

Functionality and Performance of Excipients in Quality-by-Design World Part V: *Changes in the Sourcing and Supply of Pharmaceutical Excipients*

Chris Moreton
FinnBritt Consulting

“Many pharmaceutical companies are looking to validate an alternate source of their excipients as part of a risk mitigation strategy.”

This month's column is a bit different; I am going to discuss what may appear to be, at first glance, two quite different issues, but they are linked – by the word 'change'. Change is one of the things humans tend not to handle well. Yet paradoxically, 'change' is one of the certainties in life; the others being death and taxes according to the great American statesman, Benjamin Franklin (1706 – 1790):

“In this world nothing can be said to be certain, except death and taxes.”

There are two aspects of change that I want to discuss; changing the source of an excipient, and changes from where we source excipients, particularly from overseas. These latter changes are the result of changes due to the globalization of the excipient market. Both are important topics for the FDA. In the former case, there may be implications for equivalence of the product made using the same excipient but sourced from two different manufacturers. In the latter case, there have been incidents in recent years that have exposed weaknesses and vulnerabilities in our excipient supply chains (and supply chains for other materials).

Changing Source of an Excipient

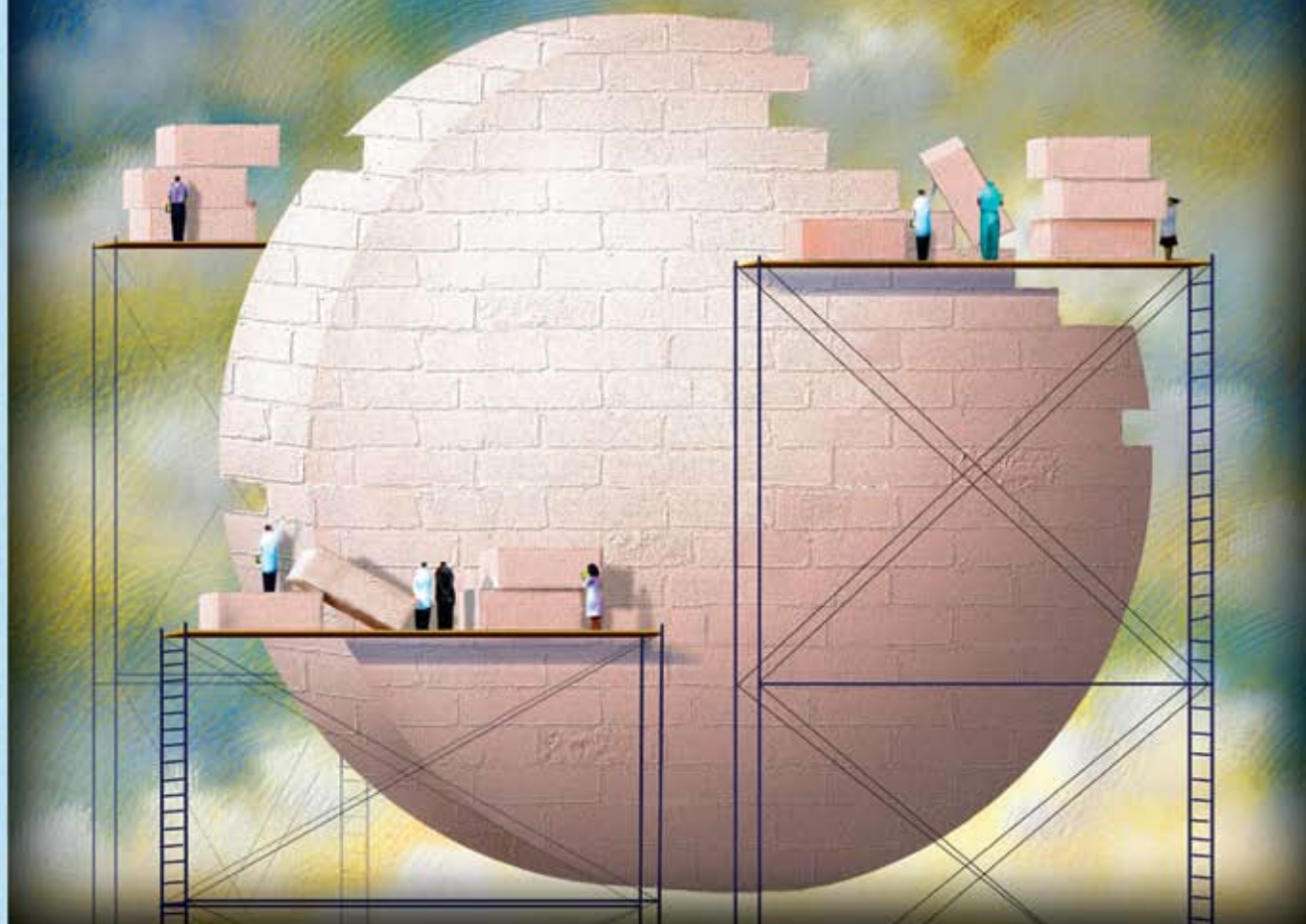
There are three main reasons we might need to change the source of an excipient; a desire to have a second source of the excipient, or because the excipient from the original source is no longer available; due to a disaster, or because the original supplier has withdrawn from the market.

