American Pharmaceutical Review™

Functionality and Performance of Excipients in a Quality-by-Design World

A Ten-Part Series by

Chris Moreton, Ph.D.
FinnBrit Consulting

A Supplement to
American Pharmaceutical Review


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Functionality and Performance of Excipients in a Quality-by-Design World:

Chris Moreton, Ph.D.

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EMD

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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.

Foreward

This collection of articles started about two years ago when the people at Russell Publishing contacted me to write a series or articles on excipients. (As some of you may be aware, I have worked with excipients more than a little over the years.) The question was the theme. At about the same time, the International Pharmaceutical Council of the Americas (IPEC-Americas) had started a working group on QbD. It seemed to me an appropriate theme. Thus was born the set of articles contained in this supplement to *American Pharmaceutical Review.*

In my opinion, Quality-by-Design (QbD) is the most significant concept to impact the pharmaceutical industry since I started my industrial career almost 40 years ago in 1972. It transcends small molecule and macromolecular drugs, formulation and analytical development, and process development. But it is more than just a concept; it has the potential to change our industry in ways we could never imagine 15 years ago. Therein lies the problem; we humans do not handle change well.

The pharmaceutical industry has done a lot to change medical practice. Today, we have treatments for diseases that we could only hope for 40 years ago. Yet the public perception of our industry is probably at one of the lowest points of its existence, and there is considerable pressure to reduce the price of medicines. QbD is an opportunity to help redress the balance, except that it is never going to get the public's attention.

This supplement did not come together on its own accord. There has been a lot of support from Russell Publishing LLC. I would like formally to thank Russell Publishing and Nigel Russell's team for all the effort they have put in to make this happen. In particular I would like to thank Maura Leon who was the Editor in the beginning, and Emily Johnson, the current Editor, who has been my main contact and guide over the past couple of years, and has kept me on track.

Finally, I hope you will get some benefit from this collection of articles on QbD. Excipients are, and will continue to be, a very important part of QbD for pharmaceutical formulation design and development. I hope some of you will publish your own contributions on QbD, based on your own experiences. The Regulatory Agencies have given us the chart: it is up to us to plot our course. I wish you all success in your endeavors.

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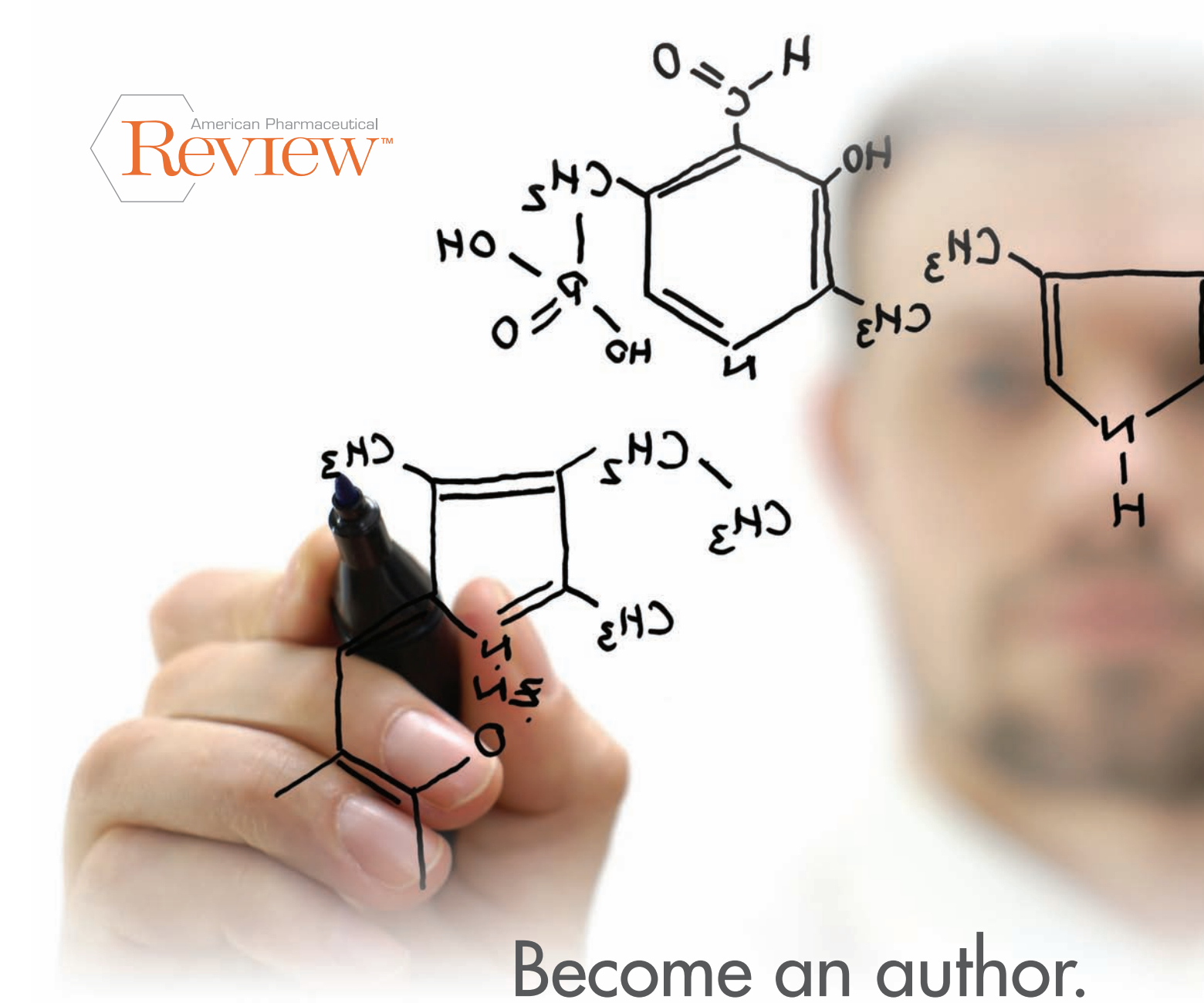

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Functionality and Performance of Excipients in a Quality-by-Design World: Part I

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This is the first of what will be a series of columns around the topics of excipients and Quality by Design (QbD). There are several reasons why I accepted the invitation to write this column. Partly it was timing, but it was mainly a sense of frustration from having listened to people expound on these issues, and yet, to be frank, having seemed to miss the point. I am a formulation scientist, although most people probably know of me from my association with IPEC-Americas. For a formulation scientist, excipients are an important part of the body of knowledge necessary to develop successful formulations. Yet there is considerable misunderstanding about excipients. QbD is part of the US FDA's Quality in the 21st Century Initiative. Parts of it, especially the Design Space concept are also included in ICH Q8 (R1). It is a recent initiative for the pharmaceutical industry and everyone is still coming to terms with it. For formulation scientists required to develop robust formulations, it is a good approach. Yet there also seems to be some misunderstanding about QbD. Over the next few issues, this column will deal with different aspects of these general topics. This first column will set the scene; and hopefully wet your appetite.

Excipients

One of the biggest misunderstandings is that there is somewhere an excipient industry. It is simply not true. Most excipient manufacturers are fine chemical companies who manufacture a small portion of their total output for the pharmaceutical industry. The reality is that very often the amount sold into pharmaceutical companies is less than 10% of the output of these materials. IPEC-Americas, and its sister organizations in China, Europe and Japan, is an association of excipient manufacturers, suppliers and users. The manufacturing members include some very large companies producing materials for the oil industry, food industry, engineering industry, and so on. The fact that they are members of IPEC shows that they recognize the importance of pharmaceutical excipients, but for some of them, if they were to cease selling into the pharmaceutical industry tomorrow, it would not make that much of a difference to their bottom line.

Pharmaceutical excipients are a very diverse group of materials. They cover all the states of matter; gas, liquid (semi-solid), and solid. They include materials of both synthetic and natural origin, including from plants, animals and minerals. Excipients comprise such materials as saccharides (mono-, di-, oligo-, poly-, etc.), inorganic compounds, fats, waxes, and hydrocarbons, amongst others, and synthetic or semi-synthetic derivatives of some of these. Each excipient has its

own process and associated know how. Excipients can also be used in a variety of dosage forms, and some may be used for more than one route of administration. Excipient manufacturing processes include harvesting, extraction, synthetic chemistry, agglomeration, size reduction and fermentation. They are very often manufactured on dedicated equipment, frequently using some form of continuous processing, but some are manufactured by batch processing. The scale of manufacture is very different to that typically encountered in pharmaceutical product manufacture.

To give some idea of the mismatch, consider the following. As a formulation scientist involved in technical transfer and production support, the largest batches I was involved with were about 2000 kg for solid dosage forms, about 3000 L for a liquid product, and about 400 kg for an ointment or cream. Working with excipients, the smallest plant I have been involved with was rated at 2000 metric tons per annum (tpa) and the largest at 30,000 tpa, and there are larger plants. Just for the 2000 tpa plant, that would translate to 20 batches of 2000 kg per week using my largest solid dosage form batch size, and thus three batches per day working 7 days per week, or four batches per day working 5 days per week. For one product, this represents 40 metric tons of material produced per week (and 40+ metric tons of raw materials). And this is for a small excipient manufacturing plant! In pharmaceutical product terms that would be a blockbuster drug with profits to match. But most excipients sell for less than $20 per kilogram, many for less than $10 per kilogram and the net profit may be 5% or less. Not only is there a scale mismatch, there is also an economic mismatch. This has important implications for how the excipient manufacturers respond to certain customer requests.

A key issue for pharmaceutical excipients is the standard of Good Manufacturing Practice (GMP) that must be applied. Under the US Federal Food Drug and Cosmetics Act the definition of a drug or drug product includes components of the drug product. As components of a drug product, excipients are thus required to be manufactured to GMP standards. In addition, the General Notices section of the USP 31-NF 26 Second Supplement includes the following requirement:

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.

However, the recent issues concerning diethylene glycol in Nigeria, Panama and Haiti (and also melamine in pet food and in milk in China) have shown that the supply of globally sourced excipients is vulnerable to adulteration and fraud. There seems to be an attitude in some parts of government that we can somehow pick up any adulterants by testing. This is another of myth that needs to be debunked. Unless we test every part of the material we cannot guarantee to detect an adulterant by testing alone. But if we do that, there will be nothing left for sale. Trying to detect adulteration at the port of entry is too late! We need to prevent adulterated materials from being shipped

in the first place, and we need to educate purchasers, suppliers and manufacturers as to what their responsibilities are; that conformance to specification is not the only criterion; that there are requirements for Good Manufacturing Practices (GMPs). The pharmaceutical industry (excipient users, agents and brokers) can do its bit by insisting on such standards. Many do, but some don't! This is the real problem, because unless those expectations are rigorously and unanimously enforced, adulterated materials will get through with all the sad consequences we have seen.

Until now excipients have been a low priority for regulatory guidance, although France has stated their intention to bring in GMPs for a restricted list of excipients ahead of the European Union. (GMP Guidance does exist for drug products, and more recently for APIs; but neither is appropriate for pharmaceutical excipients.) There is an expectation that pharmaceutical excipients will be manufactured to appropriate standards of GMP (see quote from USP 32 General Notices above), but the USP does not specify which standard is required. The question is not simply, "What level of GMP is required for pharmaceutical excipients?" Rather, we also need to understand how we can take a well established product being manufactured using continuous processing (24/7, 50 weeks of the year) and implement a system of checks, balances and supporting data to get to a state where we can be confidant that the customer will receive the correct material. Simply trying to apply finished product GMP or API GMP to excipients is doomed to fail. Excipients are not pharmaceutical finished products or APIs. They have their own particular requirements for GMP.

> "For a formulation scientist, excipients are an important part of the body of knowledge necessary to develop successful formulations."

IPEC-Americas, working with IPEC Europe, and more recently the UK-based Pharmaceutical Quality Group (PQG), have developed such a Guide. But it is a voluntary guideline; it does not have any regulatory force. The USP has also produced a General Information Chapter: <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients, which is based on the IPEC-PQG Guide. But it is a general information chapter and by definition not mandatory. Many pharmaceutical excipients are also manufactured for food use, and thus to food GMPs. But food GMPs are not always appropriate for materials intended for pharmaceutical use. The appropriateness of the GMP standard used can only really be confirmed through an on-site audit.

One final point about GMP for excipients is the increasing use of questionnaires as substitutes for on-site audits. The only proper use for a questionnaire is as a preparative tool to gather information prior to carrying out an on-site audit. It should never be regarded as a substitute for an on-site audit. And yet this is happening. For example, companies have stated that they only carry out on-site audits for the top 10 or 20% of their excipient suppliers and that for the rest they use 'paper audits' (questionnaires). How is it possible to justify this policy? What is the basis; where is the risk analysis? Are some excipients more important than others? We include excipients in the product because they are necessary. It should therefore be obvious that all excipients are of equal importance.

Functionality

We use excipients to help convert an API to a medicine the patient can use to gain therapeutic benefit. The excipients are included in the formulation because they possess properties that, in conjunction with the processing, allow the medicine to be manufactured to meet the required specification. These desirable excipient properties relate to its functional performance or functionality. Functionality has been defined in the IPEC Excipient Qualification Guide as:

A desirable property of an excipient that aids manufacturing and improves the manufacture, quality or performance of the drug product.

Two of the aspects of functionality that have been the subject of much debate are how to assess it, and how to control it. The reality is that functionality can only properly be assessed in the context of the finished pharmaceutical product, and each application (formulation) will have its own particular requirements for functionality. However, manufacture of a batch of product in order to accept each batch of excipient is not an economically viable option.

We are thus left with trying to find some surrogate property of the excipient that will allow us to predict whether or not a particular batch of excipient is likely to have the requisite functionality to produce a product that will meet finished product specifications in all respects. The relevant characteristics will probably be different for each application. It is therefore incumbent on the individual companies to identify those parameters that are critical to the correct function of the excipient for their particular application.

An issue that has come up is the role the pharmacopeias should play in functionality assessment. Most people agree that excipient monographs have not addressed excipient functionality or performance per se, and were not originally intended to. The question arises as to how functionality should be addressed in the compendia. Europe and the US are adopting two very different approaches. The European Pharmacopoeia has introduced non-mandatory Functionality Related Characteristics (FRCs) sections in certain excipient monographs. This is not an option in the US where legally there cannot be non-mandatory sections of the monograph in either the USP or NF. The introduction of the FRC sections has been controversial; in part because companies purchasing the excipients are insisting on the extra testing whether they need it or not, in part because certain of the tests included in the FRC section have in fact been i.d. tests, or tests such as degree of substitution for a polymer that are more properly part of the tests required to confirm the chemistry of the material, and in part because

some of the tests selected were not adequate to assess small variations in the material. The United States' Pharmacopeia has proposed a different approach; a General Information Chapter: Excipient Performance <1059>. By definition, it will be non-mandatory, and not tied to specific material monographs. A preliminary draft has already been published as a Stimuli to Revision article in Pharmacopeial Forum (Vol. 33(6):1311-1321 [Nov.–Dec. 2007]).

