Guide to Pharmaceutical Quality Control

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Safety. Quality. Purity. Efficacy. Predictability—What these have in common is that they are all desirable and necessary attributes of pharmaceutical products. Quality control is critical to ensure that the final drug product includes these properties and meets the guidelines promulgated by regulatory authorities, with the overall goal to provide assurances that medicines perform consistently and predictably and are safe for healthcare delivery.

The Origins of Quality Control in the Drug Industry

Quality control in the pharmaceutical industry has undergone several transformations since 1902, when a conference held by the Belgian government resulted in unification of the formulation of potent drugs. The developments are too numerous to list here, but in response to a series of disastrous outcomes involving unsafe medicines, several legislative measures were taken. Of note is the Kefauver-Harris Drug Amendments, passed in 1962 following the thalidomide tragedy.

Today, the U.S. Food and Drug Administration oversees the safety and efficacy of pharmaceutical products to ensure protections for the public. In its *Guide to Inspections of Pharmaceutical Quality Control Laboratories,* the FDA states the significance of quality control in the drug industry: “The pharmaceutical quality control laboratory serves one of the most important functions in pharmaceutical production and control.”[1]

Compliance with Industry Standards

Adherence to guidelines set forth by regional regulatory authorities is key to effective quality control in the pharmaceutical industry. Data integrity plays a major role in quality control because it involves monitoring a drug product over its entire life cycle to ensure consistency, reliability, and accuracy. The FDA issues warning letters to organizations they deem deficient in this area. Data integrity also encompasses proper data management such as maintaining electronic records and signatures, covered under FDA 21 CFR Part 11.

Pharmaceutical Testing

Thorough analytical testing procedures are required to detect products that are suspected of being fraudulent or falsified. Table 1, based on guidance from the World Health Organization, lists available methods that can be used for package identification, screening, and testing of medical products.[2]

Table 1 – Analytical Methods	
Method	**Purpose**
Attenuated total reflectance/ Fourier transform infrared spectroscopy (ATR/FTIR)	Identification
Bacterial endotoxins test (BET)	Specific testing
Disintegration testing	Finished pharmaceutical product testing
Dissolution testing	Finished pharmaceutical product testing
FTIR/Raman imaging spectroscopy	Forensics
Gas chromatography/ flame ionization detection (GC/FID)	Identification of assay impurities
Gas chromatography/ mass spectrometric detection (GC/MS)	Forensics; identification of assay impurities
Headspace gas chromatography/ flame ionization detection (HS-GC/FID)	Residual solvents; impurities
Headspace gas chromatography/ mass spectrometric detection (HS-GC/MS)	Forensics; residual solvents; impurities
Inductively coupled plasma/ mass spectrometric detection (ICP/MS)	Inorganic impurities
Inductively coupled plasma/ optical emission spectroscopy (ICP/OES)	Inorganic impurities
Light microscopy	Finished drug product testing; forensics
Liquid chromatography/ evaporative light scattering detection (LC/ELSD)	Forensics
Liquid chromatography/ high-resolution mass spectrometric detection (LC/HRMS)	Forensics; identification of impurities
Liquid chromatography/ mass spectrometric detection (LC/MS)	Forensics; identification of assay impurities
Liquid chromatography/ ultraviolet detection (LC/UV)	Identification of assay impurities
Melting point	Identification
Nuclear magnetic resonance; quantitative nuclear magnetic resonance (NMR; qNMR)	Forensics; identification of assay impurities
Osmolarity and osmolality	Specific testing
Photo scan/overlay	Forensics

Table 1 – Analytical Methods	
Method	**Purpose**
Raman spectroscopy	Identification
Refractive index (RI)	Identification
Scanning electron microscopy/ energy-dispersive X-ray spectroscopy (SEM/EDX)	Forensics
Spectrophotometry (colorimetry)	Identification of assay impurities
Sterility	Specific testing
Thermodesorption gas chromatography/ mass spectrometric detection (TDS-GC/MS)	Forensics; identification of impurities
Thin-layer chromatography	Identification of assay impurities
Transmission electron microscopy (TEM)	Forensics
X-ray fluorescence (XRF)	Elemental and chemical analysis
X-ray powder diffractometry (XRPD)	Identification

Technique Spotlight

The ability to detect impurities in drug products and measure their concentration is vital to ensure product safety and efficacy. Two important testing methods are outlined below.

Sample Preparation via Microwave Digestion
Before testing a sample for inorganic impurities, the sample needs to be digested. Closed-vessel digestion, or microwave digestion, is an effective technique for evaluating concentrations of elemental impurities. Studies on the use of microwave digestion demonstrate its suitability for the sample preparation of various drug formulations prior to ICP/MS analysis.[3,4] One reviewer concluded: "The microwave-assisted closed-vessel digestion approach represents a reliable, powerful, and fully good manufacturing practice (GMP)-compliant sample preparation technique for the determination of elemental impurities according to all current regulatory requirements (ICH, USP, Pharm Eur.)."[4]

Polarimetry Assessment
With proper polarimetry assessment, the thalidomide event mentioned above could have been avoided. Certain drug products (for example, antibiotics, steroids, and analgesics) exhibit a distinct rotation that can be determined using a polarimeter, which measures a plane of light's angle of rotation brought about when it passes through an optically active substance. This is important because a compound's enantiomeric excess, or degree of purity, can be quantified by measuring its rotation. An article on chiral drugs underscores the

importance of ascertaining the ratio of (S)- to (R)-enantiomer ratio because each has different effects, some of which are deadly. According to the author, “Enantiomer ratio is extremely important because while one enantiomer is beneficial to the body, the other enantiomer can be highly toxic to the body. A well-known example of enantiomer related toxicity is the R- and S-enantiomers of thalidomide.”[5]

Product Performance

Effective quality control measures lead to high-quality drug products that perform well. Key to the performance of a pharmaceutical formulation is a process called particle characterization, which measures factors such as particle size/particle shape, surface charge/surface area, pore size, internal structure, powder flow, and density. Characterizing these parameters is important, because they can influence the final product in various ways. For example, “The appropriate surface charge is important for preventing aggregation and agglomeration of particles in suspensions and emulsions, and therefore impacts stability.”[6]

Conclusion

The current regulatory landscape for pharmaceutical quality control facilitates the development and manufacture of drugs that are safer and more effective. Rigorous analysis and testing are a major contributor to this. For additional testing and quality control solutions, please visit https://www.anton-paar.com/us-en/products/industries/application/pharmaceuticals/.

References

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2. https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex5.pdf?ua=1
3. https://www.labcompare.com/media/1/Document/Closed-vessel-digestion.pdf
4. http://www.spectroscopyonline.com/microwave-digestion-elemental-impurities-analysis-according-ich-and-usp-guidelines-0?pageID=1
5. https://www.khanacademy.org/test-prep/mcat/chemical-processes/stereochemistry/a/chiral-drugs
6. http://www.pharmtech.com/particle-characterization-critical-drug-performance

Additional resources

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853691/
2. https://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm
3. https://www.labcompare.com/media/1/Document/Application-report-software.pdf
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