In recent years, there has been increased interest in alternate sourcing of excipients. Many pharmaceutical companies are looking to validate an alternate source of their excipients as part of a risk mitigation strategy. However, there is an obligation on the part of the pharmaceutical manufacturer to continue to use the alternate source, beyond the initial validation, on a regular basis for some of their commercial manufacture. In this way, they can confirm that

PanExcea™

Performance Excipients

Your building block for faster formulations development.



Novel Technology. High-Quality. Optimized Performance.

The PanExcea MHC300G performance excipient serves as a filler, binder and disintegrant in one homogeneous particle — eliminating formulation steps and helping you get to market faster. Designed for immediate release applications, it delivers extensive API compatibility and variable load capability, dramatically increasing formulation flexibility.

**FREE
SAMPLE!**

Find out how PanExcea performance excipients can help you build a better formulation. To collaborate with an application specialist and request a **FREE** sample, call 1-800-943-4747, 908-329-9910, or visit www.mallbaker.com/PanExcea9



Trademarks are owned by Mallinckrodt Baker, Inc. unless otherwise noted.
©2009 Mallinckrodt Baker, Inc. All rights reserved.

Mallinckrodt Baker

the validation is still current, and that nothing has changed with the alternate source excipient. It would not be acceptable, for example, to run the validation and then assume that the switch to the alternate source could be made five years later without any regular use of the alternate source excipient through the intervening period.

Until the advent of Quality by Design (QbD), the opportunities for changes to approved medicinal product formulations in the US were governed by the SUPAC Guidances (Scale Up and Post-Approval Changes). However, changing the source of an excipient is handled differently in the different SUPAC Guidances. Changing the source of an excipient is not covered by the SUPAC Immediate Release [1] or Modified Release [2] Guidances, and there was confusion as to what was required in order to change the source of an excipient. However, changes in excipient source are covered in the SUPAC SS Guidance [3] as a Level 1 or 2 change depending on circumstances. The wording in the SUPAC SS document for the Level 1 change is:

“Change in a supplier of a structure forming excipient that is primarily a single chemical entity (purity>95%) or change in a supplier or technical grade of any other excipient.”

Based on their dates of issue, the SUPAC SS and SUPAC MR Guidances must have been developed in parallel. Yet the MR Guidance does not make any distinction between sources of either non-release controlling excipients or release controlling excipients (despite literature evidence to the contrary for at least one gel-matrix, release-controlling excipient [4]). The question then arises as to whether something that is not included in the relevant SUPAC guidance is automatically a Level 1 change or a Level 3 change. As many of you will appreciate, there is a big difference between Level 1 and Level 3 in terms of reporting and approval requirements.

The FDA recently issued a further Guidance for Industry regarding the submission of summary bioequivalence data for ANDAs [5] which addresses the definition of what constitutes ‘the same drug product formulation’. This Guidance confirms the SUPAC levels and criteria for change. Change of excipient source for either immediate release or modified release products is not addressed; but it is for semi-solid products.

The introduction of the QbD initiative here in the US and the ICH Q8(R) [6] guidance document in the rest of the world has changed the paradigm. In some ways, it has made it easier to implement second sourcing of excipients. We can build second sourcing into the Design of Experiments (DoE) and development programs from the outset (although this may be overly burdensome). Or we can investigate the second source excipient after we have completed

the primary DoE and established the initial Design Space. We can then confirm that the process critical quality attributes and the product Quality Target Product Profile (QTPP) remain unchanged, or can be accommodated within a modified Design Space.

This is a great advantage of QbD; it is possible to move outside the Design Space, with some forethought and planning, in ways we could not contemplate under the old three-batch validation paradigm. We do not have to repeat the whole DoE for the alternate source excipient, and under QbD there is no validation; it is akin to a continuous validation, but is really a continuous verification that the formulation, process and product remain within the designated Design Space. We would probably carry out the initial work on the alternate source excipient at the small (laboratory) scale. Assuming all was satisfactory; we would then confirm the extension to the Design Space through scale-up, and eventually at full scale.

