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Professional paper

Regulatory requirements for verification of sampling plan for solid pharmaceutical bulk product

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Abstract

The most convenient sampling plan for routine testing at batch release for a solid pharmaceutical bulk product is a sampling plan with requirements for generating a composite sample. Verification is required before such a sampling plan can be used for routine testing. The verification needs to demonstrate that the composite sample is representative of the whole batch and is considering the most stressed part of the manufacturing process of the solid pharmaceutical bulk product.

As part of verification, increased sampling should be performed to demonstrate that the manufacturing process yields a homogeneous product. The sampling for batch release testing of a solid pharmaceutical bulk product is performed at the end of the production process from each individual container where the batch is stored. All containers combined represent the variability of the entire batch, that is, the individual samples taken from each container. The verification process should demonstrate that individual samples taken from each container gives comparable sampling variability as a composite sample is prepared from all containers. A statistical evaluation and comparison of the results from individual samples and composite sample is most appropriate when performed by using Equivalence Test (TOST).

If such equivalence is obtained between individual samples from each container and a composite sample, then it is possible to limit the routine testing to representative composite samples from predetermined containers defined in the sampling scheme. The sampling plan with a representative composite sample should be verified enough that it is suitable for all future batches.

Key words: Pharmaceutical sampling, solid pharmaceutical bulk product, representative composite sample, verification of sampling plan with composite sample, Equivalence Test (TOST)

Regulatory requirements for sampling of pharmaceutical products

The quality of pharmaceutical products needs to be evaluated at the time of batch release. Sampling from a pharmaceutical perspective is indeed an important step to control the quality of the final formulation. Physical, chemical, and microbiological evaluation of the pharmaceutical materials during and after manufacturing is one of the most important aspects from both patient safety and regulatory point of view (Raval et al., 2018). Therefore, the sampling plan of the pharmaceutical materials is a critical step in providing samples that are representative of the batch of materials or products from which they are taken and are considering the most stressed part of the process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach (EudraLex 6.12, 2014).

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The sample taking should be done and recorded in accordance with approved written procedures (EudraLex 6.11, 2014) that describe:

i. The method of sampling;
ii. The equipment to be used;
iii. The amount of the sample to be taken;
iv. Instructions for any required sub-division of the sample;
v. The type and condition of the sample container to be used;
vi. The identification of containers sampled;
vii. Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
viii. The storage conditions;
ix. Instructions for the cleaning and storage of sampling equipment.

Sampling plan is description of the location, number of units and/or quantity of material that should be collected, and associated acceptance criteria (WHO, 2005). The sampling plan should be suitable to fulfill the basic objectives of the sampling, the type of controls intended to be applied to the samples, and to the material to be sampled (Raval et al., 2018). The requirements included in the sampling plan ensure that the sample is representative of the entire batch. Requirements that have the greatest impact on the representativeness of the sample are the sampling scheme and requirements for generating individual or composite samples.

Sampling and testing finished products can only verify the quality of the products, not create it or improve it. To achieve the desired quality in final products, the individual steps of the development and manufacturing process must be well designed, properly carried out, and have achieved the pre-defined acceptance criteria. To that end, appropriate sampling and testing plans and acceptance criteria must be in place for every stage of manufacturing, from powder blends, to in-process dosage units, to finished units, and from the development batch, to the validation batch, to routine manufacturing batches (Kou et al., 2011).

Fundamental principles of sampling

Sampling is a technique of selecting individual members or a subset of the population to make statistical inferences from them and the estimate characteristics of the whole population. A major objective of any sampling plan is to select the sample in such a way as to accurately portray the population from which it is drawn. After all, a sample is supposed to be representative of the population.

Sampling in general has certain advantages. For example, if the measurement requires destroying the item being measured (destructive testing), we cannot afford to obtain data from each item in the population.

Sampling simply means selecting a portion of the pharmaceutical product for a defined purpose. Sampling should be done in such a way that all extremes are considered, and not a single control is missed out. The sampling procedure should be such that non-uniformity of the material can be detected. Representative sample is sample obtained according to a sampling procedure designed to ensure that the different parts of a batch or the different properties of a non-uniform material are proportionately represented (WHO, 2005).

