# MANAGING EXCIPIENT TESTING:
# FUNCTIONAL AND SAFETY TESTING IN A GLOBAL MARKETPLACE

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Webster's Dictionary defines an excipient ingredient as a "usually inert substance that forms a vehicle, as for a drug," implying that the lack of bioactivity makes the inert ingredient a simple filler. The active pharmaceutical ingredient receives all the glory, while the "inert" compounds added to the blend are largely insignificant.

## THE ROLE OF PHARMACEUTICAL EXCIPIENTS

However, is this a fair assessment? On the contrary, excipient ingredients do much more than act as a simple vehicles or drug diluents. They are often integral to the formulation and choosing the right excipient ingredient with the proper functional properties will make or break the efficacy of drug delivery.

Beyond functionality, these excipients are usually >99% of the formulation by weight, and as such have a high likelihood of adulterating the product if not manufactured properly. Routine and appropriate testing of these inert ingredients is critical to manufacturing safe and efficacious drug products.

## SAFETY AND FUNCTIONALITY

Of course, excipient testing is not only good business sense, it is a regulatory requirement. Global regulatory agencies require raw material testing to verify the identity and to confirm appropriate purity, strength, and quality.

It is useful to make a distinction between the functional testing and safety testing of an "inactive" ingredient. USP has published a new In-Process Revision in the Sept. – Oct. 2009 Pharmacopeial Forum. USP <1059> "Excipient Performance" is targeted for publication in USP 33 2nd Supplement. This General Information Chapter makes the distinction between functional and safety testing. It points to NF monographs for safety and basic identification tests, but it underscores that critical physical and chemical properties that influence product performance are not defined in the excipient's monograph. The vast diversity of the possible applications of excipient ingredients in different products prevents any compendia from defining all possible functional tests. Consider for example the common excipient carbomer copolymer; it can be a suspending agent, a tablet binder, or an emulsifier. Each of these attributes will require different functional testing. As a binder, you may want to confirm functionality with USP <616> Bulk Density and Tap Density. As a suspending agent, one might apply USP <911> Viscosity Test to ensure consistency in functionality testing.

USP offers some assistance in choosing the proper test. The first step is of course to understand the role of the excipient in the final formulation. USP <1059> lists 22 different functional categories, based on 5 broad categories of drug formulations (Table 1).

**TABLE 1. USP EXCIPIENT FUNCTIONAL CATEGORIES**

| TABLETS AND CAPSULES | ORAL LIQUIDS | SEMISOLIDS, TOPICALS, SUPPOSITORIES | PARENTERALS | AEROSOLS |
|---|---|---|---|---|
| Diluent | pH Modifier | Suppository Base | Pharmaceutical Water | Propellant |
| Binder | Wetting/Solubilizing Agent | Suspending or viscosity agent | Diluent | |
| Disintegrant | Antimicrobial Preservative | Ointment base | Tonicity Agent | |
| Lubricant | Chelating Agent | Stiffening agent | | |
| Glidant | Antioxidants | Emollient | | |
| Coloring Agent | Sweetening Agent | | | |
| Plasticizer | | | | |

USP recommends a General Chapter for each Functional Category. For example, Water Conductivity <645>, pH <791>, Osmolality and Osmolarity <785> for pH Modifiers, and Antimicrobial Effectiveness <51> for preservatives.

The European Pharmacopeia takes a similar view to USP regarding the importance of functionality. General Chapter 5.15 "Functionality-Related Characteristics of Excipients" became official in April 2008 and underscored the importance of the functionality testing of excipients. Although the intent is the same as USP, the presentation of information in the individual compendia is different. The European approach is to include the functional tests in the actual monographs, whether they are mandatory or not. The USP and JP approach is not to include them in the monograph unless they are mandatory. It is interesting to note that EP5.15 ends with a paragraph stressing that this difference in format should in no way slow down harmonization of excipient monographs, and that the "different legal environments of the 3 pharmacopeia allow for different formats of the monographs without affecting the international harmonization status."

## THE GLOBAL MARKETPLACE AND EXCIPIENT TESTING

It is encouraging news that harmonization is proceeding unimpeded by regional preferences for monograph styles. Choosing the proper tests to qualify excipients in a global marketplace is no easy task. As already indicated, one must tailor tests to match the ingredient's intended function.

What about local requirements for safety testing? The tests required for the same ingredient often differ in Europe, US, and Japan. There are occasions when the same excipient must be tested 3 times to enter the 3 major compendial markets. Fortunately, continued harmonization of the 3 major pharmacopeia will help resolve this dilemma. Unfortunately, harmonization is a slow process. Table 2 outlines the harmonization process.