There are, however, some further obligations on the part of the pharmaceutical manufacturer/ marketing authorization holder. It is not simply a question of taking the first alternate supply that comes through the factory gate. There is some considerable due diligence required; even before manufacturing trials begin. This due diligence should include an on-site audit. Many people automatically assume that an on-site audit just involves the Quality Assurance (QA) group. In a QbD world, I believe there is a strong case for including the formulation group in the on-site audit team; for a couple of reasons. QbD requires that we have better understanding of our raw materials (including excipients), and a site visit will help. In addition, formulation scientists and quality assurance people look at things in

different ways and will therefore ask different questions, all of which helps in the due diligence. The other part of the due diligence is the technical assessment. The International Pharmaceutical Excipients Council (IPEC) has recently published a guideline on qualification of excipients [7] which includes alternate sourcing of excipients.

There is a further element to be considered; the risk! By this I mean the risk category of the final finished product. The final arbiter of risk here in the US is the FDA. The SUPAC Guidances did begin to address this in the way that three different guidances were produced covering immediate release, semi-solid and modified release products. The FDA’s different concerns are evident in the details of the different levels of change set out in the three Guidances. In addition, in the SUPAC-MR guidance, there is a distinction between release-controlling and non-release-controlling excipient, with the former being considered as being of higher potential risk for the safety of the patient.

“As with many other industries, there has been consolidation within the fine chemicals industry including companies that manufacture and supply pharmaceutical excipients.”

There are many different types of pharmaceutical product, each with their own set of potential risks. The potential risks are higher for some products than other. There are also different types of risk. For example, for some products, the risk is failure of the product to perform as intended so that the patient gets insufficient drug, or too much. Each can have serious consequences for the patient's well-being. Examples would include dry powder inhalation products where delivery of an insufficient dose may put the patient at risk, and modified release products where there is a risk of dose dumping, and that the patient receives an overdose. Other products are at risk of becoming contaminated during processing or storage and causing harm to the patient, such as parenteral injections, ocular products and products intended to be used on open wounds where the body's defense mechanisms, including the gastrointestinal tract, are intentionally by-passed during administration. Thus modified release products, dry powder inhalation products and parenteral, ocular and open wound products would be classified as higher potential risk than perhaps immediate release oral products for example.

If we are going to make changes, including alternate sourcing of excipients, to products the FDA considers to be in the higher risk categories, then I think we should anticipate that the regulatory scrutiny applied to our justification of our new Design Space, and particularly the limits of this new Design Space, will reflect that higher risk. We had better make sure that we have the data that properly supports our justification.

Changes Caused by the Globalization of Excipient Supply

There are two aspects of the globalization of the excipient market that we need to consider; consolidation of companies due to mergers and acquisitions, and the entry of new manufacturers into the market, particularly from overseas.

As with many other industries, there has been consolidation within the fine chemicals industry including companies that manufacture and supply pharmaceutical excipients. As has been stated many times, for many manufacturers of excipients, the volume for pharmaceutical use can be quite small (often <10% of the manufacturer's output). Very often this consolidation has nothing to do with the pharmaceutical business, but with the other larger uses of the material (e.g. food or industrial applications). This can lead to the loss of manufacturing sites, or even loss of compendial grade excipient. Think it won't happen? – It already has! (See later!)

The official compendia in the US sanctioned in the US Federal Food Drug & Cosmetic Act (FRD&C Act) comprise two separate compendia; The United States Pharmacopeia (USP) and the National Formulary (NF). Although, they are published under the same cover, they are legally separate. The basic distinction between the USP and the NF is that materials having a USP monograph have uses as APIs; NF materials generally are only used as excipients. (However, some USP materials are used as excipients, e.g. mannitol and the dibasic calcium phosphate, and some NF materials may have uses as actives in drug products.)

We have always worked to the highest standards. Yours.

No one works to higher standards than the pharmaceutical industry. For more than 65 years, Sheffield has been driven by those standards in the manufacture of pharmaceutical grade excipients such as lactose, tableting systems, glycerides, coatings and flavors for innovative drug delivery systems.

You may have known us as part of Quest International or Kerry, but throughout our long history, Sheffield has always been dedicated to meeting the unique demands of the pharmaceutical industry.

When you rely on Sheffield, you can be certain you will receive superior technical and customer support, access to cGMP compliant manufacturing and a partner in risk mitigation. From the beginning of product research and development to the end of your product's life cycle, Sheffield will be there every step of the way, anywhere in the world.

