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Excipient Quality and Selection

Choosing the right excipient manufacturer can help ensure the use of quality excipients.

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Image Source/Still Factory/Getty Images;

Dan WardHow does one define quality as applied to excipients? If we pose the same question for APIs, the response would be to produce the ingredient under appropriate GMPs, and to the compendial monograph and the API assay. Because the monograph provides the minimum requirements, API quality is improved by reducing the presence of all materials other than the desired chemical. This is logical because, by definition, the API is “intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body” (1). Extraneous substances may be harmful to the patient in that they may lead to side effects, or they are inert, thus reducing API purity and thereby compromising efficacy.

Excipient quality is described quite differently. While one would again refer to compliance with the compendial monograph (if there is one) or the manufacturer’s specification, a higher assay is not always better. While this may seem counterintuitive, excipients are often complex mixtures that include constituents arising from raw materials, catalyst, solvent, initiator residue, or side reactions. The International Pharmaceutical Excipients Council (IPEC) refers to these other unavoidable substances in the excipient as concomitant components (2). The performance of many excipients in the drug formulation may rely on the presence of such substances in the excipient. Concomitant components in the excipient may aid in solvating drug components, improving excipient functionality, etc. Excipient quality, therefore, is characterized as compliance to the monograph or specification and having a consistent concomitant composition.

Specified limits for excipients

As required by clause 8.2.4.6 of the ANSI excipient GMP standard, excipient manufacturers are expected to identify concomitant components present in the excipient whenever possible and to specify limits for those components that have been shown to be either important to excipient performance or known to have an adverse impact to the patient (3). Impurities known to be present in the excipient are also required to have specified upper limits based upon safety considerations, regulatory requirements, customer requirements, and, if applicable, the compendium.

Povidone and its monograph illustrate these points. Povidone is the homo-polymerized monomer vinyl pyrrolidone. It is sold in various molecular weights. In the late 1980s, GAF Chemicals, a manufacturer of Povidone, was made aware of the presence of hydrazine, a toxic substance, in Povidone. The company identified the mechanism of hydrazine formation as a by-product of the polymerization reaction. Through modification of the process, the level of hydrazine was reduced to what was deemed acceptable for safe use of Povidone in pharmaceuticals. Because Hydrazine is not expected to be beneficial in Povidone, it is thus considered an undesirable component. A test method was developed, appropriate specified limits were established, and the compendium was updated accordingly.

In the early 1990s, vinyl pyrrolidone was identified as a suspect carcinogen. As a consequence, manufacturing methods were again modified to reduce the level of residual vinyl pyrrolidone monomer to a toxicologically safe level. Vinyl pyrrolidone has solvating properties and is a reactive molecule. Therefore, residual vinyl pyrrolidone in Povidone is more likely than hydrazine to impact performance of the excipient in some drug formulations. A test method suitable for detecting low levels of this monomer was developed, and the compendium was updated accordingly.

An additional substance, 2-pyrollidone, was subsequently found in Povidone. This substance is formed during the polymerization reaction when some vinyl pyrrolidone decomposes rather than polymerizes. While it is unlikely that the presence of hydrazine or vinyl pyrrolidone beneficially impacts the performance of Povidone in the drug formulation, the same conclusion cannot be drawn for 2-pyrrolidone. 2-Pyrrolidone is often used as a solvent, and therefore, its presence in the excipient may play a beneficial role in certain drug formulations by helping to solvate the API. While it

is possible to remove this substance through further processing, it is not feasible for the manufacturer to asses the impact on performance for all drug formulations that use Povidone. Therefore, it is important to control, but not limit, the quantity of 2-pyrrolidone so that the performance of each lot of Povidone is consistent in the various drugs that use this excipient.

Non-homogeneity
These examples with one excipient illustrate how control of all the components in the material are needed in order to assure consistent quality. Another aspect that needs equivalent control is the degree of homogeneity of solid excipients, particularly those supplied in powder form. However, many excipients are also manufactured in much larger volumes for other markets where a larger degree of variation is tolerable.

To illustrate a common cause of non-homogeneity, consider that excipient manufacture often involves drying the substance. The ability to dry material to a consistent residual moisture throughout the lot is inherently difficult due to the many operating variables. Spray drying is a case in point. Operating parameters for the spray dryer include the temperature and dew point of inlet air, burner temperature, concentration of the excipient in the aqueous solution, spray pattern of the excipient solution, rate of drying, and outlet air temperature. During a 24-hour cycle, the ambient air temperature and humidity may differ considerably from day to night. Also the excipient concentration may vary due to prior manufacturing steps. Achieving a consistent moisture level requires frequent sampling of dried material and adjustment of spray-dryer operating parameters. As drying conditions become more severe in order to maintain constant residual moisture, however, it is possible to cause some degradation manifest as charring of the excipient. This is typically manifested as burnt particles (4). Consistent moisture content in the excipient, therefore, may be a tradeoff with the quantity of burnt particles in the product.