Broadly there are two types of sampling, namely nonprobability sampling and probability sampling. Nonprobability sampling involves selection of the sample groups by the researchers leading to biases during sampling. Probability sampling involves unbiased selection of sample groups in such a way that each unit in the sample possesses an equal chance of being selected. They are further subdivided into random sampling, stratified random sampling, systemic random sampling, and cluster sampling. Random sampling involves selecting a sample in a single step from a population wherein each unit in the population has an equal chance of being selected. Advantages of this method include a fair way of selecting a sample and the easiness of assembling the sample (Raval et al., 2018).

Definition of solid pharmaceutical bulk product

An intermediate product is defined as partly processed material that must undergo further processing steps before it becomes bulk product e.g. solution prior to filling, granulates, uncoated tablets etc. A bulk product is defined as any product which has completed all processing steps, up to but not including, final packaging. A manufacturing process generally involves a series of unit operations, where intermediate product is processed to become bulk product (EMA, 2017).

Solid pharmaceutical bulk products include powdered solids or granules in containers, further processed to a finished product, or maybe directly packed into suitable final packaging materials. They also include unit dosage forms like tablets or capsules in bulk, further intended to be packed in small containers.

Sampling scheme of solid pharmaceutical bulk product

The sampling scheme provides detailed requirements on the number of containers per batch that are to be sampled. The requirements are statistically based. Various factors are included in the scheme: material properties, manufacturing process, batch size and purpose of sample.

The determination of the sampling scheme depends greatly on the nature of the manufacturing process used. It makes a significant difference if the units are produced continually over a defined period of time, such as the case when producing tablets. A degree of variation may occur

throughout the production process so samples need to be distributed over the course of production. A sampling scheme that requires sampling from each container will generate the most representative sample.

Defining individual and composite samples

Individual sample is sample collected directly from the material. The individual samples can be combined into a final, composite sample from which an analytical sample is prepared (WHO, 2005).

It is common to form a composite sample with individual samples from different containers from the same batch. This may be required depending on the intended testing of the sample. For identity testing, for example, this is not permitted, since the testing is to be performed on individual samples.

As part of pharmaceutical manufacturing process development and validation, increased sampling is performed to prove that the manufacturing process yields a homogeneous product. Based on this result it is possible to limit the routine testing to representative composite samples from predetermined containers defined in the sampling scheme. Should there be evidence of systematic or process-related inhomogeneity then this procedure should be evaluated for the specific case.

Sampling plan during process validation

Process validation establishes the critical steps, control strategy, critical process parameters (CPPs), in-process controls, finished product specifications, and the associated methods, as well as the quality attributes (QAs) and critical quality attributes (CQAs) of the product.

Process validation for solid oral dosage forms is used to develop a single control procedure to ensure homogeneous powder blend, in-process content uniformity and uniformity of content of the finished products. During process validation the sampling process of dosage units is performed at predefined intervals, collecting representative samples from specifically targeted locations in the compression/filling operation that have the greatest potential to yield extreme highs and lows in the test results. These test results are used to monitor the manufacturing process output that is most responsible for finished product variability.

During process validation powder blends, granules, and solid oral dosage forms are sampled and analyzed. A suitable sampling plan is developed and then validated to be reproducible in various batches of the solid pharmaceutical product.

Homogeneous mixing of powder blend is a prerequisite for manufacturing any solid oral dosage forms like tablets or capsules. Blend analysis is done extensively on batches by sampling the powder mix from a blender or immediate bulk containers. Blending time, the speed of the blender, dead spots, and regions of segregation are properly identified to minimize the sampling errors. An appropriate sampling procedure is developed for each product considering the influence of the sample size on the true uniformity of the powder blend. Granules samples are analyzed for uniformity of weight and size. Samples of the granules are taken from the center of the bin from the top, middle, and bottom layers, and further, the samples are pooled and properly labeled to be analyzed (Raval et al., 2018).

Process validation includes process parameters and process control of mixing of pre-blend, wet granulation, mixing of blend, mixing of final blend, control test of final blend (top, middle and bottom from all 4 containers), process control of tablets during tablet compression process from five different time points, and control test of compressing on 60 tablets (3 tablets from 20 equal time locations during the compression process).

