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Standard Guide on Sampling for Process Analytical Technology[1]

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1. Scope

1.1 This document is to be used as a guide to Process Analytical Technology (PAT) instrument sampling, and covers both the sample from which PAT data is collected and the sample that is taken for reference assay. The ASTM definition of a guide is a compendium of information or series of options that does not recommend a specific course of action. The intention of a guide is to increases the awareness of information and approaches in a given subject area, as such this guide should serve as a collation of points to consider when determining a sample practice for PAT instruments. It is not intended to serve as a practice to be followed. As a first step, one should define the overall goal of the PAT measurement. Once defined, this guide describes various considerations as they relate to the specific requirements that must be met to achieve the overall PAT goal, including the attributes to be measured, impact of the scale of the process, and interfacing of the measurement system to manufacturing equipment (including sampling system reliability). Additionally, it discusses the estimation and validation of the effective sample size and the overall contribution to the measurement. Related aspects of data collection and data processing as well as the use of risk assessments to optimize sampling and to understand the impact of potential sampling errors are also covered. Furthermore, considerations for process control and aspects pertaining to sample withdrawal and retention are also included. Lastly, continuous manufacturing processes require special considerations due to the time dependency associated with continuous operations as compared to batch manufacturing and special considerations are needed for sampling of such processes.

1.2 This guide is limited to a high level overview of sampling considerations for PAT applied to any type of pharmaceutical manufacturing (for example, active pharmaceutical ingredient (API), solid oral dosage form, etc.). It is not intended to provide technology- or application-specific sampling guidance, or both. Instead, the intent is to evoke a thought process around sampling when developing a PAT application. While the focus is mainly on sampling considerations for on/in-line applications in solids, liquids, and gases (that is, in situ PAT measurements), many of the considerations also apply to at-line and off-line applications in which a sample is withdrawn from the process and subsequently presented for analysis.

1.3 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D4177 Practice for Automatic Sampling of Petroleum and Petroleum Products

E105 Guide for Probability Sampling of Materials

E122 Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process

E456 Terminology Relating to Quality and Statistics

E1402 Guide for Sampling Design

E2363 Terminology Relating to Manufacturing of Pharmaceutical and Biopharmaceutical Products in the Pharmaceutical and Biopharmaceutical Industry

2.2 *ASME Standard:*[3]

ASME BPE Bioprocessing Equipment

3. Terminology

3.1 *Definitions*—For an extensive list of terminology related to pharmaceutical manufacturing, refer to Terminology E2363.

4. Significance and Use

4.1 Application of this guidance should enable PAT method developers to design and implement reliable PAT applications

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.14 on Measurement Systems and Analysis.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from American Society of Mechanical Engineers (ASME), ASME International Headquarters, Two Park Ave., New York, NY 10016-5990, http://www.asme.org.

that avoid many common sources of error around sampling. Sampling is a key element of method and process validation plans.

4.1.1 Many ASTM standards discuss sampling; however, almost all are very specific to a certain field or application. For example, the "Standard Practice for Automatic Sampling of Petroleum and Petroleum Products" (D4177) specifically covers information for the design, installation, testing, and operation of automated equipment for the extraction of representative samples of petroleum and petroleum products from a flowing stream and storing them in a sample receiver.

4.1.2 Other useful ASTM standards include: E105 (Practice for Probability Sampling of Materials), E122 (Standard Practice for Calculating Sample Size to Estimate, With a Specified Precision, the Average for a Characteristic of a Lot or Process), E1402 (Standard Guide for Sampling Design), and E456 (Terminology Relating to Quality and Statistics). These standards review similar considerations as those addressed in this guidance and can be consulted for additional insight on how to deal with specific sample types or situations. However, such standards should be carefully reviewed for relevance to pharmaceutical applications.

5. Summary of Practice

5.1 Representative sampling is a key aspect of successful PAT measurements. There are many aspects to be considered to develop a suitable sampling approach. Scientific and statistical principles should be used in combination with appropriate risk assessment tools to ensure that the sampling approach is suitable for the application.

