What does the future hold for pharmaceutical excipients?.

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Editorial

KEY WORDS: Future of excipients

Many of the excipients we use today have been around for more than fifty years. In many cases, the specifications for those excipients have not changed much over the years, either. During that time, we have not really thought about what happens when our existing excipients, and/or their specifications, are no longer able to provide us with the necessary performance to allow effective medicines to be formulated, developed and manufactured on a routine basis. Things are changing!

We have moved into a new era. With the advent of combinatorial chemistry, high-throughput screening, recombinant technologies and better understanding of proteins, drug-receptor interactions, monoclonal antibodies, and the like, today we have very sophisticated tools which help us to discover very effective drugs we could hardly imagine fifty years ago. However, innovation in excipients has not kept pace with the advances in drug discovery.

Today, many excipients may be considered deficient with respect to certain industry needs. Some excipients do not have adequate test methods to detect adulteration. This is a serious concern for regulatory agencies because there is a need to protect the public from adulterated medicines. Some excipients simply are not well enough understood to be able to use them to develop sufficiently robust formulations for some drugs molecules. They typically do not have tight enough specifications to allow them to be used reliably in the development of some drug products.

For the first issue, the pharmacopoeias have been introducing better more meaningful monograph specifications for some years now. This has been encouraged by the collaboration in the Pharmacopoeial Discussion Group (PDG), but also in response to some of the scandals and tragedies associated with official substances (and food items) in recent years such as adulterated glycerin in Haiti and other countries (ethylene glycol and diethylene glycol), adulterated heparin in Germany and the US (over-sulfated chondroitin sulfate), and adulterated milk in China (melamine). The FDA has asked the United States Pharmacopeia-National Formulary (USP-NF)

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to modify all monographs to include a specific identity test (i.d. test) for each official substance, including excipients. They have also identified a priority list of excipients for which the monograph does not include a specific i.d. test and the assay is non-specific thus lending the substance potentially open to adulteration. The USP-NF Expert Committees continue to work on this.

As an example of the second issue, consider the formulation of biotechnology drugs (e.g. peptides, proteins and monoclonal antibodies). The formulation of biotechnology drug products places different demands on our understanding and control of the composition of the necessary excipients. This presents the formulator (excipient user) and the excipient manufacturer with different dilemmas. The excipient user wants more information and tighter specifications for the components present in the excipient, while the manufacturer must consider how to achieve this at economic cost, and without compromising the performance of the excipient for their other customers. We must also add in the fact that many excipients are manufactured at large scale using continuous processing. Pharmaceutical use may be less than 10% of the manufacturer's total output, and the use for parenteral products may be less than 10% of the pharmaceutical use; so a very small usage - 'a drop in the ocean' so to speak. (Other typically much larger uses of excipients materials may include cosmetic, food and industrial applications.)

In essence, the users' needs (desired specification requirements) for excipients used in the formulation and manufacture of biotechnology drug products may be exceeding the capabilities of the manufacturing processes and raw material sources. So how can we overcome this apparent impasse? It depends on the excipient under consideration. Some may be amenable to simple purification methods. Others may require purification of the raw materials and reagents prior to synthesis. Yet others may additionally require further precautions to be taken beyond just purified starting materials and reagents, such as preventing the formation of by-products, etc.
All these alternatives have a financial cost. Since biotechnology products are generally very high priced, they may be able to tolerate more expensive excipients. In addition, the amount used per unit dose may be quite small which also reduces the excipient cost per unit dose.

It is clear that there needs to be new thinking regarding the use, sourcing and procurement of excipients for the manufacture of biotechnology-derived drug products. It seems likely that special (enhanced purity or super-refined) grades of some excipients may need to be considered. These grades would have reduced levels of concomitant components. However, they may not be straightforward to develop and bring to market. First, as mentioned above, there is the small volume required. It may not be easy to implement such manufacture on a manufacturing plant designed to produce '000s of tonnes per annum. The enhanced purity grade may not be appropriate for all users since the concomitant components present in the traditional grade may be necessary for excipient and/or product performance in other applications.

Consider also the dilemma of the pharmacopoeias. As noted above, part of the current objectives of the pharmacopoeias is to strengthen the monographs particularly as it relates to the detection of adulteration. How do they incorporate enhanced purity grades into the monograph for a particular material? Is it even possible in all cases?

By way of an example, let's consider vegetable fixed oils. Fatty acid composition alone is not sufficient to detect all adulteration, but when combined with sterol composition, together they are sufficient. The enhanced purity grades will likely have an altered fatty acid composition, and also a reduced content of

sterols. Will the specificity of the combined tests still be sufficient to detect adulteration at an acceptably low level? The fixed oils may not be relevant to the formulation of most biotechnology drug products; however, fatty acids are, and similar issues apply.

Super-refined oils are commercially available and used mainly in the cosmetics industry. How long before they are used in a pharmaceutical finished product? How do we incorporate them into the pharmacopoeias? Do we create a separate monograph, or can we find a way to incorporate them into the existing monograph?

For years, we have been asking for excipients to be taken seriously. That time may have arrived. I hope we are all up to the task!

One final thought! There is an old Chinese curse: May you live in interesting times! In the excipient world, those 'interesting times' may be here sooner than we think. Are we ready?