The pharmaceutical process validation performed proves that the manufacturing process yields a homogeneous product.

Sampling plan during in-process controls

In-process sampling during various pharmaceutical processes is done to maintain the quality and efficiency of the manufactured product as well as to check the efficiency of the process (Raval et al., 2018).

During the manufacturing of solid pharmaceutical bulk products sampling is performed for in-process controls regulated in the appropriate batch records at regular time intervals, providing good monitoring of the process.

During in-process control of tablets or capsules, periodic samples are taken at predefined sample intervals throughout the compression or filling process. Additional samples are taken to analyze critical events like the filling or emptying of hoppers, hopper changeover, filling or machine shutdown, and the start and end of the compression or filling operation. Samples for in-process controls are typically taken at the start, middle and end of the run.

Sampling plan of solid pharmaceutical bulk product

Requirements in the sampling plan that have the greatest impact on the representativeness are the sampling scheme, and requirements for generating individual or composite samples.

The intended sampling scheme requires sampling from each container which means that will generate the most representative samples.

The sampling for batch release testing of solid pharmaceutical bulk product is performed at the end of the production process from each individual container where

the batch is stored. This way the samples are collected from the initial and last event of a compression or filling process, thus ensuring that the sample is representative of the whole batch including the most stressed part of a process. All containers combined represent the variability of the whole batch. The individual samples taken from each container are representation of the whole batch. Analyzing individual samples from all containers during the production of each batch of a solid pharmaceutical product is not feasible, however, a composite sample can be prepared from all containers and analyzed. A composite sample is assembled by combining and mixing a prescribed amount of the solid pharmaceutical bulk product, taken from each container of the batch.

This composite sample will be used to evaluate the quality of all solid pharmaceutical bulk product at batch release. The composite sample should represent the whole batch therefore verification of the sampling plan with composite sample is needed.

Statistical evaluation of results

In order to verify the sampling plan with composite sample it is needed to prove that the composite sample is representative of the whole batch and does not mask contamination, low potency, variability, or other quality problems.

The first assumption to be made is the normality of the data and it should be checked using the Normality test.

Variability of individual assay values within container and between individual containers and the composite sample should be assessed using Interval plots, which plot the means and associated 95% confidence intervals for every group of data.

Then the variances of the composite sample and all individual samples are tested to see if they were significantly different using Test for Equal Variances, using the test based on normal distribution.

Using Capability analysis for Normal data regarding specification limits, the process should be evaluated in order to demonstrate that the process is capable, which means that the process is able to continuously yield a product that meets the specification limits.

All these statistical analyses are needed in order to determine whether the means of the 2 independent samples are equivalent. A comparison of the individual assay values gained from the composite sample and the individual samples obtained from all containers combined should be made using the Equivalence Test (two one-sided t-tests, TOST).

Equivalence Test (TOST)

The use of a simple t-test for this analysis often causes paradoxical results, especially when high numbers of experimental results or low spread is observed. In addition, only the variance contribution of repeatability (within-series precision) is taken into consideration for the t-test (Ermer et al., 2013). Two papers contain examples of why the equivalence test (TOST) is preferred over the still commonly used t-test (Chambers et al., 2005; Limentani et al., 2005). Relevant differences need to be distinguished from irrelevant ones, thus the t-test is not suitable. The mathematical tool of the equivalence test is a better approach which provides a way to assess practical significance in addition to statistical significance.

The Equivalence Test (TOST) is used when it is necessary to prove that the mean values of two sets of results do not differ too much, i.e. they are practically equivalent. It is important to understand that "equivalence" does not mean "equality." Equivalence should be understood as "sufficiently similar" for both sets of results. The definition of "sufficiently similar" is something to be decided a priori based on scientific considerations, and becomes the basis of the alternative hypothesis (USP40-NF35, 2019). Equivalence tests, with a given error probability α, are applied to decide if an estimate lies within a certain equivalence interval or not (Kaminski et al., 2010).