In my opinion, the pharmacopeias do have a role to play. Perhaps the best way they can help is to provide standardized test methods that can be used by both suppliers and customers, i.e. general chapters or general information chapters, but they need to be harmonized and unambiguous.

Quality by Design

As has been stated above, QbD is the new paradigm here in the US. For some time it had been clear that pharmaceutical manufacturing was not able to adopt more efficient practices easily, and that the traditional three-batch validation model was broken. The sad truth is that it has not prevented product recalls. There was also a realization that the old system did not encourage the development of robust formulations and processes. QbD when applied correctly provides a way to allow industry to adopt better, more efficient working practices more quickly, and encourages the development of robust formulations and processes.

A key component of QbD is the concept of 'Design Space'. Design Space is also included in ICH Q8(R1) which has now reached Step 4 in the harmonization process. In simple terms, QbD provides regulatory relief post launch if the requisite development work supports a design space that includes the proposed change(s). The key is in the definition of the Design Space, which is defined in the ICH Q8(R1) document as:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

One other concept that also needs to be considered is the 'Edge of Failure'. We can define the 'Edge of Failure' as:

The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide an output at the limits of specification. Movement beyond the 'Edge of Failure' will give rise to an output that does not meet specification.

The Design Space should not be contiguous with the Edge of Failure. The regulatory authorities quite rightly will not allow industry to operate at the Edge of Failure because of the risk of failing product getting to the patient. If we are not able to define an Edge of Failure during our development studies, we should anticipate (propose) a Design Space inside our 'Limits of Experimentation', because we do not know how close our Limits of Experimentation are to the Edge of Failure.

There will be a significant contribution to the Design Space from excipients. (Otherwise why would we use them?) So what will it mean for excipient users and the excipient manufacturers/ suppliers? We should rephrase the question to, "How do we reconcile the demands of the excipient user with the abilities of the excipient manufacturer?" because the two are approaching QbD in very different ways. Users need to consider very carefully what they need from their excipient manufacturers. If their expectations are unrealistic they may end up having to reformulate or change supplier – never good news during late stage clinical development!

Excipient manufacturers should also work with their customers. They may have some or all the information, although they may not realize it. Very often miscommunication between suppliers and users of excipients can be simply a matter of jargon; the pharmaceutical industry has its own particular jargon, but so does the fine chemicals industry. There can be a considerable discrepancy between the two sets of jargon. But this does not mean they cannot understand each other.

> "Over time, and with sufficient APIs investigated, an algorithm could be developed whereby we input the API properties from our preformulation investigations and we get the most likely successful formulation or two from the list of formulations in our development formulary."

I hope this inaugural column has wetted your appetite. Over the next few issues of this column I will discuss aspects of these and other topics of relevance to excipients and QbD. I hope the concepts raised in this inaugural column, and the solutions proposed in future columns, will be of benefit to you, the readers. As they say, "Watch this space!"United States Pharmacopeia 32-National Formulary 27, Second Supplement, General Notices, United States Pharmacopeia Convention, Inc., Rockville, MD, 2009, p. 3.

References

1. *Qualification of Excipients for use in Pharmaceuticals, International Pharmaceutical Excipients Council, Arlington, VA, 2008, p. 52.*
2. *ICH Q8(R1), International Conference on Harmonization of of Technical Requirements for Registration of Pharmaceuticals for Human Use, Geneva, Switzerland, 2008, p. 16.*

Functionality and Performance of Excipients in a Quality-by-Design World: Part II

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Excipient Variability, QbD and Robust Formulations

As mentioned in the inaugural column, excipients will play a major role in QbD development programs. Excipients are a major part of any formulation development; the other two parts being the active pharmaceutical ingredient (API) and the processing. All three together make the medicinal product, and all are equally important in a functional sense, because if we remove any one of the three, we do not have a product.

One of the issues that we have to come to terms with is variability. There is variability in almost everything. We are bound by the statistical distribution, be it normal, log-normal, or something else. There is really no way to escape variability, so we had better comes to terms with it. Excipients, APIs and medicines are no exception to this general rule, but variability is where the confusion starts. The discussion in this column will focus on excipients, but many of the same concerns apply to APIs; after all, from a materials science perspective, they are simply components of the formulation. Traditionally, we have controlled the chemical composition of our APIs, but sometimes their physical characteristics have not been as well controlled as the chemical process development people would have us believe.

Pharmaceutical excipients are typically manufactured at large scale; sometimes using batch manufacturing, but very often using some form of continuous processing operating 24/7 and 50 weeks per year. These large plants are designed to produce material at the center of the in-process specification, regardless of how they are processed. Because there is inevitably some variation, the manufactured excipient will also show some variation. The question for the formulation scientist and pharmaceutical engineer is, "How much variability will the product and processing cope with, and still produce a medicinal product that conforms to specification?" In other words, how robust is their formulation and process? This is the essence of the Design Space concept that is the vital part of QbD. One of the key questions in investigating Design Space is how to incorporate excipient variability into the Design of Experiments (DoE) that will be used to establish the Design Space and possibly the Edge of Failure.

In order to begin to cope with variability, we had better understand how it arises. If we think of the medicinal product, there are three main components, or groups of components (see above) namely:

API, excipients, and process (equipment and unit operations). They can all show variability, but that is not the whole story. Our model is lacking; it is not describing all the components; the missing pieces are how the three main components interact during manufacture, and the impact of the operator(s). Without recognizing these additional sources of variability, we are not going to be able to solve our problem. If we take the variance as an indication of variability, and there is an advantage in using the variance since variances are additive, then we can describe the total variance of the product as follows:

$$\sigma^2_{Product} = \sigma^2_{API} + \sigma^2_{Excipients} + \sigma^2_{Process} + \sigma^2_{Interactions}$$

Where:

$$\sigma^2_{Interactions} = \sigma^2_{Interaction\,(1)} + \sigma^2_{Interaction\,(2)} + \ldots\ldots + \sigma^2_{Interaction\,(n)}$$

Interactions can arise in many ways, for example; powder-powder, powder-liquid, powder-liquid-process, operator-process, etc. In any given application not all interactions will be important, but some most likely will be, and we have to find which ones are important for our particular project.

In the past, some have tried to go for tighter and tighter excipient specifications. That is not the way! The manufacturer cannot always control the variability in ways that the excipient users demand. One approach that has been tried is to select particular lots of excipient based on a particular parameter and narrow specification. My advice is DON'T! It is a disaster waiting to happen. For lot selection to work, you will probably need better than 50% of the excipient lots to comply. I say this because although the variability is probably cyclical, it is also random, and continuity of supply will be an issue for both excipient manufacturers and users. Try explaining to senior executives that the latest blockbuster product is on restricted supply because the formulation relies on a particularly tight excipient specification that cannot easily be met!

But how do we get to grips with excipient variability in the context of QbD? The usual request that goes out from the customer is for three batches at the top end of specification and three batches at the lower end of specification. There appears to be some confusion as to what the excipient user really needs and what the excipient manufacturer actually can provide. Part of this confusion seems to stem from the fact that formulation scientists are still thinking in terms of traditional three-batch validation even when they are looking to apply QbD principles. Such thinking is going to restrict the project even before it starts.

As I mentioned above, our excipient manufacturing processes and plants are typically designed to produce material at the mid-point of the in-process specification. Working at the extremes of specification is difficult and may require deliberate manipulation of the process control parameters. It will almost certainly require the involvement of the plant QA function, even if it is possible, and there is also the question of managing the special inventory; who pays? But we also have to consider the scale of operations.

Let me explain this manufacturing scale issue by giving an example. During my time with an excipient company I received a phone call from a client that went something like this:

> Client: I would like to get a different grade of [excipient X]
>
> *Me: Is this for development or commercial production?*
>
> *Client: At the moment it's development, but we will want to move to commercial quite soon.*

Me: I realize that it is development now, but I assume that you would want three batches for your validation studies and so forth, and I understand that in the short term during development you will probably only need relatively small quantities; but what is the likely annual usage if the product were to be commercialized?

Client: Oh, this could be really big. We would probably want about 500 kg a year!

Me: That's very interesting, because my minimum batch size is approximately 10 metric tons!

Client: Ah! I think I had better try a different formulation approach.

> "Over time, and with sufficient APIs investigated, an algorithm could be developed whereby we input the API properties from our preformulation investigations and we get the most likely successful formulation or two from the list of formulations in our development formulary."

The client had little or no idea of how the particular excipient was manufactured and certainly no idea of the scale of manufacture. My company would not have wanted to pass up on new business, and it wasn't that we didn't want to help or couldn't do it, the capital investment was minimal. This just wasn't an economic proposition. There had been no other requests of this nature before (over 20 years), and it did not seem to be a grade that would appeal to other customers. The 10 metric tons represented the output from about 4 hours continuous running. Allowing for equipment changeovers, etc. we would assign one eight-hour shift to such projects.

The example above is meant to illustrate the impracticality of some of the requests from excipient users to their suppliers. For a QbD development project when investigating the limits of Design Space we would not be doing all the work at full commercial scale. Working at smaller scales, the quantities of the 'special excipient lots' needed to investigate the extremes of excipient variability will be comparatively small. For the manufacturer they will be very difficult and expensive to produce. There is also the question of what to do with the extra material. The customer may only need 100 kg, but the manufacturer has produced several tons because of the scale of their manufacturing plant. It is hardly surprising that excipient manufacturers are reluctant to get involved in supplying such material.

How then can we include excipient variability in our Design Space investigations? There are several options. Different approaches will be required for different types of excipients and different applications. But before we get too specific let's consider some more general issues. There are excipients that have multiple grades available, and there are those for which only one grade is available. They will require different approaches, but if we think about what we are doing and the opportunity that is available to us under QbD, there probably will not be any need to request material at the limits of specification

For each excipient, for each type of application, and based on the knowledge accumulated over the years of use, we can make a good estimate of which excipient properties, physical or chemical, are likely to be important and should be included in some part of our Design of Experiments. We do not have to re-invent everything for each formulation project. QbD requires that we use the available information from whatever source, and it does not always have to be generated using a specific formulation. There are some general facts that apply to many formulations, e.g. disintegrants generally help tablets to break up when in contact with aqueous fluids.

For example, consider crystalline lactose monohydrate in a powder-filled hard shell capsule formulation prepared by simple blending. It is included in the formulation as a filler. Its important physical characteristic is particle size since this governs surface area, bulk density and powder flow. Do we need to include anything else in the DoE protocol for this excipient? If we look at particle size, how do we get to the limits of specification? The simple answer is no, we do not need to. Crystalline lactose monohydrate is available in many different particle size grades, so we can look at the particle size grades above and below our chosen grades and use them in our DoE. If there is no effect of particle size we are good to go, because the limits of specifications of our selected grade will be well inside the particle sizes of the two other grades. If you are worried that three points is not enough, then include blends of the different grades. If there is a problem with either, or both, of the upper and lower particle size grades, we can again use blends of grades to define our acceptable range.

This is one, very simple example of how we can use the multiplicity of grades to our advantage because, if we find a key parameter, we have options under QbD to take advantage of those other grades.

We have five options we can consider to include excipient variability in our initial DoE (lab scale):

Alternate grades (based on the distinctions used to separate the grades on the market; and including use of a technical grade material that has a different set of specifications).

Blending different grades.

1. Fractionation of the grade (e.g. sieve fractions).
2. Dilution (using some inert material).
3. Using chemically different but closely related materials (e.g. polymers with different degrees and ratios of substitution).
4. Not all of these different approaches will be applicable in every case, but one or more of them will be applicable in most, if not all cases.

One further approach we can consider is to identify ways in which we can offset variability; a form of anti-phase correction. For example, if we know that variation in a parameter leads through a series of interactions to a particular product variability, perhaps we can find a means of compensating for this. A good example would be to use end-point determination to control processing times rather than relying on fixed processing times, e.g. in wet granulation, or in dry blending. We can also consider deliberately including combinations of different grades of an excipient to compensate, e.g. if viscosity of a solution is a key parameter and we do not have the option of end-point control, then we can achieve a much tighter solution viscosity by combining grades. We might also consider dilution, but that may have other consequences.

Another way to compensate might be by including an excipient that would counteract an adverse property of another component. This would obviously have to be included in the DoE from the beginning, but under QbD it can be accommodated. Consider the following; we have an API that is hydrophobic, but for reasons we are not able to control, the hydrophobicity varies such that batches of the product manufactured using certain API lots can fail dissolution, even though we have included a wetting agent in the formulation. If we can establish a relationship between API hydrophobicity and level of wetting agent we could include this as part of our QbD development program.

This brings us to another pet peeve of mine; minimalist formulation strategies. By this I mean including the barest minimum level of excipients and as few excipients as possible in a formulation. This is not the way to design robust formulations, even for supposedly soluble APIs. They rely too heavily on everything going right; all the different components must be held to very tight specifications. Eventually it is going to come undone. Here is an example from my dim and distant past. There was a commercial tablet product that consisted of the API (which was soluble), a filler and a lubricant prepared as a direct compression tablet. All was well until the API changed into a different polymorphic form. The differences were small, but enough to decrease dissolution below the minimum specification limit (you can imagine the furor). There was another strength that also contained a disintegrant and that was able to cope with the different polymorphic form. When we formulate we should be trying to anticipate problems and produce robust formulations that can tolerate changes, even unexpected changes.

Putting all this together, we have the opportunity under QbD to do things in ways that were unimaginable five years ago. What we have to do is properly define our Design Space and demonstrate the reliability of our product. We can even look at the ultimate flexibility; the flexible formulation. By deliberately using two materials in place of one, we will be able to compensate for variability in ways that are not possible when using only one material. For example, we could imagine developing an algorithm that would allow us to adjust the composition in response to a crucial API characteristic. All of this means that the rigid qualitative/quantitative formulation would not apply, but the qualitative formulation would be fixed. (I am not suggesting that we start adding things that were not included in the QbD submission.)

The question of when to start QbD is also being discussed. I favor an approach analogous to that used in the design of a new GMP manufacturing facility – when does the design phase start? At the very first meeting to discuss the feasibility! When does QbD start? As soon as the project is designated! In my opinion, even preformulation should be part of QbD, but it does not need a formal DoE protocol. We need to ensure we use good science to support our decisions. Formulation starts with preformulation, because that is where we find out about the API. If we consider where we might investigate excipient variability, then some, perhaps the majority of the work will be carried out at the lab scale. The crucial parameters will be confirmed at an intermediate scale and then further confirmed at full scale. We do not need to do everything at large scale; it should be a considered progression from small scale through to full scale.

