Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 293–303

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Transfer of analytical procedures: A panel of strategies selected for risk management, with emphasis on an integrated equivalence-based comparative testing approach

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ARTICLE INFO

Article history:
Received 3 December 2010
Received in revised form 25 May 2011
Accepted 26 May 2011
Available online 2 June 2011

Keywords:
Analytical transfers
Chromatographic methods
Comparative testing
Equivalence
Specifications

ABSTRACT

In 2001, a multidisciplinary team made of analytical scientists and statisticians at sanofi-aventis has published a methodology which has governed, from that time, the transfers from R&D sites to Manufacturing sites of the release monographs. This article provides an overview of the recent adaptations brought to this original methodology taking advantage of our experience and the new regulatory framework, and, in particular, the risk management perspective introduced by ICH Q9. Although some alternate strategies have been introduced in our practices, the comparative testing one, based equivalence testing as statistical approach, remains the standard for assays lying on very critical quality attributes. This is conducted with the concern to control the most important consumer's risk involved at two levels in analytical decisions in the frame of transfer studies: risk, for the receiving laboratory, to take poor release decisions with the analytical method and risk, for the sending laboratory, to accredit such a receiving laboratory on account of its insufficient performances with the method. Among the enhancements to the comparative studies, the manuscript presents the process settled within our company for a better integration of the transfer study into the method life-cycle, just as proposals of generic acceptance criteria and designs for assay and related substances methods. While maintaining rigor and selectivity of the original approach, these improvements tend towards an increased efficiency in the transfer operations.

1. Introduction

The technology transfers of chemical synthesis, drug product manufacture and analytical controls characterizing critical quality attributes constitute key components of the pharmaceutical development of new drugs. For a new chemical entity (NCE), the analytical method transfer operations entail the transfer of the control monograph method from an originating laboratory (typically the research and development (R&D) analytical sciences laboratory) to a receiving laboratory (typically the quality control (QC) laboratory of the manufacturing plant).

Development of the drug market and challenges such as its globalization, perspectives of growth and development in emerging markets, strong price competition, manufacturing rationalization and increasing pressure from claims departments tend to increase transfer operations in the adaption strategies deployed by the companies. In this context, the efficiency, compliance and cost-effectiveness of technology transfers have become strategic aspects of drug development (cf. possible delays on the time to filing and marketing, loss on the production costs).

The analytical transfer constitutes now a major and integrated step in the method life cycle, entailing strong links with the validation. More specifically, inter-laboratory studies conducted usually for transfer purpose enable to address a major component of the robustness item required by industry guidelines on validation (cf. ICH Q2(R1) [1], FDA Guidance for Industry [2], and FDA Reviewer Guidance [3]): the method reproducibility assessment.

The absence of an official and harmonized regulation and the increasing scrutiny of regulatory agencies regarding the mastery, the documentation and the probationary nature of analytical transfers (see for example the numerous FDA 483 observations on that topic) have prompted the pharmaceutical industry to devote

Abbreviations: ANOVA, analysis of variance; API, Active Principal Ingredient; CI, confidence interval; CQA, critical quality attribute; CV, coefficient of variation (referred also as relative standard deviation); DP, drug product; GMP, good manufacturing practices; LoD, Limit of Detection; LoQ, Limit of Quantification; IEC, insufficient evidence to conclude; NCE, new chemical entity; OUCB, one-sided upper confidence bound; QC, quality control.

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doi:10.1016/j.jpba.2011.05.034

Nomenclature

B^*	transfer acceptance criterion for the mean bias of the receiving unit to the sending unit
Q^*	transfer acceptance criterion for the intermediate precision of the receiving unit
S	number of sites involved in the inter-laboratory study
N	number of series per sites in the inter-laboratory study
n	number of determinations per series in the inter-laboratory study
Q_s	estimated intermediate precision CV of the receiving unit s ($s > 1$) within the transfer inter-laboratory study
UB(Q_s)	95% one-sided upper confidence limit of the intermediate precision CV Q_s of the receiving unit s ($s > 1$) within the transfer inter-laboratory study
B_s	estimated mean bias of the receiving unit s ($s > 1$) to the sending unit within the transfer inter-laboratory study
CI(B_s)	half-width of the 90% confidence interval of the mean bias B_s of the receiving unit s ($s > 1$) to the sending unit within the transfer
b_0	estimated mean bias of the R&D Quality Control laboratory to the Analytical Development laboratory within the "hand-over" (covalidation) study
CI(b_0)	half-width of the 90% confidence interval of the mean bias b_0 of the R&D Quality Control laboratory to the Analytical Development laboratory within the "hand-over" (covalidation) study
q_0	estimated intermediate precision CV of the R&D Quality Control laboratory within the "hand-over" (covalidation) study

considerable attention to analytical transfers in recent years. In that framework, a multidisciplinary team made of analytical scientists and statisticians at sanofi-aventis has published in 2001 [4] a methodology which has governed, from that time, the transfer from R&D sites to Manufacturing sites of the release monograph of the Active Principal Ingredient (API) and of the formulated drug product (DP).