5.2 This guide is organized into sections each of which describes a particular aspect of sampling practices for PAT applications. Presented below is a brief description of each of the sampling aspects as well as the key objective to be addressed.

5.2.1 Attribute to be measured (see Section 6):

- Attribute(s) of interest,
- Scale or physical characteristic of the attribute: macroscopic versus microscopic, and
- Direct or indirect measurement.

5.2.1.1 *The key objective is to clearly define the attribute that is being measured.*

5.2.2 Process scale and nature (see Section 7):

- Scale, and
- Dynamics.

5.2.2.1 *The key objective is to understand the impact of the scale and dynamics of the process on sample size, frequency of sampling, and sampling locations.*

5.2.3 Estimation of the mass of sample investigated ('effective sample size') (see Section 8):

- What is the area or volume under scrutiny?
- Depth of penetration?
- Numbers of replicate measurements to achieve the required signal to noise ratio and capability of the measurement system?

5.2.3.1 *The key objective is to establish that the effective sample size and the level of scrutiny (degree of examination) are appropriate.*

5.2.4 Interfacing of measurement systems to manufacturing equipment (see Section 9):

- Locations of sensors,
- Numbers of sensors,
- Rationale for position of sensors,
- Mechanical interfacing:
  - Effect of sample interface/probe on the process, and
  - Cleaning of sensors.
- Effect of time/temperature/other parameters on the sample interface.

5.2.4.1 *The key objective is to establish how representative the sampling schedule is of the process under investigation, that is, does the sampling plan ensure that the pertinent variability in the process is captured. Also, there is a need to establish that the sampling interface is stable to changes in the process and material characteristics of the sample that may be encountered during normal operation. Furthermore, it has to be ensured that the sample interface itself has no impact on the manufacturing process and product itself.*

5.2.5 Rationalization of the contribution of a sample to a measurement (see Section 10):

- Sample mass contributing to a single measurement;
- Heterogeneity of the sample material at the microscopic level;
- Speed of analysis, data transfer rate, and relative displacement of the sample;
- Measurement reliability; and
- How representative the measured sample is of the process or product, or both.

5.2.5.1 *The key objective is to ensure that the validation of a PAT sampling system is focused on the appropriate parameters.*

5.2.6 Measurement cycle time (see Section 11):

- Frequency of measurement, and
- Numbers of measurements to be averaged, etc.

5.2.6.1 *The key objective is to establish that the timescale of the measurement is appropriate relative to the timescale of the process.*

5.2.7 Risk assessment (see Section 12):

- Use of appropriate risk assessment tools.

5.2.7.1 *The key objective is to ensure that the risks of making a sampling error are assessed and mitigated.*

5.2.8 Process control (see Section 13):

- Impact of sampling on the ability to control a process.

5.2.8.1 *The key objective is to establish the sample size that has the ability to reliably separate signal from noise for the purpose of process control.*

5.2.9 Sample withdrawal and retention prior to reference analysis[4] (see Section 14):

- Time between PAT measurement and reference analysis, and
- Procedure for sample withdrawal.

5.2.9.1 *The key objective is to consider the impact of sample withdrawal and time between PAT measurement and reference*

[4] In this guide, reference analysis is defined as the (chemical or physical, or both) analysis of a sample withdrawn from a process, typically after a PAT measurement has been performed on it, to establish the reference value for the PAT measurement. This analysis is often done in a laboratory using conventional analytical techniques.

analysis. This covers the stability of the sample between the time of removal from the process until time of analysis such that the sample analyzed is representative.

5.2.10 Continuous processing (see Section 15):

- Time dependency of continuous processes.

5.2.10.1 *The key objective is to recognize that continuous processes require special considerations due to their time-dependent nature.*

6. Attribute to be Measured

6.1 When devising a sampling interface, device, or plan for any PAT method, one of the first aspects that has to be considered is the attribute of interest, that is, what is it specifically that is going to be measured.