Putting all this together brings us to the idea, proposed by Brian Carlin of FMC, that we might have a series of formulations that would apply in particular circumstances dictated by the API properties. In such a scenario, the API would be akin to a factor in the DoE. Over time, and with sufficient APIs investigated, an algorithm could be developed whereby we input the API properties from our preformulation investigations and we get the most likely successful formulation or two from the list of formulations in our development formulary. Now that sounds like a very efficient formulation design scenario that ties in to expert systems and neural networks.

Functionality and Performance of Excipients in a Quality-by-Design World: Part III

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Excipient Quality in a QbD Context

As I wrote in my earlier columns, excipients are going to be a major part of pharmaceutical formulation Quality by Design (QbD). It thus follows that excipient quality will also be an important part of QbD and Design Space. We therefore need to consider excipient quality in all its aspect very carefully to get the most out of pharmaceutical formulation QbD and Design Space. But first we should define what we mean by quality, and then examine what it means in the context of excipients in a QbD world.

There are many definitions of 'quality', and if we look at several commonly accepted definitions we can get a broad perspective. For example, Joseph M. Duran (perhaps the 'father' of quality assurance and quality by design) defined quality in two ways:

"Quality means those features of products which meet customer needs and thereby provide customer satisfaction,"[1]

and:

"Quality means freedom from deficiencies – freedom from errors that require doing work over again (rework) or that result in field failures, customer dissatisfaction, customer claims, and so on."[2]

In addition, the American Society for Quality Control (ASQC), in its glossary, defines quality as follows:

"The totality of features and characteristics of a product or service that bear on its ability to satisfy given needs."[3]

These are not the only definitions of quality, there are other definitions; for example Wikipedia lists another nine definitions of quality from various sources.

Having defined quality, we can move on to the question of how to assess quality. The definitions listed above, and those listed in the Wikipedia entry, relate to customer needs or expectations and satisfaction. All the definitions thus suggest quality may be assessed in terms of product features, product performance and customer satisfaction. By these definitions, we should thus be assessing attributes and performance, and monitoring customer satisfaction. This applies to any product or service, and the pharmaceutical sector is no exception. For medicinal finished products, this would translate to conformance to specification, manufacture to cGMP, in vivo performance (therapeutic or clinical end-point, or bioequivalence) and customer complaints/pharmacovigilance (post-marketing surveillance).

How do these concepts translate to pharmaceutical excipients? For pharmaceutical excipients, the needs are conformance to specification, manufacture to appropriate standards of GMP (a USP-NF General Notices requirement, and also required by the FDA), satisfactory performance (functionality), and we also need to monitor customer satisfaction.

There is a distinction between these different aspects of quality in that conformance to specification and manufacture to appropriate standards of GMP are tested or implemented before the excipient leaves the manufacturing site. In fact, manufacture to appropriate standards of GMP must be decided before manufacture commences, and the appropriate systems implemented. By contrast, performance and customer satisfaction are criteria that can only be properly assessed after the excipient has been used in the manufacture of a finished medicinal product. They are therefore outside the scope of the monograph or specification. This is the gap that we need to bridge somehow for pharmaceutical excipients, in particular the performance aspect as this will be of considerable importance in the definition of the design space. Since performance or functionality can only be truly assessed in the application, i.e. in the manufacture of the medicinal finished product, we require some surrogate test(s) that is (are) predictive of ultimate performance required of the excipient.

However, before we discuss performance or any other test, we need to consider what the pharmaceutical customer requires in their excipients, and thereby what should be in the specification or monograph. It is not just about identity, assay, impurities and performance; there are other equally important customer needs. The tragic events of recent years in Haiti, Panama, Nigeria, China and the US have shown that pharmaceutical excipients and APIs, in common with many other materials, are vulnerable to adulteration and fraud. So not only do we require the excipient specification or monograph to address identity, assay, impurities and performance, we also need to consider the chemical integrity and safety of excipients.

One of the major changes in the pharmaceutical field in recent years has been the globalization of so many aspects of the industry, particularly the supply of both APIs and excipients. Considerable quantities of both are sourced from outside the US, and this complicates the issues of integrity and safety. With globalization, supply lines are both extended and more complex. In some cases the supply is from countries or regions that have different rules and regulations and where the people have different attitudes to safety and integrity. These differences have led to misunderstandings as to what is required for a pharmaceutical excipient, whether compendial or non-compendial, for use in the US market. There is a prevailing belief in some countries and regions outside that US that all that is required is conformance to specification. As recent events have shown, there are unscrupulous individuals who have deliberately tainted (adulterated) pet food, milk and heparin so that lower strength materials will pass specification. Other incidents have occurred whereby industrial grade glycerin and propylene glycol containing significant quantities of diethylene glycol and/or ethylene glycol have been intentionally relabeled (misbranded) as USP or NF grade respectively. In all these cases, patients or customers or their pets have died.

Thus, not only do we have to consider chemical integrity (identity, assay and impurities), safety and performance in our specification, we must also consider adulteration; both prevention and detection. It would be ideal if we could somehow prevent adulteration, but human nature being what it is, there will always be unscrupulous individuals for whom the chance of a quick profit will always outweigh any concerns about patient or customer safety. But detection is not infallible either as can be seen from the heparin events where the official assay did not pick up the adulteration. There is no single measure we can take that will absolutely guarantee that adulteration can be prevented.

There is no single measure we can take that will guarantee that we can detect each and every case of adulteration. Success will only come from a series of measures taken together. However, as mentioned in a previous column, such measures will need to be implemented rigorously and uniformly, by all parties, and for all excipients.

We have already noted above the requirement for pharmaceutical excipients to be manufactured to appropriate standards of GMP. We also need to extend this concept to the whole supply chain by invoking Good Distribution Practices (GDPs), including the use of excipients pedigrees. (There will be further discussion of the whole supply chain issue in a future column.)

The heparin incident, and also the pet food and milk incidents, highlight one of the weaknesses in the system that the unscrupulous are able to exploit; the use of non-specific assays for materials. In the case of heparin, the crude drug was mixed with over-sulfated chondroitin sulfate to augment the non-specific assay for sulfate residues. Although the pet food and milk incidents relate to food materials, they are examples of the same type of fraud. Melamine, a chemical used in several industrial applications and rich in nitrogen, was added to the pet food and milk in order to boost the nitrogen content because the assay for protein was a non-specific Kjeldahl nitrogen determination.

One of the priorities for the pharmacopeias and other pharmaceutical organizations must be to review all monographs or specifications that do not have a specific assay method with the object of introducing specific assay methods, where possible. It may not be possible for all materials, in which case other types of tests and/or combinations of tests may be required. This will not happen overnight; it will need time, and we will have to set priorities using an appropriate risk assessment mechanism, but we do need to close such loop holes. To me, this would seem an ideal topic for the excipient monograph harmonization teams to deal with because it is a problem common to all, not just the US. Such an approach would also avoid unnecessary duplication of effort. Perhaps the Pharmacopeial Discussion Group (PDG) can be persuaded to take this on.

> “Confirmation of identity and ‘purity’ have probably been taken for granted by most formulation scientists, but QbD and Design Space require that we understand things better, and don’t tak things for granted.”

For formulation development scientists and technologists the crucial questions regarding excipient quality will center on building in the necessary variables into the design of experiments (DoE) used to define the Design Space. There are two concerns; that the excipient is what the label purports it to be, and that its performance is not compromised. This would translate to identity and assay to confirm the label claim, and some test, chemical or physical, that has been found to predict excipient performance in the formulation (application).

Confirmation of identity and ‘purity’ have probably been taken for granted by most formulation scientists, but QbD and Design Space require that we understand things better, and don’t take things for granted. There has been ample evidence of tragic adulteration of excipients in recent years. In addition, there are the vexing questions of additives and processing aids. While adulteration may not be high on the formulation scientist’s agenda, additives and processing aids should be. This is especially important where the presence of either contributes to the stability of the formulation, or is a cause of instability.

There has been considerable misunderstanding about additives and processing aids over the years. In general, an excipient that is labeled as conforming to a pharmacopeia monograph (e.g. USP-NF) may only contain an additive (e.g. preservative) if specifically permitted in the monograph. This has not been well understood by either excipient manufacturers or users. There are cases where an excipient has been on the market for many years and included in numerous commercial products, but which strictly does not comply with the monograph because it contains an additive that is not permitted in the monograph, and is not declared on the label. Processing aids are not so clear cut, but still can have effects on the final pharmaceutical finished product. For example, butylated hydroxytoluene (BHT) is included as a stabilizer in the early manufacturing steps during the synthesis of polyethylene glycol (PEG). Some of this material is carried through the subsequent processing and appears in the final excipient. A customer decided to validate an alternate source of the particular grade of PEG, but the second source material did not contain BHT because that manufacturer had developed a process that did not require it. However, the stability of the pharmaceutical finished product was compromised with the second source because the residual BHT from the product made using PEG from the first source was contributing to the stability of the pharmaceutical finished product.

This whole issue has caused problems for the harmonization of pharmaceutical excipient monographs. There are differences between the three major pharmacopeias. The Japanese Pharmacopoeia does not permit additives, and in fact, the Japanese manufacturers will state that their excipients do not contain additives, but processing aids are permitted. In an attempt to rationalize this, the International Pharmaceutical Excipient Council of the Americas (IPEC-Americas) has been working for the past three years to develop a guide to excipient composition. Part of this effort has been to develop definitions for the different types of components that may be present in an excipient. When published, the IPEC-Americas guide will at least bring the issues into public debate.

The important point in all this is to understand as much as we possibly can about the excipients we use, including how they are manufactured and processed, their composition, the origins of their performance, and any surrogate performance test(s) that may be appropriate.

One thing we all need to remember is that many, if not most, excipients function because they are not a single 'pure' compound. They may contain other components (besides processing aids and/or additives) that have variously been called concomitant components, functional components, etc. These concomitant components may be related or unrelated to the putative compound that is the excipient. They may be identified or unknown. However, they should not be regarded as impurities; they are essential to the proper functioning of the excipient in the application. For example, it is possible to manufacture extremely pure dibasic calcium phosphate dihydrate (DCP-D). Coarse grade DCP-D has been used for many years as a direct compression filler, and it deforms by brittle fracture. The very pure DCP-D did not function adequately because it did not fracture sufficiently during compaction. It appears that a certain level of foreign ions are needed so that there are sufficient discontinuities in the crystal lattice to cause adequate fracture during the compaction process, and thus the generation of sufficient fresh bonding surfaces to form a sufficiently strong tablet. Dibasic calcium phosphate anhydrous (DCP-A) is also used as a direct compression filler, but different consideration apply to its use in such applications.

Thus, in a QbD world what do we need to consider when we think about the 'quality' of excipients? If we ignore the differences between excipient manufacturers and users for the moment; we need a common understanding, and this is what I would want to see in a specification for an excipient that I am about to include in the DoE for the latest potential blockbuster drug:

- Specific assay (where possible, or a suitable alternative)
- Identity test(s) (that can distinguish between materials that might be confused with a particular excipient)
- Full composition (if possible, or at least a declaration of the starting materials/reagents, and what additives or processing aids are present)
- Absence of adulterants
- Physical characteristics (as appropriate)
- Performance surrogate test (if available and if required)
- Manufacture to appropriate standards of GMP
- Known source and manufacturing site, (and established supply chain if possible)

I would be asking these questions before I start the work. Some of this may only be available under confidential disclosure agreement as the excipient manufacturer may consider some information highly confidential. If the excipient manufacturer refuses to disclose such information, even under CDA, I would be very suspicious. QbD demands a better exchange of information; that the manufacturer informs the user of what has been included in the excipient and manufacturing process. The paradigm has changed, and if manufacturers fail to disclose sufficient detail they may lose business. Probably the pharmaceutical business is a small percentage of many excipient manufacturers' overall business, but it is steady and very often commands a premium over commodity industrial markets. There is a balance to be struck between excessive demands for information that is probably not necessary to the DoE, and sufficient information to help the formulation scientist develop robust formulations.

Finally, I will comment about the manufacture of pharmaceutical excipients to appropriate standards of GMP. The question is often asked as to the appropriateness of food GMPs for the manufacture of pharmaceutical excipients. Food GMPs on their own may not be sufficient for a couple of reasons. There is no requirement in the food GMPs for a Quality Unit independent of manufacturing. Many QA units probably do report in to manufacturing in food ingredient manufacturing companies. (It will be interesting to review the final report on the recent peanut paste scandal). Secondly, there is no requirement for the kind of change control we are used to in the pharmaceutical industry. Many food ingredients are manufactured to a physical specification and may be blended with permitted additives to achieve that specification. It is possible to work with food ingredients suppliers to get them to institute pharmaceutical-style systems, but it should not be assumed. So in answer to the general question on the appropriateness of food GMPs, my answer would be, "No! Not without some additional systems to deal with the issues of QA and change control."

This column, at first glance, may seem a bit outside QbD, but I do believe that we have to adopt a more thorough approach to, and broader understanding of, pharmaceutical excipients in a QbD world (an holistic approach, one might say). Excipient quality will be an important part of that. There is no point in developing the best formulation possible if it requires excipients that are not and cannot be manufactured to the appropriate levels of GMP. We are all going to have to take a much closer look at excipient quality to really gain the benefits from QbD.

My next column will discuss the types of information on our excipients needed to properly define our Design Space. In particular, I will discuss where we might find it, and how both excipient manufacturers and users can work together to obtain such information.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part IV

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Obtaining Information on Excipient Variability for Formulation Design Space

*T*he objective of any formulation project should be to develop a robust formulation of an active pharmaceutical ingredient (API). We can qualify this statement by confining our objective to the final pharmaceutical finished product containing the API in question; there are different considerations for Phase 1 and Phase 2 investigations compared to commercial formulations. We should perhaps start by defining the term formulation and then going on to define what we mean by the term 'robust' as it relates to pharmaceutical formulation.

Pharmaceutical formulations may be defined as [1]:

"A mixture of the active component(s) and other materials (excipients) which, when processed, together give a product that delivers the required amount of drug to the patient in the required manner, consistently within a batch and between batches, and is stable."

Similarly, a robust formulation may be defined as [2]:

"A formulation that is able to accommodate the typical variability seen in:

- API
- Excipients
- Processes

Without compromising the manufacture, stability, performance or any other attribute of the product critical to the patient's care or well being."

These two definitions together get to the essence of pharmaceutical formulation Quality by Design (QbD). Design Space links critical quality attributes (CQAs) of the formulation components and process to the Quality Target Product Profile (QTPP). Thus, we need to have a good understanding of the physico-chemical properties and variability of the API, the performance advantages, limitations and variability of the excipients, and the advantages, limitations and variability of the unit processes, and their interactions. In many cases, knowledge of the disadvantages or limitations will be as important as knowledge of the intended performance.