After a reminder of this historical approach, this paper proposes an updated transfer methodology implemented recently within the company. Lying on the principles of risk management, this updated methodology brings a panel of strategies custom-tailored to the context from prior scientific information. Among these strategies, the equivalence-based comparative testing approach from the founding paper is increasingly integrated into the method lifecycle, along with refinements and simplifications (e.g. design and acceptance criteria for the most current situations) allowing an increased reactivity in the transfer operations.

2. Historical sanofi-aventis transfer approach and directions of recent evolutions

2.1. Historical sanofi-aventis R&D transfer approach

In the unified transfer approach proposed in the publication of 2001, mainly concerned with assay, impurity and related substances methods, the sending laboratory is acknowledged as method expert and ultimate reference (as developer and early practitioner of the analytical method); the accreditation of the receiving laboratory is pronounced after demonstration from an inter-laboratory study [4] that it is able:

- to obtain, in routine use of the method, comparable results in mean and precision to the ones that would have been produced by the sending laboratory, the original expert of the method,
- to take appropriate subsequent decisions with a good control of the risks of errors.

The statistical equivalence approach is used for the assessment of precision and accuracy [1] performances (or "trueness" according to the ISO definition [5]) of receiving units with regards to acceptance criteria predefined on need for intended use. This choice is justified by the better fit of the approach to the objective, its logical performance and the appropriate control of the risks it allows; in particular, its capacity to control the most important consumer's risk of accepting poor transfers [6–8] is underlined.

As already reported in a previous publication [9], the company disposes of a significant hindsight of application of this methodology; indeed, for more than ten years, it has been used successfully for the transfer of both assay and impurity methods of not less than 11 APIs and 15 drug products of new chemical entities; in addition, it has been applied also for the assay and related substances methods of four biological compounds.

All along this efficient collaboration, analysts and statisticians have developed a reciprocal understanding, so much so that statisticians have become permanent members of the analytical transfer teams.

From this experience, the strategy has shown a very good discriminating capacity in the sense that failure to pass acceptance criteria (insufficient precision or accuracy at the receiving units) has been always followed by the identification of root causes to non-equivalence. Then, similar performances were achieved at the end by the receiving laboratories, after additional training or improvements/clarifications in the monograph.

Hereafter, a reminder on the basics of this equivalence-based comparative approach used historically by sanofi-aventis is provided (design, end-points, acceptance criteria, statistical analysis and decision procedures).

2.1.1. Inter-laboratory study design

A statistically designed inter-laboratory trial is conducted on a single batch, after the appropriate training of receiving laboratory(ies) on the method. As far as possible, it is generally preferable to involve in the inter-laboratory study of the initial transfer as much prospective industrial laboratories (such as additional or back-up Manufacturing sites for example), instead of doing a series of pairwise transfers.

The typical study design is a twofold nested design with S fixed sites (generally $2 \leq S \leq 5$), N random series per site, and n independent determinations per series as illustrated in Table 1.

A sample size calculation (number of series N and number of independent determinations per series n) is performed on a case-by-case basis by the statistician involved in the method transfer [10]; method validation results and other historical data (such as stability results) are used to establish the assumptions for the sample size calculations.

2.1.2. Transfer end-points

For assay methods, the analytical measurement for statistical analysis is typically the titer, expressed beforehand in % of label claim. For impurity methods, it is the impurity amount in % when using manufactured batches or stressed samples; when using spiked solutions, the impurity amount may be expressed beforehand in % of the known weighed/spiked concentration.

Table 1
Inter-laboratory study design.