In classical statistical hypothesis testing, there are two hypotheses, the null and the alternative. For example, with a standard t-test, the alternative hypothesis is difference, and the null hypothesis is no difference (Hauck et al., 2009). With this classical approach, one rejects the null hypothesis in favor of the alternative if the evidence is sufficient against the null. A common error is to interpret failure to reject the null as evidence that the null is true. Actually, failure to reject the null just means the evidence against the null was not sufficient. The consequence of this understanding is that, when one seeks to demonstrate similarity, from two sets of results, then one needs similarity as the alternative hypothesis (USP40-NF35, 2019).

To be considered equivalent the means of the two groups of results should not differ more than the equivalence limit, d. The hypotheses for the equivalence test are then:

H_0: $|\mu_1 - \mu_2| \geq d$, or H_0: $|\mu_1 - \mu_2| \leq -d$

The alternative hypothesis is actually two individual one-sided hypotheses:

H_{A1}: $\mu_1 - \mu_2 < d$, and H_{A2}: $\mu_1 - \mu_2 > -d$

For this reason, this statistical tool is referred to as two one-sided tests (TOST). As one-sided tests, each can be addressed with a type I error of $\alpha = 0.05$. The TOST is conducted by rejecting the null hypothesis in favor of the alternative hypothesis if the $100(1 - 2\alpha)$ % two-sided confidence interval (90%) is entirely contained in the equivalence interval $(-d, +d)$ (USP40-NF35, 2019). When the null is rejected, we conclude that the two groups of results are equivalent in their means.

The acceptance criteria for this evaluation are set to the equivalence limit, d=3 (ISPE, 2003; Ermer et al., 2013 Ermer et al., 2015).

Interpretation of results

Normality test determines that all data follow a normal distribution. Interval plots demonstrate that the confidence intervals for means do overlap, which means the difference in means may not statistically significant. Differences between the spreads of the groups should be very small. Low variability proves that the manufacturing process yields a homogeneous product.

The Test for Equal Variances should demonstrate that variances of the composite sample and all individual samples are not significantly different.

It is important to emphasize that all obtained results should be within specification limits, which means that the process is able to continuously yield a product that meets the specification limit, i.e. capable process for all batches.

According to the results from the Equivalence Test (TOST), the manufacturer can claim equivalence between the mean of the composite sample and the mean of all individual samples combined. The entire range of the 90% Confidence Interval of the difference between the means should lie within the equivalence interval, thus can be concluded with 95% confidence that the two samples are equivalent in their means. The defined acceptable difference is a measure of the practical relevance of the observed difference.

The same results for all statistical evaluations must be observed for all three batches which are part of verification of the sampling plan.

Conclusion

This paper describes the verification process of the sampling plan for solid bulk pharmaceutical product with requirements for generating composite sample. The Equivalence Tests (TOST) is a statistical tool that could be used to demonstrate that the mean of the composite sample and the mean of all individual samples combined are equivalent with 95% confidence. The statistical evaluations and comparison of the results should demonstrate that the composite sample adequately represents the whole batch and the sampling plan is appropriate to provide a representative composite sample for the batch from which it is taken, considering the most stressed part of the production processes. Thus, it is possible to limit the routine testing at batch release to representative composite samples.

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References

Chambers, D., Kelly, G., Limentani, G., Lister, A., Lung, K.R., Warner, E., 2005. Analytical method equivalency: an acceptable analytical practice. Pharm Technol. 29(9), 64–80.

Ermer, J., Limberger, M., Lis, K., Wätzig, H., 2013. The transfer of analytical procedures, J. Pharm. Biomed. Anal. 85, 262.

Ermer, J., Nethercote, P., 2015. Method Validation in Pharmaceutical Analysis. A Guide to Best Practice, WILEY-VCH Verlag GmbH&Co.KGaA

European Commission Health and Consumers Directorate-General, EudraLex, 2014. The rules governing medicinal products in the European Union, Volume 4: Good manufacturing practice, Medicinal products for human and veterinary use, Part 1 - Chapter 6 - Quality Control.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2014- 11_vol4_chapter_6.pdf.

