

Trends in Pharmaceutical Excipients: An Update

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It is almost two years since I started to write a series of articles on the general topic of Excipients in a Quality-by-Design World which finished earlier this year. In that series, I covered a number of different topics in some detail. But things move on and inevitably things change; we call it progress. Outside of the QbD World things also have changed, and it is appropriate to consider some of the regulatory trends that have affected and will affect excipients, as there have been and will inevitably be further effects across the industry. In this update, I want to address two trends; future US regulatory policy with respect to pharmaceutical excipients and innovation in pharmaceutical excipients.

In the regulatory arena, one of the most significant events relating to excipients, in my opinion, was the presentation by Brian Hasselbalch of the FDA's Division of Manufacturing and Product Quality, Office of Compliance at the Global Outsourcing Conference held at Xavier University in June this year [1]. From this presentation, it is clear that the FDA intends to modernize the cGMP Regulations (21 CFR Part 211), in particular relating to control of raw materials, excipients and components. As a consequence, the Agency expects industry (manufacturers, distributors and users of excipients, APIs and components) to step up their efforts in these areas. Possible control improvements given in the presentation include: knowing the supply chain (including the site of manufacture and any intermediate handlers), requiring audits of all suppliers, testing of each container in a shipment, requiring tamper-evident packaging and security features, notification to the FDA of any contaminated shipments or lots, and that pharmaceutical product manufacturers only use only components recognized as safe for their intended use or included in an approved application.

During the presentation, Hasselbalch acknowledged that some of these proposals are still being worked through. He also went on to state that surrogate or third party audits would be acceptable provided the organization undertaking the audit had the requisite systems and staff to ensure the audit was to the requisite standard [2]. This latter statement is a clear indication that the FDA understands the potential audit crunch the industry faces.

In simple terms, an excipient manufacturer can probably accept no more than 100 audits in any given year (two per week), and that is pushing it. Such an audit load will require extra staff to be available, most often senior staff. Since major excipient suppliers operate on a global basis, and each manufacturing site probably has hundreds of individual customers, it is just not possible to accommodate every audit request at many sites. Excipients are generally manufactured by fine chemical

manufacturers, and their business extends into other markets, such as cosmetics, food chemicals and industrial chemicals, in addition to pharmaceutical excipients. The pharmaceutical excipient business may represent only a small proportion of their overall business.

We have seen some 'solutions' to the problem of increasing requests for audits: consolidated audits for particular industries in a given week with representatives from a number of customers being on site simultaneously, and one excipient company is reported to charge USD 10,000 for an audit. Third party audits would seem then to make sense. If properly organized, they could save time and money for both manufacturers and their customers. However, third party audits would not necessarily address issues related to customer specific requirements, but perhaps they could be addressed in a different way since they typically do not relate to cGMP issues, rather to specifications.

There will also likely be other changes to the cGMP regulations, beyond those listed above, but they are outside the scope of this discussion as they do not concern excipients.

Another major influence will be the US Congress. At the time of writing, there are several bill proposals, both in the House of Representatives and in the Senate, which could impact pharmaceutical excipients and how we use them. Not all of these proposals refer directly to pharmaceutical excipients. Many refer to food chemicals and components. However, pharmaceutical excipients and food chemicals are often inextricably linked. Quite clearly, Congress appears to have woken up to the fact that pharmaceutical excipients (and food chemicals) are a potential source of risk to patients and consumers, and that safeguards are needed to protect the public health. It remains to be seen how Congress will resolve all the different bills.

In the realm of third party auditing of pharmaceutical excipient manufacturing, there have also been some developments. The United States Pharmacopeia (USP) has had their Excipient Verification Program for some time, which is based in part on USP General Information Chapter <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients. In addition, International Pharmaceutical Excipients Auditing, Inc. (IPEA) now also has a certification program which has been accredited by the American National Standards Institute (ANSI). The IPEA certification is to The Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients published in

2006. There may be other certification schemes for pharmaceutical excipients in other regions.

There has also been a change at the USP. The USP operates on a five-year Revision Cycle. The new Revision Cycle commenced on July 1st and will continue until June 30th, 2015. There have been some changes in the way that excipients will be handled by the USP for this new Revision Cycle. In the previous Revision Cycle there were two excipient monograph Expert Committees. In the current Revision Cycle there will only be one, much larger, excipient monograph Expert Committee,



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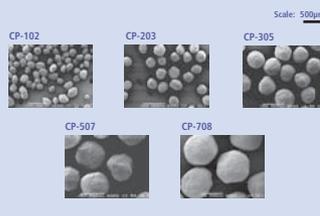
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and there will be greater emphasis on Advisory Panels for specific projects that will bring in further expertise from outside the Expert Committee. One of the innovations in the new Expert Committee is that for the first time there will be a few members who are currently employed by excipient manufacturers. In the past, members of the excipient monograph Expert Committees have not been currently employed at excipient manufacturers, although former employees and retired employees have been members. One of the tasks of the new Expert Committee will be to update existing monographs where needed, to replace outdated methods and to bring the monographs into the 21st Century.