Site 1 (R&D)			Site 2 (Manuf #1)			…	Site S (Manuf #S-1)		
Series 1	…	Series N	Series 1	…	Series N		Series 1	…	Series N
x		x	x		x		x		x
…		…	…		…		…		…
x		x	x		x		x		x

The statistical evaluation being based on the equivalence approach, the transfer end-points lie on the intermediate precision CV and bias to the sending laboratory, addressing precision and trueness of the receiving sites separately (which constitutes a very popular practice in the literature about analytical transfers in that years [10,12–17]). As such, the approach is aligned with the harmonized approach used for method validation within the company and with the ICH recommendations currently in force in that field [1].

- Precision of receiving units

  From the results of each involved laboratory, in a onefold nested ANOVA framework, one may compute estimates of the within-series and between-series variance components [18,19]; the total variance is used to calculate the CV of intermediate precision Q_s of laboratory s ($s = 1, \ldots, S$), which may be reported with a 95% one-sided upper confidence bound (95% OUCB) using the Graybill–Wang method [20] and compared to the acceptance limit Q^*. At this point, one may stress on the importance of considering the intermediate precision CV as the variability end-point of interest (intermediate precision having the property to capture the total variation within the laboratory arising from running the experiments at different days, by different analysts, on different equipments). Indeed, in the literature on analytical transfers, some vagueness or inadequacies have remained for a long time about the precision characteristics of interest in the comparative studies (see [11,12] for example). Unlike repeatability, intermediate precision should be considered as enabling an effective measure of the random variations of the method in its routine use. It should be noted that the last draft for comments of General Chapter <1224> from the United States Pharmacopeia does an explicit reference to intermediate precision on that point of view [13].
- Trueness of receiving units

  The mean bias B_s of the receiving laboratory s ($s = 2, \ldots, S$) to the sending laboratory may be estimated through contrasts in a twofold nested ANOVA framework (series nested within site) and reported with its 90% confidence interval. Note that the comparison of this $(1 - 2\alpha) \times 100\%$ confidence interval to the acceptance limits $-B^*$ to B^* is identical to a α level equivalence hypothesis test [4]. In that sense, the bias of interest may be qualified as "relative" (mean of the sending laboratory being always the reference). For impurity amounts, when using manufactured batches, this difference of means and confidence limits are generally reported to the mean of the sending laboratory for decision making.

2.1.3. Acceptance criteria

The acceptance criteria, which constitute an essential feature of the equivalence approach, are chosen on need for intended use.

For assay methods, the acceptance criteria are selected on the basis of simulation programs integrating the method performances assessed during the validation and the characteristics of the release testing procedure. The basic principle of these programs is to investigate the maximum bias and true CV values (noted B^* and Q^*, respectively) allowable for a site to make good decisions with high probability during analytical test, with emphasis on controlling the consumer's risk. Practically, the probabilities of passing the release test are calculated for a matrix of true biases and true intermediate precision CVs and plotted as contourplots. The selection of the acceptance limits for the bias and the intermediate precision CV is done in order that the performances of receiving sites ensure that truly good batches will be released with a high probability and truly poor batches will not be released with a high probability.

2.1.4. Decision procedure

A practical modification of the equivalence test is used for decision making. This procedure is inspired from the FDA guideline on Food Effect Bioavailability and Bioequivalence studies [21].

The decision procedure for the intermediate precision CV at each receiving lab is illustrated in Fig. 1:

- if the point estimate of the intermediate precision CV of the receiving unit s, noted Q_s, is greater than Q^*, the precision is considered as insufficient and the receiving laboratory as not compliant (or NE for "Not Equivalent") (d),
- if the 95% one-sided upper confidence bound (95% OUCB) of the intermediate precision CV, noted UB(Q_s), is lower than Q^*, the precision is acceptable and the receiving laboratory as showing enough precision (or E for "Equivalent") (a),
- if the 95% one-sided upper confidence bound (95% OUCB) overlaps Q^*, there is insufficient information to conclude to acceptable precision (or IEC for "insufficient evidence to conclude") (b–c); the precision is questionable and the decision has to be based on the magnitude of the observed CV and other supporting information.

The decision procedure for the bias of each receiving lab i to the sending lab is presented in Fig. 2:

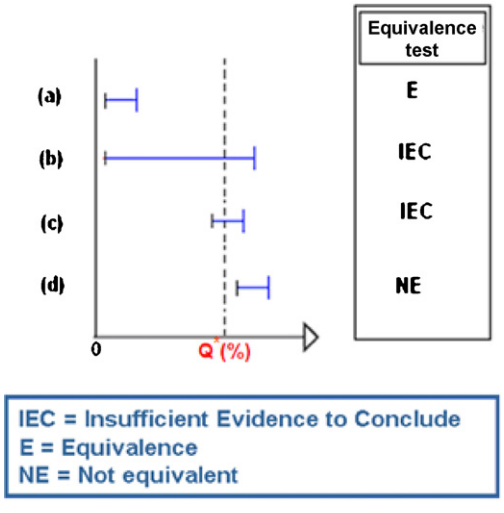

Fig. 1. Illustration of the decision procedure for the intermediate precision CV.