European Medicines Agency Committee for Human Medicinal Products (CHMP), 2017. Guideline on manufacture of the finished dosage form.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-manufacture-finished-dosage-form-revision-1_en.pdf

Hauck, W.W., DeStefano, A.J., Cecil, T.L., Abernethy, D.R., Koch, W.F., Williams, R.L., 2009. Acceptable, Equivalent, or Better: Approaches for Alternatives to Official Compendial Procedures, Pharmacopeial Forum 35(3), 772-778.

International Society for Pharmaceutical Engineering (ISPE), 2003. Good Practice Guide: Technology Transfer

Kaminski, L., Schepers, U., Wätzig, H., 2010. Analytical method transfer using equivalence tests with reasonable acceptance criteria and appropriate effort: Extension of the ISPE concept, Journal of pharmaceutical and biomedical analysis, 53(5), 1124–1129. https://doi.org/10.1016/j.jpba.2010.04.034

Kou, D., Ma, H., Bishop, E.J., Zhan, S., Chokshi, H.P., 2011. Sampling Considerations in: Nickerson, B. (eds) Sample Preparation of Pharmaceutical Dosage Forms. Springer, Boston, MA. pp 21–39. https://doi.org/10.1007/978-1-4419-9631-2_2

Limentani, G.B., Ringo, M.C., Ye, F., Bergquist, M.L., McSorley, E.O., 2005. Beyond the t-test: statistical equivalence testing. AnalChem. 77(11), 221A–226A.

Raval, N., Tambe, V., Kuche, K., Maheshwari, R. and Tekade, R.K., 2018. Basic Concept and Application of Sampling Procedures, in: Advances in Pharmaceutical Product Development and Research, Dosage Form Design Parameters, Academic Press, pp. 303–338. https://doi.org/10.1016/B978-0-12-814421-3.00009-9.

United States Pharmacopeia (USP40-NF35), March 2019. General Chapter, 1010, Analytical Data; Interpretation & Treatment.

https://doi.org/10.31003/USPNF_M99740_05_01

World Health Organization (WHO), 2005. Technical report series, Guidelines for sampling of pharmaceutical products and related materials, 929, Annex 4.

https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs929-annex4-guidelinessamplingpharmproducts.pdf?sfvrsn=f6273f30_2

Резиме

Регулаторни барања за верификација на планот за земање мостри од цврсти фармацевтски балк производи

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Клучни зборови: Земање примероци, цврст фармацевтски балк производ, репрезентативен композитен примерок, верификација на план за земање примероци со композитен примерок, тест за еквивалентност (TOST)

Најпогоден план за земање примероци за рутинско испитување при ослободување на серии на цврст фармацевтски балк производ е план за земање примероци со барања за генерирање на композитен примерок. Потребна е верификација на планот за земање примероци за рутинско испитување пред да може да се користи како таков. Верификацијата треба да покаже дека композитниот примерок е репрезентативен за целата серија и го зема во предвид најкритичниот дел од процесот на производство на цврстиот фармацевтски балк производ.

Како дел од верификацијата, треба да се изврши земање примероци во поголем обем за да се покаже дека производниот процес дава хомоген производ. Земањето примероци за испитување при ослободување на серии на цврст фармацевтски балк производ се врши на крајот од производниот процес од секој поединечен контејнер каде што се чува серијата. Сите контејнери заедно ја претставуваат варијабилноста на целата серија, односно на поединечните примероци земени од секој контејнер. Процесот на верификација треба да покаже дека поединечните примероци земени од секој контејнер даваат споредлива варијабилност на процесот на земање примероци бидејќи композитниот примерок се подготвува од сите контејнери. Статистичката евалуација и споредбата на резултатите од поединечни примероци и композитниот примерок е најсоодветна кога се изведува со користење на тест за еквивалентност (TOST).

Доколку се добие еквивалентност помеѓу поединечни примероци од секој контејнер и композитниот примерок, тогаш рутинското испитување може да се ограничи на репрезентативни композитни примероци од однапред одредени контејнери дефинирани во шемата за земање примероци. Планот за земање примероци со репрезентативен композитен примерок треба да биде доволно потврден дека е погоден за сите идни серии.