To find the highest commitment from an experienced partner that works to your standards, visit us at sheffield-products.com or call a Sheffield expert near you.



Sheffield™
B E C E R T A I N

Visit us at AAPS Booth 733

ASIA PACIFIC
460 Alexandra Road
#22-04A/22-05
Singapore 119963
Tel: +65-6270-3833
Fax: +65-6272-2979

EUROPE, MIDDLE EAST & AFRICA
Veluwezoom 62
1327 AH Almere
The Netherlands
Tel: +31-36-523-3100
Fax: +31-36-523-3110

AMERICAS
158 State Highway 320
Norwich, NY 13815
Tel: +1-800-833-8308
Fax: +1-607-334-5022

Sheffield, ©2009 All rights reserved.
a Kerry Group Business

In recent years, there have been problems with the supply of NF designated grades of at least two materials; propylene glycol stearate and corn syrup, both of which were single-sourced for the compendial grade. Propylene glycol stearate is a material used in topical formulations and probably had a low usage, which may have contributed to the decision on the part of the manufacturer to pull out of the market. But for those companies using the material, it nevertheless was a significant issue. Corn syrup was different. It

is used in many oral liquid products, and had been manufactured successfully for many years with no problems. The original manufacturer was bought by another company, and the new parent company decided not to continue to market the material as conforming to NF specification. The manufacturing plant continued to manufacture the material to the same analytical specification, and using the same quality system, just not claiming compliance with the NF monograph.

In both cases, the excipient users were forced to take steps to find ways to continue to manufacture their products to be able to supply the patients with their medicines. The first option is to look at alternative sources of the compendial grade of such materials. However, even if an alternative source is available, it may still be necessary to adapt the formulation and processing to the new source material. If that is not successful, there are really only three options; withdraw the finished product from the market and thus no longer require the material, investigate the use of a non-compendial grade, or reformulate the product to remove the unavailable excipient.

For small products, withdrawal may be the best option if alternative treatments are available. Reformulation will take time, and will certainly require the filing and regulatory agency approval of a Pre-Approval Supplement (PAS). But the use of a non-compendial grade is not necessarily a straightforward option.

Non-compendial grade materials may be produced for a variety of uses including food use, but also possibly for other industrial uses. There is a common misunderstanding, particularly in companies that are new to the pharmaceutical business, that compliance with specification is all that is required for compendial materials. In the US, this is wrong! The General Notices of the USP-NF require that official articles and products be manufactured to the appropriate standards of Good Manufacturing Practice (GMP). There is also often a further misunderstanding that food GMPs are adequate for pharmaceutical use. This is also incorrect. In the US, two of the major gaps in food GMPs compared to pharmaceutical GMPs concern the independence of the Quality Unit, and change control. ISO 9000 is often promoted as an alternative to GMPs. This too is incorrect, in my opinion. In my experience, the adoption of an ISO 9000 Quality Management System shows good intent on the part of the supplier, but it is not GMP. It should be regarded as complementary to GMP, but not a substitute for GMP.

Assuming that the non-compendial material meets all the requirements of the specification, and the quality system is found to be adequate (i.e. there are adequate checks and balances concerning the independence of the Quality Unit, and there is an adequate system of change control in place confirmed through an on-site audit), what else is needed? The key point under the SUPAC Guidances concerns broadening of specifications for a material, and a move from a compendial grade to a non-compendial grade would be regarded as such. Such a change would



TOGETHER

PROVIDING SOLUTIONS

Because of AsahiKASEI's intensive research and development efforts, we will provide excipients that will allow various dissolution patterns for your highly sophisticated drug release profiles.



Our aim is to provide you with targeted release solutions for your drug delivery applications. AsahiKASEI is totally committed to meeting our customers' satisfaction.

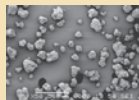
CELPHERE®

CELPHERE® a superior alternative to sugar spheres, is a 100% MCC spherical seed core that is capable of reducing agglomeration during drug layering and film coating to produce higher yields.

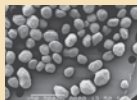
- High mechanical strength
- Fine and uniform particle size
- Low reaction
- Optimum water absorption
- High sphericity

Scale: 500µm

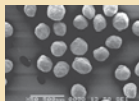
SCP-100



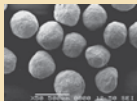
CP-102



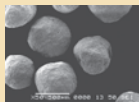
CP-203



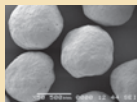
CP-305



CP-507



CP-708



Other excipients that provide solutions:

CEOLUS®

Ceolus® (KG-802 and KG-1000) is an MCC dry binder with a distinctive rod-form particle configuration that is ideal for tableting of low-compactible drugs or coated granules. It is very effective for reducing the tablet size of large doses.