## TABLE 2. HARMONIZATION PROCESS BETWEEN THE 3 MAJOR PHARMACOPEIA

| | |
|---|---|
| **Stage 1:** Identification | Based on input from users, PDG (Pharmaceutical Discussion Group) identifies monographs and general test chapters worthy of harmonization. One of the three pharmacopeia is assigned as coordinating pharmacopeia for that assignment. |
| **Stage 2:** Investigation: | Coordinating Pharmacopeia collects information of the 3 existing specs, grades of marketed products, and analytical procedures. It then prepares a harmonized monograph, along with rationale and validation data. |
| **Stage 3:** Expert Committee Review | Each of the 3 P's take the draft and forward to their respective expert committees. Comments are collected, and a commentary on the comments is put together, and sent to the secretariats of the other pharmacopeia. |
| **Stage 4:** Official Inquiry | The draft and commentary are published in each pharmacopeia's respective forums. Readers send their comments, comments are reviewed by each pharmacopeia, which in turn analyzes, consolidates, and submits comments to coordinating pharmacopeia. The coordinating pharmacopeia then prepares another draft and another commentary on the comments. |
| **Stage 5:** Consensus: | The draft is now reviewed and commented by the other two PDG pharmacopeias. All three now struggle for consensus. |
| **Stage 6:** Regional Adoption and Publication | If there is consensus, each pharmacopeia incorporates the harmonized draft to its own procedures. Users are appropriately informed. Once the text is official in all three pharmacopeia, the chapter or monograph is considered harmonized. |
| **Stage 7:** Inter-Regional Acceptance | Coordinating pharmacopeia provide documents to ICH Q4B EWG, which are evaluated and formal acceptance is posted by ICH. |

## HARMONIZATION SUCCESS STORY

Perhaps the real success story in the harmonization process is the microbial evaluation of drug products, effective January 2009 in Europe and May 2009 in the US. Previous to harmonization, raw materials were tested 3 times to enter the three different markets. Consider the process prescribed for detecting Staphylococcus aureus from an excipient sample.

**EP**
1 gm sample size
1:10 sample prep
35 – 37°C Mannitol Salt

**JP**
10 gm sample size
10:90 sample prep
30 – 35°C Vogel Johnson

**USP**
10 gm sample size
10:90 sample prep
30 – 35°C Mannitol Salt Agar

Of course, and S. aureus is S. aureus, whether it resides in Tokyo, Berlin, or Chicago. There was no scientific reason to culture them with different media in these different locations. The harmonized method is a hybrid method, taking the sample size from Europe, the incubation temperature from US and Japan, and the selective media from Europe and US.

## HARMONIZATION HOPES

The next General Test which will have the largest impact on excipient testing is USP <231> heavy metal testing. The heavy metal test is one of the most frequently performed tests in the raw material analytical laboratory. Unfortunately, the test methodology described in the current USP <231> was originally designed over a century ago. The USP admits that the method is not sensitive enough for many heavy metals, and can fail to detect mercury. The USP is in the process of updating the method and has been holding a series of workshops with the industry. The forecast is for USP to publish a method in 2010 and become official sometime afterward. A secondary benefit of the updated standards for metal impurity tests will be harmonization with Europe and Japan. Meanwhile, the manufacturer tests the same contaminant using two methods.

## MANAGING GLOBAL REQUIREMENTS AND CHANGE

Multiple monographs, non-harmonized test methods, specialized equipment, technique sensitive wet chemistry – these are considerable obstacles for the global drug manufacturer to manage. Again, excipient ingredients may play a supporting actor role, but if inadequately tested, the whole play becomes a tragedy. Contract testing laboratories are best positioned to confirm that the ingredient is safe and functional. Consider this - a drug manufacturer may see 10 or less shipments of magnesium stearate a year, a contract laboratory like SGS receives 10 shipments from hundreds of customers during the same time interval. Of the cost, 75% is in the set up and born by the first sample. Aside from batching samples to get efficiencies, a contract laboratory will have all the equipment, staffing and training necessary to perform the test. Testing is SGS's core competency, so spending for an ICP MS for heavy metal testing is a reasonable investment. However, for a contract manufacturer, the volume of heavy metal testing may not result in a satisfactory return on investment, and the opportunity cost of not focusing on discovery could be even greater. A truly global GMP pharmaceutical analytical laboratory like SGS can match the local testing needs for the global manufacturing partner. Indeed, there is a large advantage to being focused on a core competency, while achieving global harmonization with local service.

The excipient ingredients may not get the large print on the drug packaging or advertisement, but they play a crucial role. Non-functional excipients can impact the efficacy of the dosage, and adulterated excipients can have an even worse impact. It is a regulatory requirement to test these components, and as the market place becomes increasingly global and the methods begin to harmonize, partnering with a global contract laboratory is a sensible means to reduce cost and assure quality.

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