Journal of Pharmaceutical and Biomedical Analysis 160 (2018) 73–79

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Analytical Target Profile: establishment of precision requirements for assay

Joachim Ermer

Sanofi-Aventis Deutschland GmbH, Quality Control Services Frankfurt Chemistry, Industriepark Hoechst, Bldg. D711, D-65926 Frankfurt am Main, Germany

ARTICLE INFO

Article history:
Received 29 June 2018
Received in revised form 16 July 2018
Accepted 18 July 2018
Available online 20 July 2018

Keywords:
Analytical lifecycle management
Analytical Target Profile
Precision
Probability distribution
Quality-by-design
Target measurement uncertainty

ABSTRACT

Approaches are presented to establish precision (or target measurement uncertainty) requirements to drug substance and drug product assays. They are based on the simple and well-known concept of the normal distribution probability around true content values represented either by manufacturing range limits, or by the manufacturing target (usually 100% label claim). A maximum acceptable precision is derived which allows a defined probability of analytical results within the established acceptance limits of the specification and thus an objective and rational establishment of precision acceptance criteria. By this approach, α or type-I-errors are controlled, i.e. the maximum probability of failure for intrinsically acceptable results is limited. The combination of this normal distribution probability approach with guard bands allows controlling ß or type-II-errors, i.e. the acceptance of intrinsically not conforming results is limited. Here, no assumptions concerning the manufacturing range are needed; therefore this approach can also be applied for quantitation of impurities. The guard band approach allows the highest level of control, but requires in turn high demands on the precision. Therefore, it should be restricted to drug product assays or impurity determinations with larger risks, i.e. justified by a corresponding clinical relevance, such as narrow therapeutic ranges or substantial toxicity.

1. Introduction

An analytical procedure must be demonstrated to be fit for its intended purpose, which applies to its entire lifecycle. To achieve this goal, a quality-by-design approach has been proposed for pharmaceutical analyses which includes the three stages Procedure Design and Development, Procedure Performance Qualification, and Continued Procedure Performance Verification [1,2], in alignment to manufacturing process validation [3] (see Fig. 1).

A fundamental component of this approach is having a predefined objective that stipulates the performance requirements for the analytical procedure, i.e. the Analytical Target Profile (ATP). "The ATP states the required quality of the reportable value produced by an analytical procedure in terms of the target measurement uncertainty (TMU)." [2]

The performance requirements, i.e. accuracy and precision (or TMU) in case of quantitative assay procedures should be defined by the measurement objectives of the given test (Quality Attribute) which is linked to the product control strategy, such as water content in a drug substance, assay of active in drug substance or drug product, content of impurities, etc. As based on the measurement objective, the TMU should be (as far as possible) not directly linked to a given analytical method or technique. If the TMU can be established unambiguously, any method conforming to the ATP requirements can be applied. Such a concept is already applied in compendia for determination of elemental impurities [4,5]. All other performance attributes are method-specific, and eventually consolidate in either accuracy (bias), or precision, for example linearity (justification of the calibration model), specificity, or quantitation limit.

But how can an acceptable precision or TMU be derived in an objective way?

Often, these acceptance limits have been defined from the capability of the given analytical technique, for example 2.0% or 3.0% [6] relative standard deviation (RSD) of intermediate precision for HPLC assay. However, such a capability-approach ("what can be achieved") lacks scrutinization versus the requirements represented by the acceptance limits of the specification (SL) ("what must be achieved"). Even 2.0% intermediate precision are obviously not suitable for a drug substance assay with the usual SL of 98.0 to 102.0%. Although these generic SLs (as well as 95.0 to 105.0% for drug products) are also based on historical experience with no direct (patient) safety link, they have become ingrained in

Abbreviations: ATP, Analytical Target Profile; TMU, target measurement uncertainty; GB, guard band(s); SL, specification limit(s); QL, quantitation limit.

E-mail address: Joachim.ermer@sanofi.com

https://doi.org/10.1016/j.jpba.2018.07.035
0731-7085/

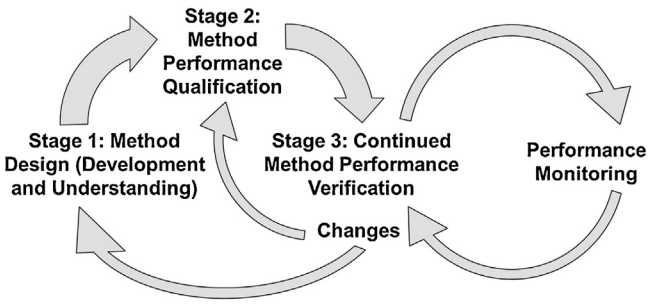

Fig. 1. Analytical performance (validation) lifecycle approach.

regulatory expectation and would need hard justification to change [28,29].

Another proposal has been to use a defined fraction of the specification range, for example 60% resulting in a TMU of 3.0% for content limits of ± 5.0%, i.e. 95.0–105.0% [7], which might be considered as somewhat arbitrary, too. However, in that paper the precision and accuracy requirements for the ATP have been further modelled using a two-sided beta-content tolerance interval approach thus providing the link to the requirements. The disadvantage of this approach is that an evaluation is only possible with the experimental precision results obtained with the final analytical procedure.