PC-10

PC-10 is a high-swelling pregelatinized starch with an extremely low water-soluble content.

TREHALOSE

A non-reducing disaccharide, Trehalose provides functions such as low reactivity with drugs.

KICCOLATE™

Kiccolate™ is a Croscarmellose sodium (Non-GMO) which is known as a super disintegrant.

CELIOSCOAT™

Celioscoat™ EC-30A is an ethylcellulose aqueous dispersion that is used for various coating purposes.

AsahiKASEI

ASAHI KASEI AMERICA, INC.
535 Madison Avenue, 33rd Floor
New York, NY 10022, USA
P (212) 371-9900 Ext. 217
F (212) 371-9050



By working together, we provide ... SOLUTIONS

www.ceolus.com

be regarded as at least a level 3 change under e.g. SUPAC IR, and require the filing of a PAS.

Since a PAS filing is required for both reformulation and the use of a non-compendial grade of material, reformulation may be a better option under the traditional development paradigm. However, it may not be a better option under QbD. The extension of the Design Space to accommodate a non-compendial grade may be less time consuming than reformulation where a whole new Design Space must be defined, always assuming the quality assurance due diligence is satisfactory.

Finally, I would like to briefly consider the case of new entrants into the market place. Very few excipients remain under patent. Anybody can make them, and in most cases, the general processing is known. However, there is still a lot of know-how associated with excipient manufacture; from raw material selection to process optimization for optimum functional performance, and reduction in undesirable components (impurities in API-speak). The one way that new entrants can penetrate the market is through lower pricing. (If the price was the same as that of the major supplier would anyone change?) However, it is incumbent on the excipient user to undertake an adequate technical and quality due diligence on the new material. Technical in terms of functional performance in all the products that use that particular excipient grade, and quality in terms of compliance with specification and adequacy of the manufacturing site's GMP implementation.

The limits on undesirable minor components are often overlooked during the due diligence. It is worth comparing the test results from the established supplier with those from the new supplier and also with the values given on CoAs. If there are limit tests for undesirable components, check just how well they comply and how they compare with material from the established supplier. I have seen reports showing levels close to 10 times those of the established supplier, but the material still complied with the monograph. In addition, there are other tests that should be considered, such as odor and color, and the absence of potential adulterants, since such attributes may have a significant impact on patient acceptability and compliance. I have seen a sample of an excipient from a potential new supplier that was tan (rather than off-white), and there was a significant odor as soon as the container was opened (as opposed to being odor-free); but it complied with the monograph specification.

Tests for absence of adulterants is a concept that is considered new, but really isn't so new when we consider plant-derived drugs. It has been re-introduced due to the recent incidences of contamination of glycerol and propylene glycol with ethylene glycol and diethylene glycol. It is certainly going to be applied to materials other than glycerol and propylene glycol, and we need to consider the potential for adulteration for any new supplier.

Change is something that we all fear, and we all need to work at accepting and embracing change where necessary. In the excipient world, there have been many changes; there will be many more to come, and we are going to have to consider changes in supply of excipients. Purchasers of excipients need to be more vigilant. We have seen the problems in Haiti, Panama and Nigeria in recent years. Our supply chains are vulnerable and we need to take appropriate steps to make it more difficult for the frauds to succeed and harm patients. The old saying 'caveat emptor' (let the buyer beware) is still as true today as it was in ancient Rome.

This column was intended to address aspects of change relating to pharmaceutical excipients. Changes will certainly impact QbD programs, but the types of changes discussed in this column are not always considered in a timely manner. The next column will revert to more conventional aspects of QbD, and will address issues relating to excipient composition.

References

1. *Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Rockville, MD, November 1995*
2. *Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation. U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). September 1997*
3. *Guidance for Industry: Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation. U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). May 1997.*
4. *Shah AC, Britten NJ, Olanoff LS and Baldamenti JN. Gel-matrix systems exhibiting bimodal controlled release for oral drug delivery. J. Controlled Release (1989) 9, 169-175.*
5. *Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs. U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). April 2009.*
6. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Pharmaceutical Development Q8(R1), Current Step 4 version, 13 November 2008.*
7. *Qualification of Excipients for Use in Pharmaceuticals. International Pharmaceutical Excipients Council, 2008. <http://www.ipecamericas.org/>*



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—Excipient Monograph Content 2. 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.

To contact the author please, email him directly at: info@finnbrit.com