In part, this initiative to update the excipient monographs in the USP-NF stems from an examination of the tragic incidents of contamination of pharmaceutical excipients and food chemicals that have been reported in the last few years (and these may be the tip of the iceberg). In recent years, we have had incidents of adulterated glycerin and propylene glycol, heparin, melamine in pet food and melamine in milk. At first glance, these are very different materials, but if we look closer, and we consider how the adulteration arose we can see some common factors.

Besides the obvious causes such as greed, there is a common thread. In all cases, the material was accepted on the basis of a certificate of analysis that was not confirmed before the material was used, the acceptance criteria was a non-specific test, and the monograph or specification did not contain a specific test that would pick up the adulteration. The propylene glycol and glycerin contained ethylene glycol and diethylene glycol; chemically they are all very similar materials, except that ethylene glycol and diethylene glycol are highly toxic, particularly to young children. (In all probability someone had deliberately re-labeled industrial grade to pharmaceutical grade, with tragic consequences.) The heparin was adulterated with over sulfated chondroitin sulfate. Heparin is a sulfated polysaccharide as is chondroitin sulfate. The assay was a non-specific test for sulfate groups. By including the over sulfated chondroitin sulfate, the suppliers were able to 'boost' the 'heparin' content of their material. Melamine is a molecule rich in high nitrogen and the assay for protein in both pet food and milk was a simple nitrogen test that was not specific for protein. The melamine was added to allow the suppliers to dilute the protein content of the feed component, or the milk, and thus sell 'more' at the price.

Thanks to efforts by the FDA, USP and industry we now have methods that can detect ethylene glycol and diethylene glycol in glycerin and propylene glycol, and we also have a requirement from the FDA that every container of each shipment received be tested for the absence of either potential adulterant. We also have better methods for the detection of over sulfated chondroitin sulfate in heparin. I think we will see more of these types of modifications to other excipient monographs and test methods. Potentially, the monograph for any materials that do not have a specific assay or specific identity test capable of detecting adulteration will be required to be updated to include a test that is specific for the material, and is capable of detecting adulteration.

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Such tests will be included in the Identification Test section of the monographs, and there is a good reason for this. Under 21 CFR Part 211 §84 identity testing is mandatory for each shipment of material received. In the future I think we can expect to see requirements for identity testing on each container of each shipment received, as has been the case in the European Union for some years unless the pharmaceutical company can provide sufficient justification as to why a reduced sampling schedule might be appropriate for an excipient received from a particular manufacturing site.

The USP Expert Committee on excipients will also continue to work on new monographs. In the 2005 – 2010 revision cycle 39 new excipient monographs were introduced (and 75 were updated). It is hoped that the new Expert Committee will be even more productive. USP will be looking for companies to sponsor monograph development for both new and existing monographs by working with the Expert Committee.

Traditionally, the rule has been that to have an official monograph accepted and published in the USP-NF, the excipient must have been included in at least one commercial product available on the US market. The lack of a USP monograph has been cited as one of several barriers to the acceptance of new excipients by the pharmaceutical industry. Now the USP can develop a monograph for a new excipient ahead of time. It will not be published in the official book or supplements until it has been used in an approved medicinal product (prescription or over-the-counter) commercially available in the US. But it will be available in the Pending & Non-US Monograph section of the USP website. This will allow it to be converted to a full monograph very quickly once the product containing it is approved, and the excipient is included in the FDA's Inactive Ingredient Database. (This pending monograph status also applies to API monographs.)

One further change in USP policy for excipient monograph development is that a more transparent approach to the development of monographs for co-processed excipients is being developed. A Stimuli to Revision article has already appeared in Pharmacopeial Forum [3] and an additional section to be included in the USP Guideline [4] is being developed.

