

ON THE DOCKET

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TAKE CONTROL OF YOUR EXCIPIENTS

WHEN I RECENTLY CHAIRED the AAPS Roundtable, "GMPs for Excipients," I was surprised to learn that FDA does not conduct regulatory-scheduled audits of excipient suppliers. This piqued my interest as excipients are generally used as purchased, with their physical and chemical characteristics, as well as their quality, being controlled by the supplier. This requires a manufacturer to have great confidence in a supplier's production and testing procedures, as well as its GMP compliance, to accept an excipient.

As a result, many pharmaceutical manufacturers perform "reduced testing" on the excipients they receive from their suppliers, as outlined in 21CFR211.84¹. This requires the manufacturer to perform minimal testing of the excipient and accept the remainder of the required test results from the excipient supplier's certificate of analysis.

Although reduced testing is allowable, there is no FDA guidance document in place outlining a suitable way to meet the requirements of 21CFR211.84. Also consider whether the supplier meets cGMPs. Since FDA is not conducting these audits, it is up to the individual manufacturers to ensure that excipient suppliers are maintaining the product under at least minimal cGMP standards. This is somewhat complicated since many excipient suppliers also provide their products for use in industries other than pharmaceuticals. So audits must be tailored appropriately.

In November 2001, the International Pharmaceutical Excipients Council

Reduced testing programs for excipients are a necessary and acceptable practice in the pharmaceutical industry. However, in the absence of FDA guidance on this subject, it is up to drug makers to develop a practical program that allows them to remain in control of their excipients and still comply with cGMPs.

(IPEC) published Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients². While this is not an FDA guidance document, it is at least a good place to start in developing an auditing program for excipient suppliers.

QUALIFYING AN EXCIPIENT

Whether you currently have a reduced testing program, or wish to start one, it is wise to be aware of the GMP requirements for such a program and what the program should include so that you can qualify the excipient. The regulation, 21 CFR 211.841, requires that each lot of components not be used until the lot has been sampled, tested or examined, as appropriate, and released for use by your QC unit. Samples must undergo at least one test to verify identity and another test for conformity, with all appropriate written specifications for purity, strength and quality.

Regulation 21CFR211.84 states that an analysis report may be accepted from the component supplier, provided that at least one identity test is conducted on the component by the manufacturer and that the manufacturer establishes the reliability of

the supplier's analysis.

Establishing the reliability of the supplier's analysis requires a lot of work. To assure that an excipient reliably and reproducibly meets predetermined specifications for physical and chemical properties, you must validate the supplier's results before the excipient qualifies for your reduced testing program.

As a general rule, establish the reliability of your supplier's analysis by "full-release testing" three excipient lots. Full-release testing demands testing all the requirements on the excipient's specification. This should comply with the compendial (USP/NF) monograph² for the excipient, if one is available. If the three lots tested provide acceptable results, the excipient qualifies for a reduced testing program.

VALIDATING THE RESULTS

Regulation 21CFR211.84 also states that the manufacturer must validate the supplier's test results at appropriate intervals. Testing frequency depends upon how often the excipient is received. If more than three lots are tested during a year due to high-volume use, there should not be a

need to perform additional validation. However, if only one lot is tested per year, then the manufacturer should consider periodic revalidation of a supplier's results every five to ten years, depending on the frequency of product receipt.

Certain situations may require requalification of an excipient for a reduced testing program. For instance, if an excipient fails full-release testing, subsequent lots should be fully tested until the requirements for

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reduced testing are met. It is recommended that a minimum of three additional lots be tested for full specification conformance before the material is reconsidered for the reduced testing program. If this is a low-use excipient, the manufacturer may want to do full-release testing on every batch, and forego the reduced testing program altogether.

Most reliable suppliers will inform a manufacturer if there has been a change in the manufacturing process or excipient specification (e.g., the addition of specific surface area testing to the monograph USP/NF for magnesium stearate). This may also trigger removing the excipient from the reduced testing program until sufficient results are available to requalify the excipient for the program. A manufacturer may want to request three different lots for

testing to ensure compliance with the new specification before maintaining the excipient in the reduced testing program. If revalidating a supplier's results each time a change is made to the specification does not seem like a viable option, then this should be addressed during the periodic revalidation process.

Once the excipient is qualified and validated, the manufacturer should assess which tests will be required for reduced testing. At the minimum, conduct an identity test as well as physical property tests. This is especially true if the property performs a function. For instance, particle size, moisture content, pH, density, etc., could all affect a finished product's performance. Therefore, the supplier assesses the critical parameters for finished product functionality, and whether these will be tested for every lot of excipient received.

For a reduced testing program, full-release testing should be conducted at least annually. For high-use products, full-release testing should occur at least once a year, and on every tenth lot. However, be aware that if you did not receive lots of a particular material in a given year, the excipient cannot qualify for a reduced testing program.

REFERENCES

¹ 21CFR211.84, Testing and approval or rejection of components, drug product containers, and closures, US FDA, Title 21, Vol. 4, Revised April 1, 2001.

² Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, International Pharmaceutical Excipients Council, www.IPEC.org.

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The most commonly used excipients in US drug products:

Magnesium Stearate

Lactose

Microcrystalline Cellulose

Starch (corn)

Silicon Dioxide

Titanium Dioxide

Stearic Acid

Sodium Starch Glycolate

Gelatin

Talc

Sucrose

Calcium Stearate

Povidone

Pregelatinized Starch

Hydroxy Propyl

Methylcellulose

OPA products (coatings & inks)

Croscarmellose

Hydroxy Propyl Cellulose

Ethylcellulose

Calcium Phosphate (dibasic)

Crospovidone

Shellac (and Glaze)

SOURCE:
**International Pharmaceutical
Excipients Council**