS15. PDG conducted an independent safety assessment using three distinguished toxicologists and issued its evaluation.

BASF then submitted a package to the IPEC–Americas Safety Committee Chair including: a cover letter requesting review and consideration for submission to FDA under the IPEC Novel Excipient Safety Evaluation Procedure, the PDG documents, and the same documents originally submitted to PDG as noted above. IPEC forwarded BASF's submission to FDA, and the agency sent its review letter back to the IPEC safety committee chair who then informed BASF, Wyeth, and PDG of the agency's findings (11–13).

New USP monograph

BASF approached the United States Pharmacopeia (USP) for consideration of an official *National Formulary (NF)* monograph for Solutol HS15 on the following grounds: the FDA review of Solutol HS15's safety data under IPEC's excipient safety evaluation program; the excipient's monograph status in the *European Pharmacopoeia* and its use in approved drugs in countries outside the US; the excipient's EMA safety evaluation and its approval to be used as an excipient in veterinary drugs. As part of their procedure, USP contacted the FDA Compendial Operations office. Based on FDA's feedback, USP asked BASF to submit materials for monograph development. Efforts by BASF and the USP monograph development group led to the publication of an official polyoxyl 15 hydroxystearate (Solutol HS15) *NF* monograph in *USP* 33–*NF* 28, Reissue Official Oct. 1, 2010 (11–13).

Conclusion

The need for novel excipients, especially solubilizers, is growing throughout the pharmaceutical industry because pipeline compounds have shifted toward lower solubility in the advent of high-throughput screening during discovery. The successful use of a novel excipient can only arise from a close partnership between the supplier (i.e., excipient manufacturer) and the user (i.e., pharmaceutical company). Using Solutol HS15, the IPEC Novel Safety Evaluation Procedure has proved to provide a venue for verification of regulatory acceptability of novel excipients before late-phase clinical trials and NDA filing. The authors therefore encourage additional excipient innovation and novel excipient use by drug product manufacturers.

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