Challenges, Considerations, and Benefits of Raw Materials Testing

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Raw materials testing ensures that the raw materials used in pharmaceutical products are suitable for their intended use. Conducting raw materials analysis using appropriate test methods and successfully meeting the challenges of such testing can prevent costly production problems and delays.

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Before finished pharmaceutical dosage forms are produced, the identity, purity, and quality of raw materials must be established with the use of suitable test methods. Pharmacopeial and formulary monographs such as the *US Pharmacopeia–National Formulary* (*USP–NF*), the *European Pharmacopeia,* and the *Japanese Pharmacopeia* provide standardized test methods for the most common and widely used materials.

Manufacturers take various approaches to raw materials testing compliance. Some qualify a raw materials supplier by performing an initial detailed vendor audit followed by an annual qualification consisting of full pharmacopeial monograph testing on three lots of material. If the qualification lots test successfully, then subsequent material shipments will require only monograph identification testing. However, companies that take a more conservative approach to raw materials release require full monograph testing for each lot of supplied material.

Analytical approach and instrumentation

Raw materials analysis requires a wide range of analytical chemistry expertise. The most common tests performed in a raw materials laboratory include titrations, loss on drying, Karl Fischer moisture determination, heavy metals limit tests, and infrared spectrophotometry. Full monograph testing often requires as many as seven different analytical techniques. For example, to perform full *USP* monograph testing for methylparaben, eight different tests using six analytical techniques ranging from infrared absorption to gas chromatography are required. Therefore, the most efficient organization of a raw materials laboratories is by function so that analysts can specialize in specific techniques.

To perform even basic monograph testing, laboratories must contain a wide spectrum of instrumentation. The most commonly specified instruments include

- pH meters
- balances
- gas chromatographs
- high-performance liquid chromatographs (HPLCs)
- infrared spectrophotometers
- ultra violet/visible (UV–vis) range spectrophotometers
- Karl Fischer moisture titrators
- general titration apparatus
- vacuum ovens
- melting-point apparatus
- thin-layer chromatography apparatus
- polarimeters
- refractometers
- viscometers
- muffle furnaces.

To expand the number and variety of excipients that can be tested, additional instrumentation is required. These include

- flame atomic absorption spectrophotometers
- graphite furnace atomic absorption spectrophotometers
- elemental analyzers
- differential scanning calorimeters
- thermogravimetric analyzers.

Because of the number of different tests a raw materials laboratory must be prepared to perform, much of the equipment is underutilized at any given time. Because of this, some companies consider outsourcing their raw materials testing as an alternative to investing heavily in equipment.

Quality assurance

From a quality assurance standpoint, three critical factors should be considered when assessing a raw materials laboratory: instrument validation/qualification, deviation management, and out-of-specification (OOS) procedures.

The diversity of instrumentation used by raw materials laboratories places a heavy burden on validation efforts. Instrument vendors often provide installation qualification (IQ), operational qualification (OQ), user training, and after-purchase support, but a large portion of the validation efforts falls on the laboratory, especially with regard to computerized systems. Therefore, the laboratory must define instrument function requirements to outline operational needs and compliance requirements and provide criteria against which the instrument is validated.

To provide evidence that the entire system (i.e., hardware, software, associated instrumentation or components) meets user-defined functional requirements and specifications and that performance meets predetermined levels of accuracy, reliability, and data integrity, performance qualification (PQ) must be conducted using test cases that represent and challenge the production environment. In addition, 21 *CFR* Part 11 issues must be evaluated by the laboratory with regard to system security, data integrity, data archival, and audit trail capabilities. For instrumentation to remain in a validated and controlled state, changes and enhancements must be performed under a formalized change-control system.

Compendial methods should be modified when not robust, and deviations and modifications to

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methods must be controlled and justified by additional validation data. The required deviations and modifications, along with the supporting validation data, also should be communicated to the pharmacopeia for amendment consideration.