In very simple terms, our knowledge and understanding about the API will be gained via preformulation screening (also referred to as physical pharmacy screening), and is outside the scope of this

column which is directed at excipients. Likewise, the knowledge and information about the unit processes is also outside the scope of this column, although, as with excipients, some of the necessary knowledge will only be gained through experience, both individual and collective (corporate).

So how can we gain the necessary knowledge and understanding of excipients? At the moment, I hear the same complaint from different sources; it seems that everyone complains that we do not have enough information about excipients. In some ways I agree, but very rarely have I heard of a drug development project being terminated because of formulation issues. I personally have never had this happen. I have had projects abandoned for lack of efficacy (despite absorption being demonstrated), adverse pharmacokinetics and metabolism, and unacceptable safety/toxicity issues. So, despite our lack of information, most times formulation scientists have been able to develop viable formulations. My point is that there is knowledge available; it is simply a question of finding it, and tapping into it.

Going forward, things may not be so easy. There has been a trend over the last few years where the molecular weight of drug molecules has increased with a concomitant decrease in solubility. As we all know, or should know, poor drug solubility does complicate formulation development. This is reflected in the US FDA's Biopharmaceutical Classification System (BCS) [3] which many formulation scientists use as a pointer in formulation development. I think we can expect the molecular weight of drug molecules to continue to gradually increase. There may be ways to address poor solubility, for example using soluble pro-drugs that are designed to promote dissolution and absorption, and that break down after absorption from the gastro-intestinal tract. But to make a pro-drug, the molecule has to have a convenient group to couple to the pro-drug moiety; not always the case! Poorly soluble drug molecules are going to be with us for the foreseeable future. Can we assume that the formulation design and development scientists are always going to be able to develop a suitable formulation? Who knows? But whatever happens, I think we are going to need better trained formulation scientists to work with these awkward, poorly soluble and/or poorly stable molecules, and those formulation scientists are going to need the information on excipients and their variability to be able to develop robust formulations.

For each excipient, there are three questions that we need to address:

- What information do we need to develop robust formulations?
- Where might the information be stored?
- How can we obtain it?

The information required for the excipients will vary with the API, route of administration and type of formulation (from the QTPP). This product-related information will allow us to make an informed choice as to which excipient information is likely to be relevant to the project. However, a note of caution! Simply because a particular parameter may not be a high priority for a particular application does not mean that we can ignore it. The physical and chemical properties of the excipient are inherent; they will not go away just because we do not need them. An excipient may be suitable in many ways for a particular application, but if it is not stable in that type of application, for example, there is no point in using it.

I want to concentrate on excipient variability, since this is a priority issue at the moment, and something we have not really addressed in a systematic manner in the past. Excipient variability needs to

be built into the Design Space. In a previous column, I noted that there is inherent variability in most things, and that excipients are no exception. [Note: we should be suspicious if there is no variability in the lot to lot data for an excipient.] It would be ideal if we understood enough about a particular excipient to be able to predict performance in the finished product based on a physico-chemical parameter. Unfortunately, we probably do not know enough about any excipient to do this on a routine basis, and across different formulations. So how can we get information on excipient variability, and where can we find it without having to institute a massive program of investigation?

> “In the context of QbD and Design Space, there are two questions we should be asking: Is this the best way to present the results for the lot? Is there any other data that would be of benefit to the user?”

Excipients are supplied to a specification. For excipients having a monograph in a pharmacopeia, e.g. United States Pharmacopeia-National Formulary (USP-NF), the monograph will form a substantial part, if not all, of that specification. There will probably be several different specifications for a particular excipient; in-process specification, release specification, sales specification and customer specification. The excipient will need to meet all these specifications. In addition, each lot of the excipient should have been tested to ensure compliance with specification, and each shipment to the customer will be accompanied by a certificate of analysis (CoA). The data covering the manufacturing output over a number of batches will show the actual variability in those parameters that have a numerical value (as opposed to ‘complies with specification’, or ‘not greater than’ a set limit). It must be acknowledged that the parameters on the CoA may not link to excipient performance in a particular application, but overall through such data we will still get an understanding of the variability of the excipient in general, whether or not it is random, cyclical, seasonal, or a combination. It is a start!

Such data should certainly be available to the manufacturer; the user may also generate some data of their own to confirm the data in the CoA. We need to consider how best to use such information, and how relevant the data might be to a particular application. With a body of data we can undertake different statistical analyses and gain a better understanding of variability. However, we need to determine the best way to carry out such analyses, since any statistical analysis should be compatible with the underlying data distribution.

So how can the manufacturer/supplier help? As stated above, the manufacturer typically provides a CoA with each shipment of the excipient, and for each batch within the shipment. The CoA will give details of the specification, the limits and the results obtained for the lot in question. In the context of QbD and Design Space, there are two questions we should be asking: Is this the best way to present the results for the lot? Is there any other data that would be of benefit to the user?

How else can we/should we present the data on the CoA, to make it more relevant and maximize its value in a QbD setting? There are many options, but two that could be considered are to include summary statistics of the last few batches of the particular excipient grade delivered to the site, and to include summary statistics of the total output of the particular grade of excipient over the same period covered by the site shipments. I can already hear the howls from my excipient manufacturing colleagues, but I would respectfully point out that, in this age of computerization, enterprise resource management systems, etc., this only requires the correct subroutines to be written into the software to pull and summarize the relevant data, and to post the results to the appropriate report.

There is one other point that excipient manufacturers should consider. They have a wealth of historical data in their archives, much of it from recent years in electronic form. This data may be of great value to both the excipient manufacturer and their customers. If they have not already done so, it would behoove the excipient manufacturer to compile and analyze this data to get an even better understanding of variability; possibly even relating back to the variability in their raw materials if such data is available. In the first instance, this would help the excipient manufacturer better understand their own raw materials and processes. It will also be of value to their customers. I am not suggesting that this data be made available to all customers on a routine basis, but it will certainly help their technical service or support functions answer questions from the customers relating to QbD and variability. It may also be appropriate to share portions of such data with a particular customer under certain circumstances.

As discussed, this would only worth doing for those parameters that have numerical test results. This brings me to another of my pet peeves; the way most limit tests are carried out and reported. Typically we are asked to compare the color of two solutions in test tubes and the sample should not be darker than the standard. If that is indeed

the case, we can then claim conformance to specification. It would be far better to have a numerical result for the color comparison, e.g. spectrophotometric absorption. The reason I say this is that excipient composition is gong to become more important in QbD and will be addressed in a future column. The more we understand about excipient composition and its variability, the better we will be able to understand our excipients. Excipients are typically not a single compound but are mixtures of different components. Some of the other minor components (concomitant components in the USP-NF) may be important for excipient performance, and a true value, rather than a statement that it conforms to a particular limit, will be much more useful going forward. Things are changing; for example the USP is proposing to revamp General Chapter <231> Heavy Metals to include better methods of sample preparation and better, more specific methods of detection [4]. There is a downside to some of this. The new methods are generally more sophisticated, and require more expensive equipment. This may be difficult for smaller laboratories, but there is always contract analytical testing.

The provision to customers of in-process data, and other data not included on the CoA, is less straightforward. Many excipient manufacturers will consider such data proprietary information, i.e. a 'trade secret', because general knowledge of such data would be of value to their competitors. There are legal means to address such concerns. Sensitive data can be exchanged under the auspices of a confidential disclosure agreement (CDA). In the past, such agreements may not have been routinely used for excipients. Going forward, this will probably need to change if we are going to make QbD work properly. [Note: if a CDA is put in place, it will be best implemented as a 2-way agreement to allow a proper exchange of information between the parties.] The manner in which such confidential information is exchanged will vary; however, it should probably be communicated separately from the routine documentation that accompanies a lot or shipment.

The final type of information we need to consider is the data related to customer specific specifications. There are two types of such data; data related to a parameter that is routinely listed on the CoA, but for which the customer has a tighter specification than the excipient manufacturer's normal specification, and data for customer specific test parameters. For the routine test, the only change to the CoA will be the tighter customer specification. For the customer specific test, the customer may well regard that information as confidential. It can be added to a customer specific CoA, but it could equally be submitted as a supplement to the CoA, which could be marked as confidential under the terms of a 2-way CDA.

We have discussed what the excipient manufacturer can do. Now let's consider what the excipient user can do. As stated above, the exchange of information for QbD to be truly successful needs to be 2-way, i.e. a dialog. The user needs to provide feedback to the excipient manufacturer on how a particular lot or shipment of excipient performed during product manufacture and testing. What trends has the product manufacturer (user) observed during the manufacture of their product and when using the particular excipient lot? It is probably unrealistic to expect the pharmaceutical product manufacturer to disclose too many details, but it should be possible, under a 2-way CDA, to share a redacted version of the data where the product name and strength are coded to provide extra security and confidentiality.

There is still the question of now to build excipient variability into the Design Space. In general, many people still seem to be fixated on the old validation paradigm; three lots at the top and bottom extremes of specification. As I have stated elsewhere, it is not easy to provide such samples for a variety of reasons. And, in my opinion, such a strategy is not necessary for a QbD approach. Many excipients are available as different grades based on such parameters as viscosity, particle size, moisture content, molecular weight, etc. Working on the premise that the differences in these grades may relate to performance, and that the within grade variability is less than the between grade variability, then if we include the grades near to our preferred grade, or combinations of different grades, in our Design of Experiments (DoE), we can determine if a particular parameter is critical for the performance of the product. Even for single grade excipients there are options, including fractionation or dilution, we can use. We should also use our experience to target those excipient parameters that are likely have an influence on excipient performance on product manufacture and testing. In a QbD development setting, there is no need for batches at the extremes of specification; QbD gives us better options.

The intent of this column was to look at excipient variability, and how to obtain the necessary information and thus understanding. I think I have shown that there is probably a wealth of information available; it is simply a question of finding ways to exchange that information. In the next column, I will discuss changes in excipient sourcing and supply.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part V

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Changes in the Sourcing and Supply of Pharmaceutical Excipients

*T*his 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 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.

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

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 gastro-intestinal 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.

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

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 Unites 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.)

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 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.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part VI

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Excipient Composition

*H*ow much do you know about the composition of the excipients you are using? How much does anyone know about the composition of the excipients they work with? If we do not know about the composition of our excipients, can we efficiently design and develop robust formulations with an adequate design space? My point is that we really do not understand enough about the excipients we use. This is not meant as a criticism, so much as a plea; a plea to share the information we have about our formulations, and in particular about our excipients, that can be disclosed to the public domain (work on placebo formulations, work on formulations of drugs that never made it through development, work on formulations of drugs that have been withdrawn from the market, etc.). No one knows it all, and I suspect that formulation scientists are working in isolation, continually discovering what has already been discovered elsewhere. This is wasteful of resources at a time when our industry is under pressure to reduce the prices of medicines, and when industry is looking to cut costs.

This was the premise for the development of the Katalog der Pharmazeutische Hilfstoffen by the major Swiss pharmaceutical companies in the 1970s, and which, in turn, inspired the development of the Handbook of Pharmaceutical Excipients, the 6th Edition of which was published recently. The Handbook is not perfect, but it is a good start. However, it is only as good as the information that is available, and to emphasize my earlier point, I suspect a considerable amount of information is not available in the public domain.

In this column, I want to explore several questions concerning excipient composition. I use the word explore because there are no hard and fast answers to many of the questions. In part, the answers will depend on whether or not we really understand an essential difference between excipients and active pharmaceutical ingredients (APIs). This difference is that APIs are in the formulation to treat the patient, excipients are there to help convert the API into a medicine that the patient can use; they bring functionality or performance to the formulation. Unformulated, most APIs are quite inappropriate for patient use.

An essential element of Quality-by-Design (QbD) is that we are able to show increased understanding of our formulations. Part of that increased understanding must relate to excipients since excipients are one of the three components of a pharmaceutical formulation (along with the API and the processing). The important questions are therefore; "How does excipient performance arise?" "What is the composition of a particular

excipient?" and "How does excipient composition influence excipient performance?" I use the word performance because, like Greg Amidon (University of Michigan, and Chair of the USP Excipient General Chapters Expert Committee), I think that 'functionality' is a horrible word! We all know what it means, but I much prefer the term 'performance' which is the term I shall use in this article where possible. I also want to explore the question of impurities in pharmaceutical excipients.

Excipients are a very diverse group of materials. They comprise all the different states of matter; gas, liquid, semi-solid and solid, many different chemical types, such as: inorganics, carbohydrates, hydrocarbons, amino-acids, oligopeptides and proteins, synthetic polymers, natural polymers and other materials, and they can be of animal, vegetable, mineral or synthetic origin. There is also now an excipient/adjuvant manufactured using recombinant technology. Excipients may be harvested in some of the least developed areas of the world, or they may be manufactured in large, modern chemical plants using comparatively sophisticated chemical technology, and everything in between. This is part of the problem with excipients; they are impossible to categorize simply, and there are often as many exceptions as there are examples that prove the rule.

How Does Excipient Performance Arise?

In answer to this question, my reply is that excipient performance must derive, in part, from the chemical composition of the material, and in part from its physical structure (including polymorphic forms). At first glance, this sounds quite straightforward, but it isn't, and this is what can catch people out. If there is one message for you to take away from reading this article; it is that, for the most part, excipients work because they are not pure, but are in fact mixtures containing different minor components which are necessary for their performance. Hiroto Miyamoto, formerly of JPEC (Japanese Pharmaceutical Excipients Council) has termed these components functional components. The USP refers to them as concommitant components. I much prefer Miyamoto-san's terminology. Although having regard to Greg Amidon's preference, we should probably call them performance components.

A further important point to understand is that these functional components or concomitant components are not impurities in the API sense. (In my opinion, 'impurities' is a term that should be reserved solely for APIs.) These functional components are very necessary to achieve optimum excipient performance in the formulation. Let me give you a couple of examples to illustrate this point.

Dibasic calcium phosphate dihydrate is a common pharmaceutical excipient, and the coarse or un-milled grade may be used in the manufacture of tablets by direct compression. This material comprises monoclinic crystals/crystal fragments which deform by brittle fracture during tablet compaction. It is possible to make very pure dibasic calcium phosphate dihydrate today, using a precipitated calcium source and very high purity phosphoric acid. However, this material does not work as well in direct compression. Quite simply, without other ions to disrupt the crystal lattice arrangement, the individual crystals of the ultra pure dibasic calcium phosphate dihydrate do not fracture in the same manner as the regular material during compaction. It appears that dibasic calcium phosphate dihydrate requires some dislocations in its crystal lattice to acts as point defects, and encourage the fracture of the particles, and that foreign ions provide these dislocations. Thus we need a certain quantity of foreign ions for optimum performance; not too many, and not undesirable ions such as lead, but not too few either.