6.1.1 The physical scale of the attribute is of significant importance as the sampling strategy may change depending on whether the attribute to be measured is microscopic (for example, excipient distribution, morphology) or macroscopic (for example, crystal or granule properties such as density, size/distribution, etc.) in nature; this ties with the physical properties of the material(s) being examined.

6.1.2 Additionally, the type of measurement has to be taken into account because the sampling requirements for a direct measurement, that is, attribute of interest is measured directly, can be different as compared to those for an indirect measurement, that is, attribute of interest is derived from the measurement of another (set of) attribute(s) or process parameters.

6.2 If multiple attributes are to be determined by means of a single measurement process or system, then the sampling plan has to cover requirements associated with all the individual attribute measurements. The goal is to implement the appropriate PAT measurement system(s) and associated sampling plan with the appropriate sensitivity for the attribute of interest and ruggedness/insensitivity with respect to interferences from other factors.

7. Impact of Scale of the Process

7.1 The scale of the manufacturing process may have an impact on the sampling requirements.

7.1.1 During development at small scale, the sampling frequency may be higher than at full commercial scale as product and process knowledge and understanding are the focus. At commercial scale a lower frequency of sampling may be appropriate if the process is well characterized, understood, predictable, and controlled.

7.2 The fact that commercial scale manufacturing may be subject to an increased likelihood of subpopulations (substrata) which would increase sample-to-sample variations should be considered. Sample heterogeneity would have to be taken into account in this case. Further, depending on the size and physical structure of the manufacturing equipment used, a different number of sensors may be needed to accomplish the same measurement at small and large scale. Additionally, as the size and physical structure of the manufacturing equipment changes not only the number of sensors may need to change, but also the location thereof. Lastly, depending on differences in process dynamics related to scale, different sampling plans may be required (see also Section 10). Note though that a larger manufacturing scale does not always automatically necessitates an increase in number of sensors, a change in location, or a different sampling plan; this will depend on the process, system, and PAT measurement.

8. Estimation of the Amount of Sample Which is Being Investigated ('Effective Sample Size')

8.1 On-line and in-line PAT measurement applications typically do not involve removal of samples from the system or process. Measurements are generally made using sensors or probes that are in direct contact with, or inserted into the system or process.

8.1.1 However, even though there may be no physical removal of samples from the system or process, all such PAT measurement techniques are effectively evaluating a sub-set of the material under investigation. This derives from the fact that such techniques have a limited field of view or operation; for example, they will penetrate a sample matrix or process to a finite depth and can only make measurements at a finite rate.

8.1.2 It is recognized that estimating or calculating an effective sample size for analysis by the PAT system may be difficult. For powders or solids it may be possible to approximate the effective sample size for a spectroscopic technique using some reasonable assumptions. In such cases, for example, the effective sample size can be a function of illumination area, average penetration depth, material density, sampling frequency and other factors depending on the type of analyzer and material characteristics. However, in many liquid and gas phase applications this can be significantly more difficult depending on the measurement technique and the system under investigation.

8.1.2.1 When possible, as a general principle, the effective sample size should be calculated (or, at least, estimated) based on the contributions from the factors discussed above, that is, volume or size of the system or process being monitored (and this, in turn, may need to be estimated based on the area of examination and depth of penetration). Matrix properties of the system or process being monitored should be understood. This may change during the measurement cycle, so an average value or estimate may be needed.

8.2 *Frequency/Averaging of Measurement*—Where multiple measurements are averaged, or the output from several sensors is combined, these factors should also be considered:

- The relevance of a single point or multiple point measurement to assess the matrix properties of a large mass of (moving) material.
- The signal to noise characteristics of the measurement system at the sampling size and sampling mass used in the application; in other words, the fundamental capability of the instrument to perform the required measurement.

8.2.1 Once the effective sample size is established or estimated, it must be reviewed in terms of the level of scrutiny required for the specific application. For example, a powder blending application involving blend homogeneity determination needs to be conducted at a scale that is comparable to the nominal tablet unit dose level. If the effective sample size cannot be established or estimated, other means should be