Excipient impurities
Excipient impurities are specific entities that should not be present and/or need to be controlled for safety, toxicological, or other reasons. Common impurities in excipients, which are not needed for excipient performance, may include residual process aids, additives, by-products, and material that sheds from filter media. In addition, contaminants, which are to be avoided, can occur from environmental factors such as personnel hygiene, equipment failure, contact with packaging, etc. and include rust, oil, grease, insect fragments, extractable and leachable materials, etc.

Excipient quality is, therefore, best expressed as conformance to GMPs as well as to compendia or a specification and consistent composition, lot to lot. Consistent composition within each lot is also an expression of excipient quality, but oftentimes such consistency is difficult to achieve without a blending step.
Generally, it is expected that a more consistent excipient composition will result in a more predictable performance in the final drug formulation. In the selection of an excipient for a drug formulation, consideration should be to include an excipient whose composition profile has known and tolerable variation with minimal number of concomitant components and impurities.

Selection of excipient suppliers
The European Union *Directive Guidelines on the Formalized Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products of Human Use* (5) provides the following characteristics for assessing the manufacture and supply of excipients:

Potential presence of transmissible spongiform encephalopathy (TSE)
Potential for viral contamination
Potential for microbiological or endotoxin contamination
Potential for the presence of impurities
Supply chain complexity and security
Excipient stability
Tamper-evident packaging.

Each of these characteristics can be related to excipient “quality” and used to assess excipient suppliers. Note that each of these considerations is in addition to manufacturing the excipient in conformance to excipient GMP.

In addition, the ANSI excipient GMP standard (3) highlights the following criteria to assess for risk to protect an excipient from contamination:

Hygienic practices: excipient contamination due to personnel hygiene, illness, attire, unauthorized access, food, medication, tobacco, etc.
Infrastructure, building: excipient contamination, cross-contamination, mix-ups
Infrastructure, equipment: excipient contamination due to material of construction, utilities, water, process materials, and work environment (air handling, cleaning/sanitation, pest control and drainage).

Minimizing contamination risk
Using an excipient manufacturer that produces the excipient in dedicated equipment is a lower risk to excipient quality as a result of reduced risk of cross-contamination. Equipment can be considered dedicated when it is used to manufacture products utilizing the same chemistry and raw materials. Equipment used to manufacture an excipient in various particle size, density, viscosity, or molecular weight, therefore, can be considered dedicated. Also equipment used to produce various grades of an excipient that are then sold in different markets (e.g., food, cosmetic, or industrial applications), but produced using the same chemistry and raw materials, should also be considered dedicated.

Using dedicated equipment reduces the risk that the excipient will be contaminated by the presence of other substances (e.g., other raw material, intermediate, or finished product residue in the production equipment). Using multi-purpose equipment relies heavily on verifying cleaning effectiveness and the ability to detect potential residual contaminants to assure the minimization of potential cross-contaminants in the excipient. Where multi-use equipment is used, it is advisable to review the excipient manufacturer’s cleaning validation report.

When possible, it is preferable to source the excipient from a supplier that does not use animal-derived raw materials at risk for bovine spongiform encephalopathy (BSE)/TSE in the manufacture of the excipient. Otherwise, the excipient user will have to ensure the excipient presents minimal risk from TSE contaminants. A risk assessment should include confirmation the animals used in the manufacture of the animal-derived raw material come from a country designated as negligible TSE risk.

Alternatively, the excipient manufacturer should demonstrate that the animal-derived raw material was processed under conditions that have been defined to inactivate the TSE risk materials if present.

TSE risks are also present when the excipient is manufactured in multi-purpose equipment where the other products are animal derived. If there is a risk of TSE material residue on equipment, the excipient manufacturer should demonstrate cleaning procedures that show residual TSE risk material is either reduced to an acceptable level on the equipment surface or is inactivated.

The risk of viral, microbiological, or endotoxin contamination arises from raw materials, water, and the environment. Where the manufacture of the excipient uses viral agents or there is a risk of contamination with viral agents, adequate measures of sanitation or sterilization by the supplier are expected.

Excipient manufacturers should use at least potable water where water is used in the process after the starting point for GMP or when water is a potential source of microbial contamination in the finished excipient. Water that is used for temperature control that does not contact excipient during manufacture poses minimal risk under normal operating conditions and therefore need not be potable. For excipients that are intended for drug products where the presence of endotoxin poses a risk to patient safety and water comes into direct contact with the excipient during processing, higher purity water such as United States Pharmacopieal Convention (USP) water for injection may be expected to be used.

There is also the potential for airborne microorganisms to contaminate the excipient. Generally, airborne microbes that can contaminate the excipient can be controlled by filtering the air, such as when the excipient is exposed to the air during packaging, to remove particles. Removal of airborne particulate to reduce the risk of microbial contamination only requires use of a HEPA filter if the excipient is purported to be sterile.

Contamination of the excipient with undersirable components can arise from such sources as nearby manufacturing operations, processing equipment (e.g., filters and traps), and utilities. Filters pose a risk from shedding their material of construction and from traps that are improperly maintained, allowing trapped impurities through. Utilities such as nitrogen, compressed air, and steam may contaminate the excipient with impurities such as compressor oil and boiler additives.