Another point that many people may not be aware of is that dibasic calcium phosphate dihydrate, although somewhat stable at room temperature, is unstable at elevated temperature; even quite modest elevated temperatures (<100ºC). In practice, the surface of the dibasic calcium phosphate dihydrate crystals is converted to calcium pyrophosphate to stabilize the material. Dibasic calcium phosphate dihydrate will dehydrate to form the anhydrate. The surface of the anhydrate appears to be more acidic than the dihydrate [1], and dehydration to the anhydrate will release a lot of water of crystallization. There is an accompanying change in the crystal habit from monoclinic to triclininc. This can have implications for film coating, particularly modified release coatings, and packaging.

Microcrystalline cellulose is a very popular excipient and has many uses in formulation science. It is prepared by the acid hydrolysis of wood pulp. But what does it contain, because it is not all α-cellulose (also known as cellulose-I)? Some of the minor components include cellulose-II, hemicelluloses, sugar residues (from the hydrolysis), formic acid residues and ammonia residues. In addition, different pulps seem to have a different optimum degree of polymerization value (indicative of polymer chain length). If we over hydrolyze or under hydrolyze the pulp we will not get optimum performance. What this all suggests to me is that we do not know enough about the composition of microcrystalline cellulose, and that degree of substitution may be a poor surrogate for performance.

> “In a QbD world, we do need to understand excipient composition better, and in particular we need to understand the composition profile of our excipient.”

The more important point is that we do not know enough about the composition of microcrystalline cellulose to be able to say which component is important for maintenance of performance in any pharmaceutical application. And that is more of a concern.

What is the Composition of a Particular Excipient?

It should be apparent from the dibasic calcium phosphate and microcrystalline cellulose examples described in the preceding paragraphs that the composition of excipients, and its implications for formulation performance and stability, can be complex; not just for polymers, but also for supposedly simple molecules. In addition to the components derived as a consequence of the raw materials and processing, there may be other components. For example there can be processing aids and additives. Processing aids are used to improve some aspect of the manufacture or isolation of the excipient, for example antioxidants to suppress oxidative side-reaction, or surfactants to improve the removal of oily residues from a raw material. Additives, by contrast, are added after final isolation to improve the storage or handling of the excipient, for example anti-caking agents.

The International Pharmaceutical Excipients Council (IPEC) has recently published a guide to Excipient Composition. They have been working to address these, and other issues, to try and provide some much needed understanding of excipient composition. In a QbD world, we do need to understand excipient composition better, and in particular we need to understand the composition profile of our excipient. (This is analogous to an impurity profile for an API.)

To paraphrase this IPEC Guide, excipients can include several different components, including: the nominal component, concomitant components, additives, processing aids, degradants, residual solvents, unreacted starting materials, residual catalysts or metallic reagents, reaction by-products or raw material components. Some of these will be present at very low levels in the final excipient, but can we state categorically that they do not influence functionality? – I don't believe so. What we can state is that there are certain components, such as toxic heavy metals, that are undesirable and should be kept to a minimum.

How Does Excipient Composition Influence Performance?

The examples of dibasic calcium phosphate dihydrate and microcrystalline cellulose given above show that excipient composition does influence excipient performance, and these are not isolated instances.

Polyethylene glycol is available in a wide range of different pharmaceutical grades; some are liquid, some are semi-solid. It is manufactured by the reaction of ethylene oxide and water at elevated pressure, and in the presence of a catalyst. However, all grades can undergo autoxidation and may give rise to peroxides and free radicals [2]. There are two ways to counteract this; the addition of an antioxidant or the use of an inert

atmosphere, such as nitrogen, to exclude oxygen. In this case, the antioxidant is a processing aid, not an additive. A company wished to validate an alternate source of a particular grade of polyethylene glycol for one of their products. Imagine their dismay when the preliminary batches failed on stability. The upshot of the investigation was that the original supplier used an antioxidant as a processing aid, but the alternate supplier used the inert atmosphere method. Unfortunately for the excipient user, the residual antioxidant from the excipient was stabilizing the whole product, hence the stability disaster during the preliminary investigation of the alternate source material.

This raises another point that is often misunderstood by excipient manufacturers and users alike. The USP-NF does not permit additives in materials stated to conform to the relevant monograph, unless specifically permitted in the monograph [3]. However, since few people read the USP-NF General Notices, the use of additives has traditionally not been declared, but they have been used in some excipients for many years, even predating the development of the monograph. The USP has made a concerted effort in recent years to update such monographs to include the presence of an additive, but also to include a labeling requirement that the additive be declared. The current NF monograph for Polyethylene glycol (NF 27, 2009) permits a suitable antioxidant to be included, but less than 10 years ago (NF 19, 2000) there was no such statement.

It is not just the presence of other components that can cause problems. Sometimes a change in polymorphic form of the excipient can present problems. Lactose is a very common excipient and available for pharmaceutical use in different forms and different grades. Lactose is also a reducing sugar and will undergo a Maillard-type reaction with primary or secondary amines. The Maillard reaction has been known for many years. An interesting twist was reported in the early 1970s by Blaug and Huang [4]. These researchers showed quite clearly that spray-dried lactose was more reactive than crystalline lactose monohydrate. It is believed that spray-dried lactose comprises lactose monohydrate crystals stuck together by a thin layer of amorphous lactose. The enhanced reactivity should not be a surprise because the amorphous form is a high energy form. The formation of the amorphous form during spray-drying should also not be a surprise since the removal of the water is very quick and such rapid drying would favor the formation of amorphous material from the lactose present in solution prior to drying. Even today, I am surprised just how many formulation scientists are not aware of or do not understand such very basic chemistry.

Are There Impurities in Excipients?

I would argue no, there are no impurities in excipients! For example, in the case of dibasic calcium phosphate dihydrate cited above, the foreign ions required to disrupt the crystal lattice during deformation could include heavy metal ions such as lead. I suggest that excipient components can be divided quite simply into desirable components and undesirable (potentially toxic) components. In my opinion, the term 'impurity' should be reserved for active pharmaceutical ingredients (APIs) where it does have a place. This is possibly an extreme view, but I believe it is justified by our understanding of excipients, and the facts. I will accept that undesirable components should be controlled to below acceptable safe levels. I will also accept that is would be desirable to control certain acceptable components to within a specified range to ensure a consistent performance from the excipient. However, I do not know of any one instance, where I can state categorically, that if we control component 'x' between these limits, we will have an excipient giving a consistent performance.

Thus, our lack of understanding of the link between excipient composition and functionality forces us to search for surrogate tests that can be used to try and predict whether or not a particular batch of excipient will be acceptable for a certain application. There is also the question of variability; both between batches and within batches, as discussed in Part IV of this column [5], and we have not even begun to address this. There are plans and proposals for different projects to investigate aspects of excipient performance and variability. But this is not something that can be developed as a short-term project. As I explained at the beginning of this column, we do not know enough about our excipients, and what makes them perform the way they do. In a QbD world, is this acceptable? I do believe that there is plenty of data that could be useful and should not compromise intellectual property, if made public. As I stated above, I would like to see such information published for the benefit of all of us working in pharmaceutical formulation development. A pipe-dream? Maybe! But if we do not ask, we will never get there!

Excipient composition is a complex issue. I do not think there will be any quick fixes, but if we do not start to investigate, we will never find the answers. I hope this column has provided you with some food for thought. The next article in this series will address aspects of risk management as they relate to excipients and QbD.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part VII

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Quality Risk Management

Quality by Design (QbD) is a means of developing more robust formulations that will benefit the patient because the quality risks are minimized. Quality Risk Management complements QbD and helps to identify risks and weaknesses associated with systems, development projects and products.

What do we mean by risk? Risk is a very broad concept. The Merriam-Webster dictionary [1] defines risk as:

"… exposure to possible loss or injury …"

In pharmaceutical circles we have the ICH Q9 [2] document, Quality Risk Management, which defines risk as:

"The combination of the probability of occurrence of harm and the severity of that harm."

In the context of excipients, what do we actually mean by risk and harm? As with all pharmaceutical operations and materials, ultimately we mean risk to the patient: risk of overdosing, suboptimal dosing, harm due to contamination or adulteration, etc. This is the trust the pharmaceutical industry has with the patient, that the pharmaceutical products we manufacture will do a lot of good (cure a disease, improve the quality of life, help in a diagnosis, etc.), and very little harm; the least harm possible. I have stated it in this way because all drugs and drug products have associated risks, e.g. side-effects. To paraphrase Lord Scowen, a former chair of the UK's Committee on Safety of Medicines, "Show me a drug without side-effects, and I will show you a useless drug!" Lord Scowen was, in effect, restating Paracelsus who, over 400 years ago, noted that everything is harmful; it is only the dose that determines whether it is safe or not. Or put another way, the difference between a drug and a poison is the dose, and how it is administered. Botulinum toxin is one of the most toxic natural materials known, yet it is used at a very low dose, probably on a daily basis, in cosmetic surgery.

The risk that we refer to in Q9 is the risk that we inadvertently cause harm to the patient because the materials and/or processes that are used to manufacture the patient's medicine are not adequate for the purpose. In the case of excipients, there are risks from contamination, adulteration and inadequate performance. The key issues are how we reduce those risks to acceptable levels (risk mitigation strategies), and what constitutes reasonable precautions to take to reduce the risks below an acceptable upper limit.

The FDA has categorized pharmaceutical products (formulations) into two groups; those that present increased risks because of their route of administration or have a potential to do harm through failure, and those that do not present increased risks from the FDA's perspective. (However, they do still have associated risks.) According to the FDA's current thinking there are three groups of products associated with increased risk:

- Parenteral products, ocular products, and products intended for application to open wounds. These products must be sterile and injections must be endotoxin-free. Parenteral injections and products for application to open wounds or compromised skin can by-pass the patient's natural defense mechanisms, i.e. the skin and gastrointestinal tract.
- Dry powder inhalation systems. These products can fail in use and not deliver the correct dose of drug to the patient leading to an increased incidence and severity of asthma attacks.
- Modified release products, both prolonged release products (also termed controlled or extended release products) where failure can lead to dose dumping and potential overdose, and products targeted for release beyond the stomach where failure will lead to premature release and may result in loss of the active drug, or increased side-effects.

In some instances, the critical issues are process-related, e.g. for parenteral injections. However, in others the properties of the materials used to manufacture the product, the API and excipients, will be critical for the proper functioning of the drug product once it is administered to the patient.

It is not just these categories that are associated with risk; they are associated with increased risk. All types of pharmaceutical product are associated with risk, including immediate release products. The digoxin bioavailability issues in the early 1970s [3] should serve to remind us of the potential to cause harm if we do not adequately assess what we are doing. In the early 70s we did not have the understanding we have today, and the change (increase) in bioavailability caused by changes to the manufacturing process was completely unexpected.

We have also known for some time that excipients obtained from different suppliers are not always truly equivalent. There is a least one literature report concerning the inequivalence of a gel-matrix modified release excipient [4] as was already mentioned in a previous column [5]. There are other reports showing that there can be differences between supplies of very common excipient grades obtained from reputable suppliers [6] leading to changed product performance in some way.

The risks to the patient from the inequivalence of individual excipients have been recognized for some years. What we have not done, perhaps, is looked at the wider implications, and realized that there are potential risks associated with all excipients, and all formulations. For every formulation there will be some excipients that will have a greater potential to cause failure of the formulation in some way, and thus increase the risk to the patient. (In this context, performance may be during manufacture of the drug product, during stability, or after administration to the patient. Changes in any of these may affect the patient's therapy.)

So how can we reduce the risks associated with excipients? From the author's perspective, the answer is straightforward, although not necessarily what senior management wants to hear. There is really no substitute for knowing your materials (both API and excipients), and knowing the processes used to manufacture the product. Knowing our excipients, means both technically and logistically; not only how they are manufactured and how they are used, but also how they get from the site of manufacture to the site of use. However, there are a couple of further pieces to the puzzle; we also have to understand how the excipients and processing interact, and what can go wrong and why.

> "Quality risk assessment, when used properly, can be a very useful tool in maintaining the quality of pharmaceutical products."

If we now focus on excipients; what are the risks that might impact the patient in some way, and how might we mitigate (reduce) those risks to acceptable levels? Please note we can neither eliminate risk completely, nor can we necessarily mitigate all risks to the same extent, and ICH Q9 implicitly recognizes this in the sections Risk acceptance and Risk control. However, we should try to reduce all risks, especially those that are assessed as being unacceptably high.

The risks related to excipients can include, among others:

- Risk of dispensing and using the wrong excipient
- Risk of dispensing and using the wrong grade of an excipient

- Risk that a particular lot of excipient is outside an unrecognized part of the Design Space (e.g. an interaction that occurs within a particular range of an excipient specification that was not included in the Design of Experiments)
- Risk of obtaining and using an adulterated excipient

The first two items on the above list really come down to the user's internal quality management system. The latter two items require a lot more effort on the part of the excipient user.

It is up to the excipient user (pharmaceutical product manufacturing site/product license holder) to assess and reduce the overall risk to an acceptable level. The overall risk is the sum of the individual risks, and the individual risks according to ICH Q9 (as stated above) are a combination of the likelihood and severity. ICH Q9 also recognizes that detectability may be a factor in the estimation of a particular risk.

The first part of any approach to risk reduction or mitigation is to assess the potential risks inherent in a particular product (risk assessment), and this must obviously include an assessment of the risks linked to the excipients. This is where 'know your excipients' really becomes important, because the more we know and understand about the excipients we use, the better we will be able to assess the potential risks. To emphasize what has been stated above, the knowledge and understanding of our excipients must include both the technical issues and the logistical issues; the logistical issues may also include how the excipient starting material is obtained by the excipient manufacturer.

ICH Q9 emphasizes that risk assessment and mitigation is usually undertaken by multi-disciplinary teams and the document gives examples of the types of people that would make up such teams including [1]:

"… e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical."

When it comes to excipients, the 'experts from the appropriate areas' should also include formulation design and development, and purchasing. Without representatives from these two particular areas, the technical and logistical understanding of excipients will probably be incomplete.

There is a second advantage in having a representative from purchasing as it emphasizes to purchasing the importance of maintaining sources of excipients. Perhaps not in major companies, and perhaps not in all smaller companies, but some purchasing agents do not always understand that there can be disadvantages to lower priced sources of excipients. The switch to an alternate source of a common excipient can cost more in production problems than is saved in the direct cost savings from the purchase of the cheaper source of excipient. However, the purchasing agent's bonus will be tied to their performance in meeting their targets as a purchasing agent, not in helping the production department meet its targets.

