From Inactive Ingredients to Pharmaceutical Excipients

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In this article, the authors trace the evolution of the industry's opinions and developments that have led to the current perception and use of excipients. From their initial use as inert ingredients to the present practice of using them to aid the release of active ingredients, high-purity excipients now are considered to have more importance in the industry.

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In the past three decades, the pharmaceutical industry has seen the development of drugs that actually cure disease rather than just offer symptomatic relief. During these years, the concepts of improving efficacy and good manufacturing practices (GMPs) have grown in importance. In addition, toward the end of the last quarter of the previous century, many new concepts and terms had come into common usage. For example, the concept that a dosage form must act to release the active ingredient has become generally accepted. Words like *disintegration*, *dissolution*, and *bioavailability* also have gained prominence and meaning. Accompanying these terms and concepts was the realization that inactive ingredients frequently are critical to ensure storage stability, safety, and efficacy of drug dosage forms. The transition from excipients being perceived as inactive, inert ingredients to the present status of pharmaceutical excipients was well on its way.

When *Pharmaceutical Technology* was a new magazine 25 years ago, most tableting and encapsulation largely were performed using common foods, food additives, and salts — only the first polymers were then in use (1). For the most part, users had to refine the materials for pharmaceutical use and had to conduct any necessary performance testing.

As industry became more interested in faster and lower-cost drug production, new processes such as direct compression, fluidized-bed granulation, automatic capsule filling, and film coating were introduced (2). Therefore, new and improved excipients were required to make this progress possible.

As technology was advancing, significant changes also were occurring on the business side of the pharmaceutical industry. Owing in part to the introduction of new national regulations and the influence of regulators, companies in the industry grew as national entities. Companies with headquarters in one country and subsidiaries in other countries tended to operate each of the subsidiaries as national businesses. It wasn't until the development of the European Union (EU) that many recognized the advantages of an EU regional industry rather than a country-by-country approach to marketing. In addition, acquisitions, mergers, and business growth fostered a growing realization that the pharmaceutical industry, like other large industries, truly was global in its reach. With this expanded view came an increased recognition of the need for global standardization of quality standards.

To that end, first came the trade name excipients, which were marketed in as many venues as possible. The *United States Phar-*

macopeia, through its *National Formulary* (*USP/NF*), contained a compilation of excipient standards. In the EU, the *European Pharmacopoeia* became the standard, supplanting more than 20 national pharmacopeias. In the same time period, the first edition of the *Handbook of Pharmaceutical Excipients* (1986) was published.

Both the excipient and pharmaceutical industries came to realize that materials such as crystalline cellulose, spray-dried lactose, anhydrous lactose, cocrystallized sugar, povidone, crospovidone, sodium starch glycolate, various cellulose compounds, acrylates, and others had different monographs in different pharmacopeias. Each major geographic area's governing body had developed its own regulations and guides, and each reflected its own cultural characteristics and local idiosyncrasies. Thus, multiple products and/or multiple standards and tests were required for international distribution (3).

Recognizing that something had to be done, the three primary pharmacopeias formed the Pharmaceutical Discussion Group (PDG) in the late 1980s and began a program to harmonize monographs. It soon became apparent that the PDG needed outside help, and at a USP open meeting in late October 1990, the concept of an international industry association composed of both users and manufacturers of excipients first surfaced.

That evening, after a paper was read reviewing the lack of regulation and guidance for the safety evaluation of a candidate excipient, several dozen representatives of excipient user and producer companies agreed to form what became the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas), which was officially implemented in April 1991 in Washington, DC. Other IPECs eventually were formed in Europe and Japan (e.g., IPEC Europe and JPEC). The need for geographical separation was necessary because of the practicalities imposed by distance and differing regional practices and national regulations. One should note, however, that IPEC has spoken and will speak with one harmonized voice when the need arises. The organization also has demonstrated, through the harmonized guidelines it has published, that it is an important voice for international users and producers of excipients.

To accomplish its goals, IPEC formed working committees, composed of representatives of producer and user companies, to address safety evaluation, excipient GMPs, monograph harmonization, assistance for new drug chemistry reviewers, and other issues that surfaced. IPEC also made provision for assisting regulatory and international governing bodies when they were faced with new and unusual challenges. Some examples of this assistance involved the Centers for Disease Control, the World Health Organization (WHO), and the Pan American Health Organization in its reviews of the Haiti cough syrup issue. IPEC also is partnering with the PDG to harmonize excipient monographs.

The unfortunate occurrence in Haiti in 1996, which involved the mislabeling of a product that was used in a cough syrup that ultimately killed more than 90 people, highlighted the need to address the quality and control of excipients. The incident drew attention to several weaknesses in the entire process of manufacturing, shipping, handling, and labeling excipients. Some of these problem areas are aggravated by inexact requirements for certificates of analysis, a lack of GMPs followed by developing country manufacturers and distributors of excipients, a growing necessity to audit suppliers and distributors, and the need for development of impurity profiles — to name just a few.

IPEC-Americas responded to the need for industry guidance and developed several guidelines such as the

- GMP Guide for Bulk Pharmaceutical Excipients
- GMP Audit Guide for Distributors of Bulk Pharmaceutical Excipients
- GMP Audit Guide for Suppliers of Bulk Pharmaceutical Excipients
- IPEC Significant Change Guide for Bulk Pharmaceutical Excipients
- New Excipients Safety Evaluation Guidance (4)
- IPEC Guide for Development of an Impurity Profile
- Format and Content of a Certificate of Analysis.

The first three have been harmonized with IPEC Europe.

WHO has incorporated the IPEC GMP Guide for Bulk Pharmaceutical Excipients into its guidances offered to national member states, and USP has published in *USP 24/NF19* both the IPEC GMP guide and a slightly modified version of the IPEC-Americas safety evaluation guidance as general information chapters. In addition, as an aid to manufacturers and users of excipients, IPEC-Americas recently developed a third-party auditing program. A subsidiary of IPEC-Americas called International Pharmaceutical Excipients Auditing, Inc. (IPEA) was formed late last year. This organization, through use of IPEA-trained international auditors, will be able to audit facilities in Europe, Asia, Australia, and North and South America following IPEC and International Organization for Standardization guidance standards. As a result, international auditing costs are expected to be substantially lower for companies that no longer will need to send their own auditors on long overseas trips.

The increased sophistication in functionality associated with some of the newer excipients is consistent with the shift from the concept of excipients as inactive, inert ingredients to being materials that help deliver the active ingredient to target organs or body areas. Some of the sophistication stems from products produced through biotechnology, and these requirements will undoubtedly expand IPEC's future role.

References

1. R.F. Shangraw, "Pharmaceutical Excipients: Characterization, Functionality and Harmonization," presented at Land-o-Lakes Conference, Merrimac, WI, June 1992.
2. R.F. Shangraw and D.A. Demarest, "A Survey of Current Industrial Practices in the Formulation and Manufacture of Tablets and Capsules," *Pharm. Technol.* **17** (1), 32–44 (1993).
3. R.C. Moreton, "New Excipients — From Idea to Market," *Eur. Pharm. Rev.* **2** (3), September (1997).
4. M. Steinberg, et al., "A New Approach to the Safety Assessment of Pharmaceutical Excipients," *Regul. Toxicol. and Pharmacol.* 24 (2), October (1996). **PT**