In a raw materials testing laboratory, analytical chemists must be experienced in troubleshooting methods using various analytical techniques and instruments. Often working with raw materials supplier laboratory staff, the chemists must balance scientific need for deviations or modifications with the regulatory requirement to adhere to compendial methods.

OOS situations can be a common occurrence in the raw materials laboratory. Contributing factors include the lack of robust compendial methods, the purchase of raw materials not suitable for their intended use, and the fact that many raw materials suppliers do only a fraction of their business with pharmaceutical companies.

Paying close attention to the materials purchased, such as reviewing the certificate of analysis

OOS investigations are complicated when the supplier and the manufacturer are not able to compare results.

supplied with the material, can prevent many problems. Identifying methods used to generate the certificate of analysis results and determining how close these results are to the specification limit of the material are crucial steps in qualifying a material before it is tested.

Other challenges

The lack of harmonized standards among the various pharmacopeias is a major challenge. Companies that produce finished goods for a global marketplace must ensure that their raw materials meet the standards of multiple governing pharmacopeias. However, differences exist among the three major pharmacopeias. To solve this problem, some companies choose to perform full-monograph testing according to the pharmacopeia appropriate for each country where the product will be sold. Although this approach ensures that the data are accepted by the governing regulatory agency, it is also expensive.

The time and expense of testing for multiple pharmacopeias has prompted efforts to harmonize monographs. Organizations such as the AAPS Excipients Focus Group and the International Pharmaceutical Excipients Council of the Americas were formed to facilitate the development of harmonized pharmacopeial excipient standards and good manufacturing practices (GMP) guidelines. Although their efforts have had a positive effect on the industry, limited success has been reached in harmonizing the various pharmacopeia methods during the past several years.

Maintaining compliance within a testing laboratory also presents several challenges. For example, the pharmacopeias contain monographs using wet-chemistry techniques rather than more-robust instrumental methods. As a result, even an experienced raw materials chemist may have difficulty with specific compendial tests. Many monographs requiring a titration to assess the purity of a material could instead be upgraded to a much more robust HPLC method.

Another challenge is that raw materials chemists typically do not have access to the validation data associated with the monograph. This limits the ability of the analyst to perform effective troubleshooting of a particular test method. Compounding these problems is the fact that many raw materials manufacturers use noncompendial methods to support their certificate of analyses. As a result, if an OOS result is obtained during the compendial analysis, the supplier and the manufacturer are not able to compare results,

thereby making the OOS investigation more difficult.

Functionality testing

Currently, the primary function of the pharmacopeial monographs is to establish minimum standards that set the identity, purity, and quality requirements for raw materials. During the past few years, however, the excipient industry has tried to expand the pharmacopeial monographs to include functionality tests for excipients. These functionality tests would facilitate establishment of consistent performance of excipients by identifying and controlling their critical physiochemical properties.

Of the roughly 270 monographs described in *USP–NF,* approximately 88 contain labeling sections that set specific functional tests for the material. For example, there are particle-size requirements within the labeling section of microcrystalline cellulose and specific surface-area requirements within the labeling section of magnesium stearate.

USP–NF test method General Chapters include

- optical microscopy
- specific surface area
- particle-size distribution estimation by analytical sieving
- density of solids (gas pycnometry)
- bulk and tapped density
- laser diffraction measurement of particle size
- X ray powder diffraction.

Debate continues about whether functionality testing should be included in the pharmacopeia. Meaningful functionality tests can assist formulation scientists in the selection of excipients during product development and would help ensure consistent manufacture of the product. However, proponents of setting minimum standards relating to identity, purity, and quality argue that for some applications of the raw material, functional tests are not critical to the product. As a result, if functional tests are included as requirements of the monograph, they would require unnecessary, sometimes expensive, testing. A possible compromise may be to include it within the monograph for information purposes.

Conclusion

Although the challenges associated with raw materials testing are extensive, manufacturers can prevent costly production problems and delays by confirming early in the production process that the raw materials in their products are suitable for their intended use. **PT**