The major problem with excipients is that we do not know enough about them, hence the exhortation above to 'know your excipients'. Our understanding of the excipients we use is not as good as it should be. We frequently do not know why an excipient performs as it does, and we often do not know enough about excipient composition [7]. On top of this many excipients can be used in more than one type of pharmaceutical formulation, e.g. oral immediate release tablets vs. oral immediate release hard capsules vs. oral suspensions. It seems reasonable to suggest that the critical quality attributes necessary for proper functional performance might be different when the excipient is used in such different applications.So how can we undertake a proper risk assessment and implement appropriate risk mitigation strategies for materials that we do not properly understand? We have to start with the formulation (application), and look at what is likely to be important in that particular context. For example, there is no point in worrying about the compaction profile of an excipient if we are undertaking a risk assessment for a dry powder encapsulation formulation. However, bulk and tapped density and the wetting characteristics probably will be important for dry powder encapsulation (and also for tablet compaction and performance).

Once we know the application we can begin to assemble the necessary information, and to prepare e.g. an Ishikawa diagram (also known as a Fishbone diagram or Cause and Effect diagram) to visualize the process, the inputs and areas of potential risk.

Risk assessments may be carried out at any stage during the product lifecycle. It is a good idea to begin the formal quality risk assessments at the start of a development project, and to continue to update the

assessment as the project progresses. Even before we have started our laboratory experiments we can make some very preliminary assessments. For example, for an immediate release solid oral dosage form, we know that there are potential risks for product failure with the use of magnesium stearate as a lubricant. If we are looking to develop a modified release product, we know from the SUPAC Modified Release Guidance that we will need to look especially carefully at the release controlling excipients. (We also need to look at the non-release controlling excipients, and we should not forget this.) This kind of assessment will help us with the initial stages of our development work in a QbD world.

Part of the information necessary for the final pre-launch quality risk assessment is the information obtained through our design of experiments as we move up through the various stages of scale up until we have defined our Design Space that is acceptable to the regulatory authorities.

We have focused on the technical aspects of risks associated with excipients. In recent years it is the non-technical issues associated with excipients (and APIs) that sadly have captured the headlines; glycerin and propylene glycol adulterated with diethylene glycol, heparin adulterated with over-sulfated chondroitin sulfate, and pet food and milk adulterated with melamine. When we look at these incidents there are some common issues (besides greed); inadequate specifications and test methods, lack of specific id test (and often the assay as well), inadequate monitoring of supply chains, etc.

The manufacture and supply of pharmaceutical excipients is a global business, and many excipients are sourced overseas. Raw materials (starting materials) for excipients may be sourced under very primitive conditions. They may be harvested from the land or the sea or may be dug from the ground. When assessing the risks associated with excipients, the excipient raw material supply chain may need to be part of the equation. On-site audits (including third party audits) of the manufacturing site, and the immediate supplier if a distributor is involved, are of paramount importance (80-page questionnaires are no substitute). The use of pedigree documents showing the chain of custody and transportation of materials is another means by which we can assess if there is a risk for adulteration, etc.

However, we must never forget that if we want to reduce the risks from adulteration for our excipients then we need to be vigilant, not just for what has gone before, but also for what may be ahead. No one method will absolutely prevent adulteration, we need to invoke multiple measures and make it less attractive to those committing such frauds. It is not the absolute cost which drives such fraud, but the difference (premium) between industrial and pharmaceutical grades of a material, or the cost benefit obtained by being able to dilute e.g. milk by 50% and still maintain the assay (and price) due to the addition of melamine.

We have not really discussed the question of what constitutes reasonable precautions to take to reduce the risks below an acceptable upper limit. In part, there will be an economic component. The ICH Q9 document2 acknowledges this:

"The amount of effort used for risk control should be proportional to the significance of the risk."

There is also an ethical component. To paraphrase what was stated above, the patient trusts the pharmaceutical industry to provide robust reliable products that do the maximum amount of good for the minimum amount of harm. If anyone thinks that risk mitigation is too expensive, try having a product that does cause harm to patients. The key is to assess the severity of the risk and to decide what is acceptable in both the short and long term. The image of the pharmaceutical industry has suffered in recent years, mainly because companies have been perceived as having put profit before patient safety. That perception will not be altered if companies continue to be seen to place the emphasis on profits rather than mitigating the risk to the patient.

Quality risk assessment, when used properly, can be a very useful tool in maintaining the quality of pharmaceutical products. Excipients are part of the equation, and the more we know about the technical issues and logistics of our excipients, the better for the patient, the pharmaceutical manufacturer and the excipient manufacturer.

I hope this column has been a useful contribution on ICH Q9 and excipients. The next column will look at Excipient Specifications in the context of QbD.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part VIII

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Excipient Specifications

What I hope to do in this column is to go through some of the points to be considered in establishing a user specification for an excipient. However, I am going to start with some more general considerations by way of introduction, and then look at how we might set specifications for excipients.

Background

To many people, the specification defines the material. However, we all know that products made with APIs and excipients properly conforming to their specifications in all respects can sometimes fail, for reasons we do not fully understand. Sometimes the cause is human; for example, there was an error in operating the process, or taking samples. Sometimes there is no explanation, and sometimes it becomes apparent on investigation that there is some property of a component that needs to be added to the specification. This component can be the API, or it can be an excipient.

Over the past 40 years drug molecules have become more sophisticated and more potent. Manufacturing equipment has become faster, and analytical methods have become more sensitive. In general, and in this author's opinion, some formulations appear less robust. By contrast, we can argue that excipients have largely stayed the same, but we are expecting more from them. Excipients are an important part of formulation science, and it seems logical to suggest that if some of our formulations appear to be less robust, then part of the problem may lie with excipients, and in particular how they are used. And this may be a key point in some cases.

In part this may be due to the fact that formulation science is no longer taught in pharmacy schools, and has not been taught elsewhere until the recent introduction of pharmaceutical sciences curricula. Even with the recent introduction of such curricula, is our teaching about the uses and limitations of excipients sufficient for the needs of future formulation scientists? In part, it also implies that we do not understand enough about the excipients we use in the context of the modern sophisticated molecules we have to formulate. This is a theme that has been discussed before in this series of articles, and elsewhere [1].

Excipients, are an important part of any pharmaceutical formulation, and are an important part of the Quality by Design (QbD) design space. Not all

excipients will have a critical impact on the performance of a particular pharmaceutical product. For those that do have a critical impact on the performance of the pharmaceutical product, they need to be built in to the design space in some way. In order to incorporate the excipient into the design space, we need to understand what aspect of the excipient specification is responsible for its impact on the formulation, and how it varies. Sometimes it appears obvious, sometimes it is less obvious, and this is where experience and small scale experiments might be needed prior to deciding on the Design of Experiments (DoE).

What Do We Mean by Specification?

Before we can build excipient performance and variability into our DoE, we need to understand what we have. For this, we have to look at the specification; but which specification? And what do we mean by specification? If we look in the dictionary, we find that 'specification' means 'something specified' – not particularly helpful since according to the same dictionary 'specify' means 'to mention or name explicitly' [2]. A more helpful definition is presented in the Joint IPEC-PQG Guide for Good Manufacturing Practices for Pharmaceutical Excipients [3]:

'A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material'.

But what are the appropriate procedures and acceptance criteria for an excipient? The answer to this question is one of the keys to successful formulation design and development in our Quality by Design (QbD) world. Once again, I must emphasize, "Know your excipients!"

Historically, excipients have mostly been sold and purchased to rather broad specifications (also referred to as the sales specification). Typically this is the specification contained in the pharmacopeial monograph (compendial specification), or something analogous for excipients that do not have a pharmacopeial monograph. However, compendial specifications were often set many years ago, and may have been deliberately set wide because process controls and test methods were less precise than they are today, or there was some variability observed and the wide limits were designed to allow for that. In a QbD world such wide limits may not always be appropriate.

Besides the sales specification there can also be other types of specification associated with an excipient; these may include: in-process specification, manufacturing specification, customer specification, end of shelf-life specification, etc. In general, the sales specification will be wider than all these other specifications. If it isn't, then it is likely that the excipient will not routinely meet specification, and then there will probably be problems with excipient lot selection and inventory control.

The most important specification in a QbD world is the customer specification. What does the customer want? Unfortunately, the customer does not necessarily know what they want, and we end up with two extremes. There are customers who will simply accept the sales specification for the excipient and assume (hope!) the excipient performs consistently. Other customers try to over specify their excipient requirements in the mistaken belief that by tightening the specification they can somehow cancel variability. This belief is based on the misunderstanding that the variability in the product is due to the variability in the excipients. (In the author's experience, the active pharmaceutical ingredients are often more variable from a physical perspective than excipients.)

For some applications there will be no problems that can be attributed to excipients. The formulation is sufficiently robust to accommodate the variability in the API and excipients. However,

> "Excipients are an important part of formulation science, and it seems logical to suggest that if some of our formulations appear to be less robust, then part of the problem may lie with excipients, and in particular how they are used."

for other formulations there will be unexplained failures and out-of-trend results some of which may eventually be assigned to an excipient. Then the fun begins as the customer and manufacturer try to resolve matters, and arrive at a workable specification. The emphasis is on 'workable' because it will inevitably be a compromise. There is inherent variability in all manufacturing and excipients are no exception. We must also remember that the scale at which most of the common excipients are manufactured, and how they are manufactured (using some form of continuous processing) mean that it is not always possible to control things to the level the customer may desire (think they need).

Setting Excipient Specifications

So how can we set good specifications that the excipient manufacturer can meet on a routine basis, and that allows the customer to have confidence that the excipient will perform satisfactorily in the manufacture, storage or use of the finished pharmaceutical product? There are two interrelated components; the inherent capability of the excipient manufacturing process, and its inherent variability, and the factors in the formulation and processing, and how they interact, in the manufacture of the pharmaceutical finished product. However, this almost becomes a circular impasse; we need to know what influences the formulation before we can begin to put together a meaningful specification for the excipient, but we need to understand the inherent variability of that particular facet of the excipient before we can build it into the DoE.

In practice, we need to understand what we are looking to achieve and how the excipients can be used, in particular any limitations on their performance (again, "Know your excipients!"). Then we can begin to make some progress. In a QbD world we are not going to pull our DoE out of the air. We are going to undertake what effectively amounts to a risk assessment to decide which particular properties of an excipient are likely to have a major influence on a particular characteristic of the pharmaceutical finished product. In other words, even before we start any practical work, we are going to consider all the attributes of all the excipients and the API and look to see if there is a reasonable likelihood that they can influence the quality target product profile (QTPP). Then we can begin to establish our DoE. It may be appropriate to carry out some limited preliminary experiments to examine the influence of a particular excipient property to see if it should be classified as a potential critical quality attribute (CQA).

> "In most instances in oral solid dosage forms, particle size is a factor that should be investigated for most excipients."

It seems that there may be some confusion that everything has to be built into the DoE from the outset. That is not what the FDA requires. What is required is that we should be able to justify our formulation design space, and the DoE will obviously be a major part of the justification. However, there is nothing to stop us performing some preliminary experiments to clarify issues, but we should document what we do and include those preliminary experiments in our justification. We can also use literature reports, internal company reports and our own experience to justify the DoE, and this is where our risk assessment fits in.

In a QbD world, we formulation scientists need to get a lot smarter at setting specifications for our excipients, but we must not over-specify because that may hurt us in the longer term. There is no point in trying to impose a specification that the excipient manufacturer cannot meet on a routine basis. As has been discussed elsewhere [4], it is a disaster waiting to happen. I have discussed in previous column the perils of excipient lot selection. In order for it to work about 50% of the manufactured excipient lots should comply with the required specification.

So what is the best recourse if you find that you have a formulation problem requiring excipient lot selection that does not meet the above criterion? There are really only two options besides accepting excipient lot selection. One option is to reformulate the product to include an alternate excipient or combination of excipient and processing that can accommodate and neutralize the unacceptable variability. The second option is to look at the API because it is presumably some interaction, direct or indirect, that involves the API. Is it possible to engineer the physical form of the API in some way to allow the manufacture of a pharmaceutical finished product with more consistent performance during manufacture, on stability or after administration to the patient? Unfortunately, both options require time and resources and senior management is usually unsympathetic to such delays. This is where QbD should really help because, if done properly, it can help us to avoid such late reformulations.

Assuming that we have developed a robust formulation using an appropriate DoE, what should we include in our excipient specification? Let us look at the requirements for the API and drug product. We are concerned with four things: purity, efficacy, safety and that the product has been manufactured to the appropriate levels of good manufacturing practice (GMP). With excipients we should not be concerned with efficacy; excipients should not possess therapeutic efficacy, although they may have physiological effects. However, we are concerned with purity, safety and GMP. In addition, we are concerned with the performance of the excipient (how it works, and how consistently it works in our formulation).

Based on these considerations, we can begin to define what tests and limits need to be included in our specification for the excipient; we need to include tests that address chemical composition, tests that address the physical form of the excipient, and possibly tests that address performance. Excipient composition was discussed in

a previous article in this series [1]. Understanding and monitoring excipient composition will address the issues of purity (do we have the correct chemical material?) and safety (are there undesirable toxic components present in the excipient above the recognized safe limit?) These types of tests are often those included in the main part of a pharmacopeial monograph.

The tests for physical form include those tests that are typically contained in the Labeling Section of a USP-NF monograph. These labeling requirements are generally tests that can be used to distinguish between different physical grades of a pharmaceutical excipient that are commercially available. These will relate to performance in some way, otherwise why would there be different grades? But there may be other, more relevant tests that relate to performance that are not included in the labeling section; possibly composition tests, possibly tests that are extra to the monograph. We must remember that excipient performance can relate to manufacturing, stability or in vivo release of the API from the pharmaceutical finished product.

Some excipient monographs of the European Pharmacopoeia contain non-mandatory sections relating to functionality-related characteristics (FRCs). This approach is not an option in the US. There cannot be a non-mandatory section in a USP-NF monograph. In the USP-NF, any such tests might be included in the labeling section, if appropriate.

Before we include any customer specific requirements in our monograph, we need to know what we are dealing with, and what control the excipient manufacturer has, if any, over the particular parameter. As stated above, it does not make sense to include parameters or limits in our specification that the excipient manufacturer cannot meet. Let me illustrate this by way of an example.

In most instances in oral solid dosage forms, particle size is a factor that should be investigated for most excipients. (An exception can be made for wet granulation binders that are prepared as a solution before adding to the granulator.) But before we start rushing to produce tighter particle size specifications for all our materials we need to take a step back, and look to see if the excipient manufacturer has any control over particle size. I can already hear people asking, "But why wouldn't they?" For many materials they do, but if we think about the starches, does the starch producer control the size of the starch grains, or does Mother Nature? The answer is that the size of the starch grains is a function of the plant source (species) and the growing conditions, and will vary from season to season and region to region. When we process corn, potatoes or any other starch source to obtain the starch, all we are doing is releasing the intact starch grains, not changing their size. If we did change their size we would be likely causing irreparable damage to them, and destroying the very characteristics we are looking for in order to use the starch as an excipient. The lesson here is to only specify what can be controlled during manufacture, but perhaps to monitor what cannot be controlled.

