PHARMACEUTICAL & MEDICAL Packaging NEWS

Viewpoint

Pseudo-Empirical Modeling Essential to True Quality by Design

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The movement for Quality by Design (QbD) has the potential to significantly streamline the development and approval for pharmaceuticals. A pilot program from FDA (started in July 2008) has gained headlines and many drug developers are now seriously considering the concept.

Quality by Design (QbD) is a systematic approach of reaching quality standards by looking at the entire developmental system and product life cycle. It brings to the forefront some of the essential, yet often overlooked elements of quality assurance throughout the stability profile of a drug product.

For example, maintaining the stability of a drug product formulation requires controlling the relative humidity and/or oxygen concentration of a pharmaceutical package's headspace and drug product's free moisture level over time. But this critical step in the process is seldom taken into account until a problem arises late in the development or even approval process. QbD principles help avoid such problems by providing a framework for controlled development, manufacture, and commercialization of pharmaceuticals.

Developing a knowledge base necessary to achieve QbD can be daunting, as many facets of drug formulation, manufacturing, and packaging have become increasingly complex. What will it encompass? And how will developers efficiently implement QbD standards without extensive and expensive trial and error? There are some tools, however, that can help simulate how drug formulation, manufacturing, and packaging will interact with each other throughout the life cycle of the product.

PSEUDO-EMPIRICAL MODELING

One of these methods involves sophisticated simulation modeling of the drug product in its packaging—a unique analytical tool that takes into account conditions during all stages of drug processing, from pharmaceutical formulation to the packaging environment and throughout the distribution chain. The analysis helps formulation chemists and packaging engineers provide drug manufacturing companies with specifications and recommendations for the ideal drug product and packaging combinations.

Referred to as pseudo-empirical modeling, this tool can be used early in the development process to help formulators achieve QbD standards. To illustrate how it works, let's take an example: an analysis of a solid drug packaged in a high-density polyethylene bottle would take into account three interdependent parameters: the

moisture vapor transmission or oxygen transmission into the bottle over time; the adsorption isotherm for the drug, and finally, the adsorption isotherm (desiccant) or absorption profile (oxygen scavenger) for the sorbent, which is needed to manage the moisture and/or oxygen within the given packaging presentation. Such calculations can be complex because they involve multiple covariates and dynamic processes. Given its performance advantages in reducing total moisture and oxygen ingress, the use of a foil-laminate heat induction seal is always assumed.

Linking these variables together mathematically predicts the conditions within a package over time in a given environment. This resulting information will ultimately determine the means by which manufacturers can maintain a drug's chemical and physical characteristics over time and aid in prediction of the stability outcome.

CURRENT SYSTEM VERSUS QBD

Currently, pharmaceutical manufacturers rely on quality by testing and inspection where stability tests are applied to packaging. This seems to be a logical, intuitive approach: a product package is tested, and if it passes, quality is assured. However, this approach is inherently inefficient. It requires numerous tests, providing results that are often difficult to quantify. This heavy reliance on testing tends to have a cascade effect leading to over packaging as well as difficulties in optimizing processes in the post approval period.

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Looking at these basics of QbD in packaging, it becomes clear that pseudo-empirical modeling is necessary to inform many of these quality, process, and design parameters. The tool allows packaging engineers and formulation chemists to "look into the future" and see how packaging environment controls can actively protect a product as it moves through packing, transportation, storage, and consumption. This modeling would lead to more intelligent choices in packaging and sorbents, saving time and money by minimizing trial and error as well as over packaging.

FDA's movement toward a QbD approach will do much to speed approval processes, but the industry has been moving in this direction regardless.

With additional tools like pseudo-empirical modeling, developers can choose packaging and sorbent options systematically. As drugs and drug delivery methods become more complex and less stable, this will be essential to succeeding in drug development in the 21st century. ■

Multisorb Technologies has been an innovator in sorbent technology for more than 45 years. Founded in 1961 by John S. Cullen to protect products against the damaging effects of moisture, Multisorb today is a world leader in the development and production of active packaging components.