In the CITAC-Guideline [8], an approach is described to calculate the target standard uncertainty by dividing the specification range ("compliance interval") by a factor of 16. This includes a coverage factor of 2, which gives a level of confidence of approximately 95%. As often the underlying manufacturing processes are not symmetrical to the specification ranges and a shift of the process mean can be expected, in the following the literature approaches to define TMU will be adjusted to a one-sided calculation. For the TMU calculation, always the tighter range between SL and process mean or true assay value is relevant. Such a one-sided approach can also be directly applied to one-sided specification limits. Thus, in the CITAC-approach, the one-sided specification range is divided by a factor of 8 to obtain the TMU.

In analogy to the six sigma approach to process capability [9], the method capability is calculated by dividing the one-sided specification range by 3 times the (actual) standard deviation (SD). The method capability should be at least 1.0, but usually a "safety margin" is applied and 1.33 or 2.0 is recommended. In the precision-to-tolerance ratio approach (PTOL), even an index of 3.33–10 should be applied [10]. Transforming this calculation, the TMU corresponds to the one-sided range divided by a factor of 4–6 or even 10–30. Note that by this transformation, not the actual analytical variability is addressed (i.e. capability-based), but the maximum one allowed conforming to the SL (i.e. requirement-based).

The tolerance interval can be defined to contain a defined fraction (e.g. 90%) of future results with a defined confidence (e.g. 95%) [11] with tabulated tolerance factors for the number of determinations used to obtain the standard deviation. Alternatively, the Student-t-factor can be used for the defined level of statistical confidence and the degrees of freedom in the respective precision study [12]. General tolerance or coverage factors, e.g. 2 (corresponding to 95% level of confidence) or 3 (corresponding to 99% level of confidence) have been proposed to be used directly as a division factor to obtain the TMU [13].

For volumetric titrations, an acceptable repeatability is proposed as one third of the one-sided content limits, for example 0.33% RSD in case of acid/base titrations with content limits of ±1.0% [14]. In order to take intermediate precision into account, a division factor of 4 can be assumed for the TMU.

All these approaches are related to probability distributions, but the division factors larger than 2 (95% confidence) or 3 (99% confidence) try to include additional or unknown (long-term) uncertainty sources, i.e. they add up worst-case scenarios. This often results in unfeasible requirements, in particular for HPLC drug substance assay. With SL of 98.0–102.0%, a TMU of 0.25%, 0.50%, or 1.0% would result for the CITAC-approach, the method-capability-approach, and the 95% tolerance approach, respectively. If the tighter TMU requirements would be really necessary, usually obtained intermediate precisions for drug substance assays (pooled averages 0.80% up to 1.4% [15,16] would result in a much larger frequency of out-of-specification results due to random variability than observed in Quality Control (QC) practice.

Although these simple division factors are also related to a probability distribution, they do not consider the possibility that the distribution may overlap with both specification limits, which would alter the probability of results outside the limits. Therefore, this article proposes approaches to establish TMU criteria for assays of active in drug substances and drug products directly based on calculations of the normal distribution probability.

2. Fundamental assumptions

The starting point to derive the TMU criteria are the established acceptance limits of the specification, as representation of the measurement requirements for the given Quality Attribute. Usually, these content limits follow in pharmaceutical QC traditional regulatory expectations, i.e. 98.0–102.0 or 95.0–105.0 for drug substance and drug product, respectively. As acceptance ranges of the specification must include both manufacturing and analytical variability, assumptions for the manufacturing part of the specification range (i.e. the range of the true content of manufactured batches) have to be made to establish the TMU.

In principle, accuracy (bias) and precision can be evaluated simultaneously, or separately. The former would allow a "trading" between bias and precision, i.e. a larger bias might be acceptable in case of high precision (or vice versa). However, a combined experimental approach for drug product assay necessitates that spiked samples which are usually needed for accuracy are representative enough to allow a routine sample preparation. The latter is crucial to obtain the precision of the reportable value, i.e. that of the routine application of the analytical procedure.

The main objective of Stage 1, analytical procedure design, is the elimination of bias (systematic errors). When this is achieved, the main focus can be directed to the investigation and control of precision (random variability). Statistically, a true bias of zero is assumed, with an acceptance criterion for the observed bias in the ATP based on the expected range of random experimental variability.

The derivation of the TMU for assay from SL is based on the assumption of a normal distribution, which is almost impossible to prove, but can be expected with good reason for physico-chemical assay techniques usually applied in pharmaceutical analysis.

Although strictly the thus obtained TMU represents only the allowed random variability, it should also include any systematic bias which cannot be specified. However, the preferred approach should be to determine the bias and eliminate or correct it. Any shift which may develop over time, such as stability-relevant degradation will reduce the specification range available for the analytical procedure and has to be added to the manufacturing range.

3. Establishment of TMU for drug substance

The maximum allowed manufacturing range for an active ingredient in drug substance is defined by the allowed sum of impurities