So to get to where we want to be – a 'workable' specification that the manufacturer can meet and that will provide an excipient that the user can accept and rely on, we need to include sufficient tests in the specification to meet the requirements of composition and safety. We may also need to include tests that will distinguish between different physical grades of the same pharmaceutical excipient. The key question is what tests beyond this should we include? My answer would be as few as possible. There will be times when this will be necessary, but they should be exceptions rather than the norm. For example, special limits on trace components to improve stability could be considered, provided the excipient manufacturer is confident they can meet them as required. However, trying to include as many extra parameters as possible in the hopes that you can avoid some as yet undiscovered problem is, in my opinion, a pointless exercise that may cause the user more grief than benefit. The old adage, "Be careful what you ask for!" is very relevant, because if we ask for it, and put it into our application, we will have to live with it. For excipient specifications, as for many things, the 'kiss' principle applies (Keep it simple, stupid!). In my opinion, we should be looking to use QbD to avoid the need for too many customer-specific tests and limits in our excipient specifications.

I hope this article on excipient specifications has been helpful. Some of the ideas may be controversial to some of you. They are offered in the spirit of helping formulation scientists, and others, understand that although they do not treat disease or improve patients' quality of life, we formulation scientists had better take our excipients seriously and recognize that they have limitations, as do excipient manufacturers. In the next article of this series I will consider new excipients.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part IX

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New Excipients

Introduction

*T*his installment of the column is a little different. I hope to address some of the issues with new excipients. In general, it appears in recent years that small molecule drug candidates have become more sophisticated and chemically complex. There has been an increase in molecular weight, with a commensurate reduction in solubility, and newer drug molecules maybe less stable (more prodrugs). We continue to need new excipients. I think all formulation scientists would agree that, despite the number of excipients available (perhaps 1500 or so by current estimates), there are still gaps in the range of excipients available. We need new excipients to cope with the increasing number of poorly soluble and more labile compounds, and also to allow manufacturing and filling equipment to operate at high speed. There are also existing deficiencies, such as a vehicle for oral solutions that is not cariogenic and does not have a laxative effect, and a soluble tablet/capsule lubricant that is as effective as magnesium stearate, but is non-irritant to mucosal tissues and the eyes. These gaps have been known for many years, and perhaps one should ask if they are still worth pursuing, or if they are in fact impossible dreams. (Contrary to the traditional definition of excipients as 'inert carriers', excipients can have physiological effects, some more obvious than others, and perhaps we are coming up against a physiological barrier.)

Some years ago I gave a series of presentations and wrote a paper on the future for new Excipients [1], which suggested we were unlikely to see very many new chemical excipients because it was a difficult economic proposition. It seems appropriate to revisit this topic, in part to see whether much has changed, and in part to reflect on the needs of formulation scientists and manufacturing scientists as we embrace Quality-by-Design (QbD) and accommodate the trends in drug candidates. In general, as I shall explain, QbD may provide more impetus to the introduction of new excipients and/or new grades of excipients.

Before we consider the progress that has been made, we need to take a step back and look at the definition of new. For excipients, 'new' can be defined in several ways, according to the context, including:

- A new chemical material, never before used in man or animals, e.g. ß-cyclodextrin sulfobutyl ether.
- New semi-synthetic derivatives of existing types of materials, e.g. different semi-synthetic fatty acid triglyceride esters such as the polyethylene glycol ester of hydroxystearic acid.
- An excipient that has been used in animals (veterinary medicines) and now being proposed for use in humans.
- An existing excipient that has been used in man, but is now proposed for a new route of administration, e.g. ß-cyclodextrin sulfobutyl ether for oral use.
- A food material that is now proposed as an excipient for oral use, e.g. ceratonia (locust bean gum).
- New chemistry, e.g. degree of substitution, for an existing semi-synthetic or synthetic excipient.
- A new botanical source for an existing excipient, e.g. hardwood-derived vs. softwood-derived microcrystalline cellulose.
- A new physical grade of an existing excipient, same route of administration, same botanical source, e.g. large particle size grades of microcrystalline cellulose, low density grades of microcrystalline cellulose.
- New co-processed combinations of existing excipients, e.g. silicified microcrystalline cellulose, mannitolized microcrystalline cellulose, combinations of lactose with powedered cellulose, microcrystalline cellulose, or corn starch, etc.
- An alternate manufacturing source for an existing excipient, e.g. the alternative sources of microcrystalline cellulose, etc.

As we can see, there have been examples of many of these categories in the past 25 years.

We use excipients, along with appropriate processing, to convert active pharmaceutical ingredients (APIs) into medicines that then patient can use. Unformulated APIs are mostly quite inappropriate for use by the patient. We formulate APIs into drug products to make them acceptable to the patient or care giver, and much more convenient to use. From a QbD perspective, what we are looking for is consistency, both in chemical and physical attributes, and in performance.

If we consider the list of definitions of 'new' given above, and look at the number of 'new' excipients that have reached the market in the past 25 years, we can see that most effort has been concentrated in a few areas. In particular, new grades of existing excipients have emerged, and also new co-processed combinations of excipients have been introduced. There are good reasons for this. The introduction of a new chemical excipient is expensive and uncertain, and there must be a compelling unmet technical need that overrides the natural conservatism of most pharmaceutical companies when it comes to innovation outside API molecules. However, there have been some limited successes in introducing new chemical excipients such as ß-cyclodextrin sulfobutyl ether and the polyethylene glycol ester of hydroxystearic acid.

New Chemical Excipients

New chemical excipients will continue to be needed. New grades of existing materials and new co-processed combinations of existing excipients will still have the same drawbacks, e.g. incompatibilities,

they have always had. One of the few ways to reduce incompatibilities is to change the chemistry, i.e. develop a new chemical excipient.

It is worth considering briefly how both ß-cyclodextrin sulfobutyl ether and the polyethylene glycol ester of hydroxystearic acid. gained acceptance. They did not achieve acceptance in the US market in quite the same way.

ß-cyclodextrin sulfobutyl ether was developed some years ago now, specifically to address drug solubility issues, and to overcome some of the issues relating to the existing ß-cyclodextrin materials. But how did it get into two marketed products? There are several things that must come together for a new excipient to be used/approved for use in a pharmaceutical product. We have already mentioned the unmet technical need. In addition, there must be sufficient confidence in the safety of the excipient, and there needs to be someone in the company developing the new drug to act as 'champion' for the new excipient, i.e. sufficiently senior and sufficiently convinced of its potential to promote its use for the project. All this happened with ß-cyclodextrin sulfobutyl ether. In addition, both the drug developer and excipient manufacturer worked closely together to obtain the requisite safety data.

The polyethylene glycol ester of hydroxystearic acid is a more recent introduction to the US market, and its use in a medicinal product and approval took advantage of recent developments in the regulatory area for excipients. Since ß-cyclodextrin sulfobutyl ether was included in the formulation of an approved medicinal product, there have been some developments that have helped clarify the FDA's expectations and also to provide support to both developers and users of new excipients.

The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) produced a guideline on the safety studies required for new chemical excipients that was published in 1996 [2]. (The United States Pharmacopeia also has General Information Chapter <1074> Excipient Biological Safety Evaluation Guidelines which is similar to the IPEC-Americas recommendations.) The FDA then issued their Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, initially as a draft, which became final in May 2005 [3], the requirements of which were very similar to the IPEC-Americas recommendations published earlier. However, the FDA Guidance Document rightly carries much more weight. The important point was that we now had a defined set of studies that was required to be carried out on the new excipient. Prior to the publication of the IPEC-Americas recommendations and the FDA Guidance there was nothing established for the evaluation of new chemical excipients.

However, it was still a big leap of faith on the part of a pharmaceutical company to accept a brand new chemical excipient for use in a potential new drug. There are many things that can go wrong during the development of a new drug candidate, and many of the same issues can arise during the development of a new excipient candidate. However, the real issue was not how well the new excipient would perform in the formulation, but its safety. There was the question of how the FDA reviewer would regard the data, particularly the safety data, and whether or not the safety package would be accepted. There is now a scheme set up by IPEC-Americas whereby excipient safety packages can be reviewed by an independent panel of toxicologists to assess whether or not the safety package would, in the opinion of the independent experts, be likely to be accepted by the FDA review staff. The first materials to be assessed using this scheme was the polyethylene glycol ester of hydroxystearic acid. In this particular instance, the FDA agreed to review the findings of the expert panel to provide a further independent assessment of the scheme. The expert panel review of the polyethylene glycol ester of hydroxystearic acid was well received by the Agency.

Co-processed Excipients

One major area of innovation in excipient technology has been in the development of co-processed excipients. The regulatory hurdles are much reduced, although other hurdles remain such as the very conservative nature of the pharmaceutical industry, and its reluctance to accept anything 'new'. Co-processed excipients are not new. Some have been available for many years. What may be changing is the general attitude to co-processing on the part of the pharmaceutical industry. There appears to have been more acceptance of co-processed materials in recent years. In the past the perception was that there was little no benefit in co-processed excipients for the innovator companies. This seems to be changing, in large measure because of examples of co-processed excipients whereby the same performance cannot be achieved by combining the components using unit processes typically of the manufacture of pharmaceutical finished product.

Acceptance still requires that there be an unmet technical need, but the height of the regulatory and safety barrier is much lower (but not absent). The key distinction between new chemical excipients and new co-processed excipients is that the primary components of co-processed excipients should not be combined using covalent bonding. However, there still needs to be a safety assessment, but this assessment may be more of an analytical investigation to confirm the absence of significant covalent bonding, thus allowing bridging to the safety studies and data for the individual component excipients. Tobyn and co-workers published an example of the types of such analytical bridging studies [4]. In summary, using a range of different spectroscopic analytical techniques, the authors were able to demonstrate that the combination of microcrystalline cellulose and colloidal silicon dioxide in silicified microcrystalline cellulose was not covalently bonded, thus confirming the link to the safety data for the component excipients.

Economic Considerations

The economic factor is also important. It can cost USD20 – 30 million to undertake all the safety studies required for a new chemical excipient, depending on the route of administration, and then there is the cost of the CMC (Chemistry, Manufacturing and Controls) part of the project. This will all be reflected in the commercial cost of the excipient. There is a further economic component that is sometimes forgotten; for new drug products there is the possibility of an extension of patent exclusivity under the Hatch-Waxman rules because of long development times. No such extensions are available for new excipients. Without some form of combination safety evaluation ('piggy-back' study), as was done for ß-cyclodextrin sulfobutyl ether, the patent of the excipient may well have expired before commercial approval of the first drug product [1].

Co-processed excipients, by contrast, are less expensive to develop, and can be introduced without having to undertake an expensive and long safety evaluation. Thus, a much longer proportion of the patent exclusivity will be available at commercial launch. Co-processed excipients are thus a more attractive proposition for excipient companies, and this is reflected in the relative numbers new excipients introduced compared to the number of co-processed excipients introduced commercially since 1995.

Implications of Pharmaceutical Formulation QbD for New Excipients

The principles of QbD can be applied to any development project, including the development of new excipients. However, the objective of this paper is to consider the implications of pharmaceutical formulation QbD for new excipients. As has been stated many times and by many authors, we use excipients to help convert active pharmaceutical ingredients (APIs) into medicines that the patient is able to use conveniently. Pharmaceutical formulation QbD requires that we have better understanding of our materials (including APIs) and processes. In a QbD development program it is likely that information on the API will be more important than ever, particularly the information concerning potential degradation pathways and incompatibilities. This suggests that formulation development groups will focus sooner on the short comings of the available range of excipients. Might this lead to requests for the development of new excipients or new grades of excipients?

It seems logical to suggest that there may be opportunities out there for new materials. However, there will need to be a balance between what the user is willing to pay, and the cost of manufacture and economic viability. If the excipient cannot be manufactured at a price that the market can support, then it is not a viable project.

New grades of existing materials may be a further opportunity. This is where our understanding of our excipients becomes important. The mantra "Know your excipients!" cannot be emphasized enough; we can never know too much about our excipients. Most excipients for non-parenteral applications (and even some for parenteral applications) function because they are not single compounds, but are de facto combinations of materials. They will contain the nominal component, but they will also contain other components that are necessary to achieve the requisite performance. Sometimes it is these minor (concommitant) components that are responsible for drug excipient interactions and eventual stability problems. Is there a way to remove the offending minor component(s) without compromising the performance of the excipient in the particular formulation? This could create a new grade of an excipient; perhaps specific to a particular customer; a 'designer excipient' if you will. Such an approach may not work for every excipient, but it may be possible for some.

Again, the economics will be an important factor in the success of such a project. However, there are also a couple of other factors that must be taken into account; the willingness of the formulator company and the excipient manufacturer to communicate effectively, and the willingness of the excipient manufacturer to look at such projects. In the past the excipient manufacturers have been willing to look at changes to particle size distribution, for example, but what is suggested here concerns extra processing steps, and perhaps different processing in part. Looking forward, there may be intellectual property benefits for both the product manufacturer and the excipient manufacturer.

Pharmaceutical formulation QbD is a great opportunity for the formulation scientists carry out projects in a more scientific manner. There may also be opportunities for excipient manufacturers to become more involved and develop better, more lasting relationships with their customers by providing a more individual service.

I hope this paper has provided some food for thought. It is a departure from the main stream QbD, but I think it is a topic that needs to be considered in the context of new pharmaceutical product development and QbD. The next, and final, installment of this series of articles will address the issue of continuous manufacture of pharmaceutical products.

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Functionality and Performance of Excipients in a Quality-by-Design World: Part X

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Continuous Processing of Pharmaceutical Finished Products

Introduction

*I*n this paper, I plan to discuss excipients and Quality-by-Design (QbD) in the context of the manufacture of pharmaceutical products using continuous processing. Continuous processing is not new; it has been around for many decades. It is just that the pharmaceutical industry has been even more reluctant to consider it than they have QbD. (QbD has only been around as a concept since the mid 1980s [1]; continuous processing has been around for a lot longer.) The reasons for this slowness to adopt new technologies and concepts in general are worth exploring because, in my opinion, they may provide some understanding of how long it could take for QbD to become generally accepted. (But hopefully it will be much quicker because continuous processing can bring real benefits to the pharmaceutical industry.)

The pharmaceutical industry has always hidden behind a façade that we cannot change things because the Food and Drug Administration (FDA) will not accept it. If this was ever the case, it is not so today. In my opinion the FDA has always tried to provide Regulations and Guidances that are not prescriptive, but simply set out the minimum standards the industry is expected to attain. However, the Agency rightly has an expectation that a certain standard will be achieved. Unfortunately, we have two things that work against that concept; the 'corner-cutters' and the 'dinosaurs'.