Turning now to innovation in pharmaceutical excipients, what trends do we see, and what are the likely future trends? In 1995 (fifteen years ago), I gave a presentation on the future as I saw it then for pharmaceutical excipients [5]. In that presentation I suggested that the likelihood of truly new chemical excipients being introduced was remote, and that we would most likely see innovation in pharmaceutical excipients as new grades of existing pharmaceutical excipients and innovative co-processed materials. In general terms, the same is still true today. However, we have seen the introduction of a couple of new chemical materials in the past 15 years. For example, β -cyclodextrin sulfobutyl ether sodium has been successfully introduced. Polyoxyl-15-hydroxystearate was introduced more recently in the US, and also now has a monograph in the NF. Interestingly, Polyoxyl-15-hydroxystearate was also the first excipient to be evaluated under the IPEC-Americas

Novel Excipient Evaluation Procedure. However, it can be argued that both these examples should be classified as chemical variations on existing materials, rather than truly novel chemical structures. That is not to take anything away from their discovery and development; they do solve formulation problems.

There have been some recent introductions of new grades of existing monographed pharmaceutical excipients such as microcrystalline cellulose grades having lower bulk density and increased compactibility, and most recently a pelletized from which is claimed to have superior disintegrating characteristics. There have also been introductions of new co-processed pharmaceutical excipients in recent years including combinations of lactose and starch, microcrystalline cellulose and mannitol and starch and pregelatinized starch.

These innovations in excipients appear to be driven by two separate motivations; to address traditional deficiencies such as poor flow or carrying capacity, and to provide excipients designed to facilitate the formulation of non-conventional oral dosage forms such as orally disintegrating tablets. It is good to know that there are still companies seeking to innovate in the field of pharmaceutical excipients and drug delivery.

One further area of innovation that we need to consider is the field of nanotechnology as it applies to pharmaceutical excipients. The definition of what constitutes a 'nano' material is still not decided; should it be less than 100 nm, or less than 10 nm? Recently, the European Union has announced an initiative to define the term 'nano' and has requested input.

In the pharmaceutical sciences, we have been aware of nano-sized materials for many years. In years past, we would have referred to them as colloidal systems, although colloidal systems cover a larger range of particle sizes than many people today would consider nano-particles. Colloidal particles were considered to have at least one dimension in the range 2 to 200 nm [6]. We have had colloidal excipients for many years. For example, consider the fumed silicas (colloidal silicon dioxide) where the primary particles typically have a particle size <20 nm, although they are mostly in the form of much larger agglomerates.

The concern with nano materials is the enhanced properties they possess compared to non-nano materials. This has benefits, particularly for poorly soluble APIs, where the use of nanoparticles can increase the bioavailability of the drug. However, there are also concerns that absorption of undesirable nano-sized materials could occur across biological membranes. The outcome of the debate will be important for excipients, because it will possibly have an effect on some useful excipients that have been used safely for many years. The same debate will also influence future innovation around excipients. We need to watch the 'nano' debate very closely to ensure objective science and sound scientific methods prevail. It may be that the details of some of the methods and procedures used in the safety evaluation of non-nano materials will need to be modified for use with nano materials.

¹ The USP is only one part of the book, which comprises both the Pharmacopeia and the National Formulary (NF). In general, excipient monographs are included in the National Formulary, and active pharmaceutical ingredients (APIs) and official preparations are included in the USP. However, certain materials, e.g. Mannitol and Dibasic Calcium Phosphate, can be used as either an excipient or an API. In such cases, the monograph appears in the USP section of the book. There are some other materials included in the NF which also have therapeutic uses. These materials are referred to as 'atypical actives'. When any material is used as an API, ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients applies.

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Author Biography

Dr. Moreton has over thirty years' experience in the pharmaceutical industry. He has worked as a formulation scientist developing a variety of different dosage forms, and has experience in the design, development, scale-up, technical transfer and validation of drug products and associated analytical methods, both during clinical development and eventual transfer into commercial manufacture, and working with licensing partners and contractors. He has also worked in QA/QC, Regulatory Affairs and Technical Support in excipients and drug delivery.



He is a past Chair of the AAPS Excipients Focus Group, and of IPEC-Americas. He is a member of the International Steering Committee of the Handbook of Pharmaceutical Excipients, and of the USP Expert Committee on Excipients. He has authored and co-authored scientific papers and book chapters, and lectured extensively in the areas of excipients, drug delivery and formulation at universities, training courses and symposia in the U.S. and Europe.



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