

Functionality and Performance of Excipients in Quality-by-Design World Part 4: Obtaining Information on Excipient Variability for Formulation Design Space

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The 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).

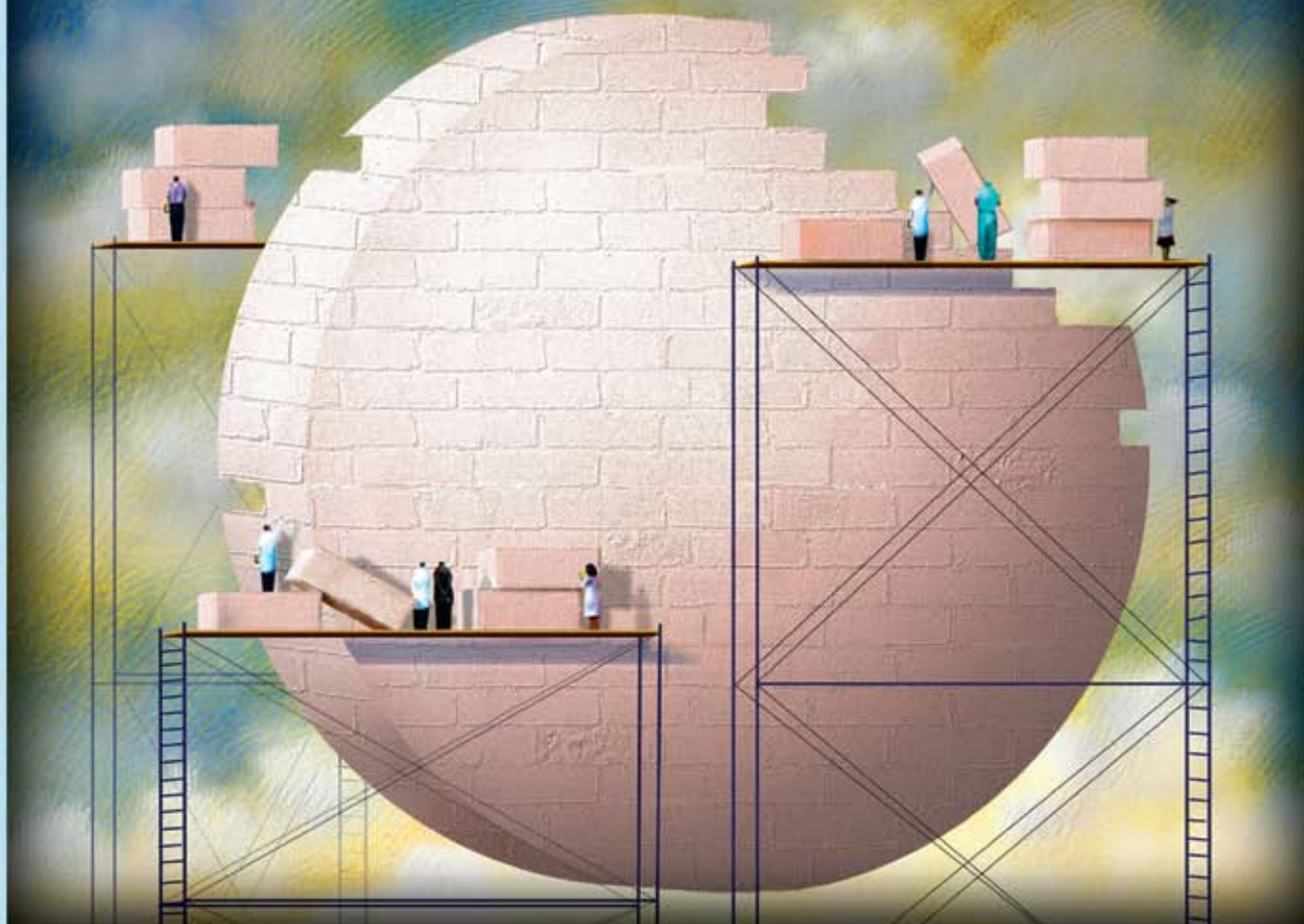
So how can we gain the necessary knowledge and understanding of excipients? At the moment, I hear the same complaint from different sources; it seems that everyone complains that we do not have enough information about excipients. In some ways I agree, but very rarely have I heard of a drug development 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

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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:

1. What information do we need to develop robust formulations?
2. Where might the information be stored?
3. 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?

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

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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 going 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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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,

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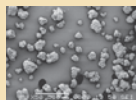
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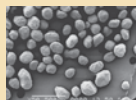
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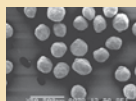
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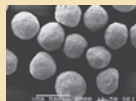
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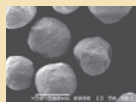
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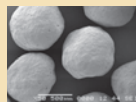
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