There are people who will always seek to cut corners, or otherwise undermine the regulations, to maximize profits at the expense of patient safety (e.g. the generic drug scandal). The Agency has therefore responded to such events with tighter regulations and more specific Guidances. The FDA's mandate is to protect the public health, and they must respond to such threats, and be seen to respond to them. But the Agency has also responded to strong scientific justification and withdrawn a Guidance document that was found to be flawed. They withdrew the Blend Uniformity Guidance in the light of the work carried out by the Product Quality Research Institute (PQRI) Working Group, and we now have a better, scientifically-justifiable approach.

There are some people in the pharmaceutical industry who may be likened to 'dinosaurs'; not in age, but in thinking. They are not comfortable unless they are told exactly what to do; i.e. they do not have to think about how to justify their decisions. They prefer to work to a very detailed Regulation or Guidance. The following quote from Leonardo da Vinci (1452 – 1519) is as relevant today as it was in the great man's day:

"Anyone who conducts an argument by appealing to authority is not using his intelligence; he is just using his memory."

When validation was first proposed there were no detailed requirements; the wording was a lot more flexible. The pharmaceutical industry; however, went back to the FDA and asked how many batches they should make as part of a validation program. The FDA gave a number which, although statistically correct, was not well received, and we arrived at the 3-batch validation paradigm we still use today (unless we have opted for a QbD program). Statistically speaking, three batches are not particularly useful, and it can be argued that this 3-batch validation paradigm has held back the pharmaceutical industry from adopting better concepts in manufacturing (such as continuous processing). But the 3-batch validation paradigm is easily justified by the 'dinosaurs'.

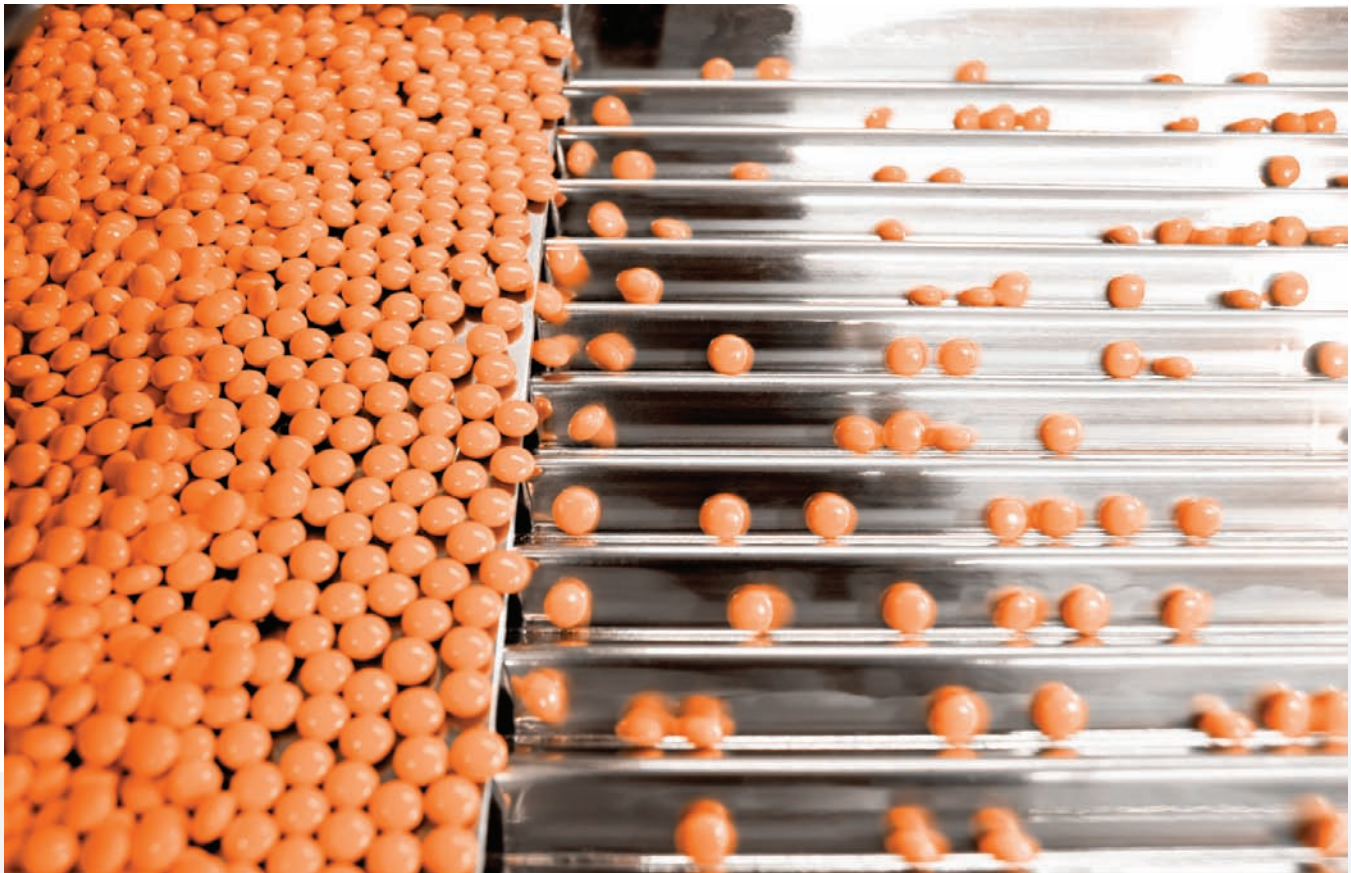
Now we have 'Quality in the 21st Century' which includes QbD and Process Analytical Technologies (PAT), and is arguably the most significant change in the pharmaceutical regulatory environment in 30 years, and which is designed to be flexible. Yet some sectors of industry are still reluctant to embrace it, i.e. step outside their comfort zone. The FDA is looking to reduce the regulatory burden on the pharmaceutical industry, but some parts of the industry it seems are not prepared to even consider it. Perhaps this is not so surprising given the history and our reluctance to accept change as a constant in life. It took several years for GMP to be well accepted; probably it will take just as long for QbD to be generally accepted.

However, there are also some people in the pharmaceutical industry who are prepared to seriously consider continuous processing. For example, Novartis has a project on continuous processing with the Massachusetts Institute of Technology. At least one other major pharmaceutical company also has an active project on continuous processing. Another encouraging sign is that some of the pharmaceutical equipment suppliers are offering continuous processing systems.

But without QbD, I am not sure that it will be easy to introduce continuous processing because we will not have the enhanced understanding of critical quality attributes (CQAs) of the active pharmaceutical ingredient(s) (API) and excipients, and critical process parameters (CPPs), and how they relate to the quality target product profile (QTPP) that QbD brings, and is necessary for the development and implementation of an adequate Design Space to achieve a robust continuous manufacturing process for a pharmaceutical product.

Continuous Processing

So why should we consider continuous processing? Quite simply, it is a logical extrapolation/conclusion from the combination of the QbD and PAT concepts. In addition, scale up of manufacture becomes much simpler (scale up of continuous processing means running the process for longer), operator safety is enhanced, and the opportunity for operator error is removed. With proper development of robust formulations through the application of the principles of QbD, and the requisite controls linked to PAT, there is every reason to believe that the finished product manufactured using continuous processing will be less variable than product manufactured using traditional batch processing. Mollan et al. [2], and Trout [3], among others, have reviewed the advantages of continuous processing.



The principles and details of continuous processing, as they might apply to pharmaceutical product manufacture, have been worked out in other industries, notably the food processing industry, but also the fine chemical industry. As was explained in an earlier article in this series [4], many pharmaceutical excipients are manufactured using continuous processing. It is also interesting to note that some of the unit processes and equipment used in pharmaceutical product manufacture are inherently continuous such as tablet machines, encapsulation machines, roller compaction, milling, sieving, spray drying, bottle filling, etc. Some of the current batch unit processes and equipment can be adapted to continuous processing, e.g. material dispensing, wet granulation, powder blending, liquid mixing, fluid-bed drying, film coating, etc.

Two of the key points to be resolved for any continuous processing operation are the time to achieve 'steady state' at start-up, and when the steady state conditions are no longer maintained at shut-down. These will both directly relate to the amount of reject material at the beginning and end of a run. There may be ways to minimize this wastage using a combination of engineering design and equipment control. A third key component will be the effective integration of the different units in the equipment train with the appropriate PAT systems and control systems.

However, the transition from a batch manufacturing process to a continuous process for a pharmaceutical finished product may require that we re-think exactly how we do things so that we can get maximum benefit from continuous processing. For continuous processing we need to think about processing in a different way, and we should be asking and answering the following questions (and probably others too):

- What are we trying to achieve?
- How does the process or equipment operate, and what are the limitations of the process or equipment?
- What are the properties and limitations of the materials? (Know your excipients!)
- What else do we need to do to make it work in a continuous process?
- Can we adapt the batch process to a continuous or semi-continuous process (several smaller units operating in parallel, but staggered, referred to as a 'multi-cell operation')?
- Are the individual units of the equipment train matched for throughput?
- What in-process controls (e.g. PAT) can we use, and do we need?
- How can we integrate the equipment, sensors and in-process controls effectively?

By way of an example, let us consider lubrication of a tablet or capsule powder blend using magnesium stearate. Magnesium stearate is a hydrophobic boundary lubricant that can cause problems due to over-mixing (reduced tablet strength and extended disintegration and slower dissolution). In addition, the risk of magnesium stearate over-blending is increased as we scale up. With continuous processing, scale up simply means extending the run, and the size of the units in the process equipment train will be smaller than the processing units in commercial scale batch processing. Thus once we have established the continuous process, validation will be more straightforward since there will be no further scale up.

We typically add magnesium stearate to the blend after the main mixing is complete, and then further blend for a short period to disperse the lubricant. When we lubricate a powder blend, what are we looking to achieve? Is it a homogeneous mix of magnesium stearate, or a mix of magnesium stearate that is sufficient for its intended use, and how do we achieve it? We need a mix whereby there is sufficient magnesium stearate available within a unit dose to lubricate the granule, but we do not want to over mix so that we effectively coat the total granule or blend surface with a hydrophobic layer of magnesium stearate. Neither do we want the magnesium stearate to be insufficiently mixed with the other components of the formulation such that it compromises product content uniformity. Effectively we require an incomplete film of magnesium stearate on the surface of the granule or powder blend. The way we typically achieve this in batch processing is to blend in the magnesium stearate for a relatively short time. But there may be another way; we could add a much smaller amount of magnesium stearate and blend for longer. For continuous processing the latter may be the preferred option.

However, conversion to continuous processing will seldom be easy, and we must consider how we can best make it work. We must first consider what project-specific information we need to have the best chance of success. The detailed requirements will need to be assessed on an individual project basis. We would not expect to need the exact same kind of information for every project; the API, formulation and route of administration together will influence the details of the information required. However, in general terms, we will require the QTPP and a robust formulation and process.

The QTPP provides the details of the release specification for the formulation and thus sets the acceptance criteria.

A robust formulation and process can be defined as;

A formulation and process which together provide for the manufacture of the drug product, and which together are able to accommodate the normal variation in both APIs and excipients without compromising any aspect of the safety, efficacy and purity of the drug product during manufacture, stability, in vivo performance of the drug product, or any other attribute of the drug product critical to the patient's care and well-being.

Excipients in Continuous Processing

As with any formulation and manufacturing process, excipients will be an important part of, and have a significant influence on, the design of a robust formulation and continuous manufacturing process for a medicinal product. As with batch processing, we will

have to deal with the inherent variability of our excipients (as well as with the API). This will not change, and cannot change. This is why we need better understanding of our excipients, and particularly their variability and limitations.

So how do we accommodate such variability into continuous processing? There are at least two approaches:

- Use the multi-cell approach and appropriate end-point detection to ensure the output from the particular unit process provides a consistent input to the next unit process in the process chain.
- Design the formulation and process so that we can achieve a degree of over-processing that still gives a satisfactory output, and that provides a consistent input to the next unit process in the process chain.

An example of the application of the multi-cell approach could be wet granulation, where three or four small high-speed mixer/granulator units are used in staggered rotation and the granulation taken to its end-point for each small granulation before being transferred to the next unit in the equipment chain for subsequent processing.

An example of deliberate over-processing would be the magnesium stearate lubrication example cited above.

However, we will need the better understanding of our excipients, because without such enhanced understanding, we will not be able to establish our design space that will allow us achieve a robust formulation and process. Without a robust formulation and process and its inherent design space, it is unlikely we will be able to establish a continuous process that is sufficiently robust for the needs of the pharmaceutical product, and ultimately the patient.

The problem of establishing the design of experiments and thus the Design Space, and particularly how to incorporate excipient variability into the design of experiments, is always going to be a factor in any QbD development program. As has been stated in a previous article in this series, if we think about what we are trying to achieve, and the opportunities QbD affords, there should be no need for the formulation developer to be looking to obtain lots of excipient at the limits of specification; they are unlikely to be available, and QbD provides us with better options [5]. As stated in the previous article, these options include:

- Alternate grades (based on the distinctions used to separate the grades on the market; and including use of a technical grade material that has a different set of specifications).
- Blending different grades.
- Fractionation of the grade (e.g. sieve fractions).
- Dilution (using some inert material).
- Using chemically different but closely related materials (e.g. polymers with different degrees and ratios of substitution).

We also have the option, in principle, to develop formulations that deliberately use two grades of an excipient, or even two different excipients, in combination to balance out variation in e.g. another component such as the API. However, it is difficult to see how this might apply in continuous processing, except possibly in a multi-cell approach. Over-processing in some way may be easier to implement in continuous processing.

Conclusion

To achieve a successful implementation of continuous processing for pharmaceutical product manufacture, as with QbD, a better understanding of the excipients we use will be a key component of that success. This understanding will probably include a better understanding of how excipient chemical composition and physical structure relate to performance. It will include a better understanding of the limitations of our excipients, and probably how these limitations relate to chemical composition and physical structure. Superimposed on all this is excipient variability, and we have to develop formulations and processes that are able to routinely accommodate the inherent variability in all our component materials, rather than try to restrict it through overly tight excipient specifications that cannot guarantee continuity of supply of our excipients, and thus products for the patient.

Continuous processing is in the future still, but the FDA has given the pharmaceutical industry the tools with the introduction of the QbD and PAT concepts. It is now up to the industry to make it work. However, we will still have to justify our implementation and our decisions and choices for the formulation, processing and equipment train using hard science-based principles. This will always be the necessary.

This was the final article in this series on Excipients in a QbD World. I hope this article and the preceding ones have provided useful information for you, and provoked useful discussion. I would like to thank the Editors and Russell Publishing for the opportunity they have provided, and you for reading these articles.

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