It is common for the excipient to be produced at a site where many other products are also manufactured. Some of these other products may be toxic (e.g., herbicides or pesticides) or they may use toxic ingredients in their manufacture. Where toxic substances are volatile enough to become airborne contaminants, manufacturers should take appropriate measures to minimize the risk of contamination. It is important for the user to assess the risk of airborne contamination and the measures taken to protect the excipient during an onsite audit.

Supply chain considerations

The complexity of the supply chain from excipient manufacturer to pharmaceutical facility is also a consideration in selecting a supplier. Although delivery from an excipient manufacturing site directly to the pharmaceutical manufacturing facility provides the least opportunity for the excipient to become contaminated or tampered with en route; generally direct delivery is uncommon and only applies to full truckloads of the excipient. More often, less-than-truckload quantities are shipped by common carrier. Oftentimes, the shipment goes from the manufacturer to a warehouse of the transport carrier. There, the shipment may be cross-docked to a truck heading to the desired destination or another intermediate destination. While tampering with the excipient at the transport warehouse is unlikely, there is the possibility for the packaged excipient to be exposed to extremes of weather (temperature, humidity, and precipitation), for the packaging to be damaged through mishandling, or for the tamper-evident seal to be accidentally broken.

Excipients are often sold through a distributor. Distributors can sell the excipient in the unopened excipient manufacturer's package or the distributor may repackage the excipient into smaller packages. Excipients may also be shipped in bulk to a manufacturer's terminal or a distributor where the excipient is either stored in bulk tanks or packaged from the tank truck or rail car into discrete containers. Any time the excipient is handled other than in the original container is an opportunity for the excipient to become contaminated, adulterated, or otherwise compromised. Therefore, the fewer such activities in the supply chain, the lower the risk.

Where delivery is not direct from the excipient manufacturer, the pharmaceutical company should periodically establish the pedigree of the excipient. As discussed in the IPEC-Americas and IPEC-Europe Excipient Pedigree position paper of 2008 (6), the pharmaceutical company should verify through the paper trail that the shipment of an excipient lot has come from the excipient manufacturer.

The stability of the excipient can pose a risk if the material is likely to degrade during storage or shipment when temperature and/or humidity are not controlled within acceptable limits. Generally, excipients such as inorganic salts, minerals, modified food ingredients, and synthetic substances are stable materials. Also, many excipients have been in commerce for an extended number of years and, therefore, their stability has been well established and characterized. Stability issues occur more frequently from exposure to moisture or oxygen rather than temperature extremes. However, unless studies have shown the excipient to be affected by extremes of temperature, humidity, or exposure to oxygen, there is little cause for concern regarding excipient storage.

For moisture- and/or oxygen-sensitive excipients, the excipient packaging should be considered and assessed when selecting a supplier. The excipient supplier should provide evidence for the suitability of the packaging used to protect the excipient from moisture and oxygen.

Finally, tamper-resistant packaging is an important consideration in the selection of a supplier. Though packages can be sealed with tamper-evident closures, the package materials can be susceptible to tampering via a puncture. However, impervious packaging such as steel drums may not be appropriate for some excipients. High-density polyethylene (HDPE) drums may be compatible with the excipient and are more resistant to product tampering than fiber drums or bags. Though bags and supersacks are a challenge to make tamper resistant due to their material of construction, oftentimes they are the only packaging available.

Package openings should be protected with tamper-evident seals unique to the excipient manufacturer. Such seals are characterized by their having to be opened to gain access to the excipient, cannot be reapplied if broken or otherwise removed, and are unique in that they have the manufacturer's name, logo, or inherent design

characteristic. While numbered seals are desirable, they are impractical for excipients where the number of containers in a lot often exceeds 100 and can be in excesses of 1000. Using a tamper-evident seal, however, provides no benefit if incoming inspection by the pharmaceutical firm fails to match the appearance of the seal to an authentic seal (or photo) provided by the excipient manufacturer.

Conclusion
Excipient quality is best characterized as conformance to GMPs and the compendial monograph or specification with a consistent composition profile lot to lot and within lot.

In the selection of an excipient supplier, the following characteristics minimize the risk to excipient quality:

The excipient is manufactured using dedicated equipment or mixed-use equipment with sufficient cleaning validation.
No TSE risk material is used in excipient manufacture unless an adequate assessment has been made and the risk is kept to an acceptable maximum.
No viral risk material is used in excipient manufacture unless an adequate assessment has been made and the risk is kept to an acceptable maximum.
Adequate measures are taken to control the contamination risk from microbes or endotoxin unless an adequate assessment has been made and the risk is kept to an acceptable maximum.
The risk of contamination is mitigated through the implementation of GMP controls.
Transport of the excipient from the manufacturer is directly to the user.
The excipient is stable under the conditions of storage and shipment.
Each excipient package is tamper resistant and, if feasible, closed with a tamper-evident seal.

These considerations will help to ensure the use of quality excipients in the manufacture of pharmaceuticals.

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