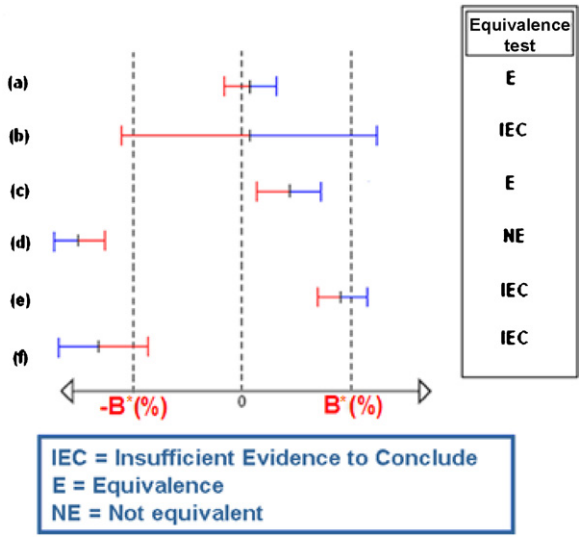

Fig. 2. Illustration of the decision procedure for the bias.

- if the 90% two-sided confidence interval for the bias, noted $B_S \pm CI(B_S)$, is totally outside the acceptance region $[-B^*; B^*]$, the bias is considered as significant and the receiving laboratory as not compliant (NE) (d),
- if the confidence interval (CI) is totally within $[-B^*; B^*]$, the bias is considered as irrelevant at the 5% significance level and the receiving laboratory as showing enough accuracy (E) (a–c),
- if CI overlaps $[-B^*; B^*]$, there is insufficient information to conclude no relevant bias (IEC);
  - in the case where the point estimate of the bias is outside the acceptance region, the performance of the receiving laboratory are considered as questionable for using the method (f);
  - in the case where the point estimate of the bias lies within the acceptance region, the decision has to be based on the magnitude of the observed bias and other supporting information (b–e).

In case of insufficient evidence to conclude for the intermediate precision CV or the bias (IEC), the analyst in charge of the transfer is undertaking an investigation as based on the collected results. In this case, three situations may be encountered:

- after investigation, some root causes have been identified; in that situation, further experiments may be decided and new statistical analyses conducted;
- after investigation, the results are close to the acceptance criteria and no evident analytical differences between the sites have been identified; in that situation, considering the performances revealed by the inter-laboratory study, an ad-hoc statistical evaluation of the potential incurred risks limited to the analytical decision (producer's and consumer's risks) may be performed and support the final decision of accreditation; the total error approach may be of particular interest in this context for its lower false rejection rates [22];
- after investigation, the results are far from the acceptance criteria and no evident analytical differences between the sites have been identified. The analysts can ask to re-launch the inter-laboratory studies; actually, this latest situation should not occur.

In our experience, root causes of non-equivalence for a receiving laboratory generally fall into the four main categories of the Ishikawa fishbone diagram [23]:

- man (ex: insufficient training of one technician),
- method (ex: insufficient light protection of solution for a photosensitive compound, different ways of weighing, tablet dissolution, integration practices),
- machine/apparatus (ex: spectrophotometer generation),
- materials (ex: material of tubes).

2.2. Risk management: a key direction of evolution of analytical transfer practices

In the industry, the principles of quality risk management described in the ICH Q9 guideline [6] have been gradually integrated in the analytical transfer operations [7,10]. Therefore, nowadays, the applicants endeavour to arrange transfer operation so that it:

- remains an integral part of organizational processes,
- explicitly addresses uncertainty,
- takes into account the best available information,
- is transparent and inclusive,
- enables continual improvement and enhancement of the analytical methods.

Otherwise, as not all assays provide the same level of risk to product quality, a variety of complementary transfer strategies have been proposed to answer appropriately to the two main principles of this guidance:

- the evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient,
- the level of effort, formality and documentation should be commensurate with the level of risk.

It is exactly in that perspective that Quattrochi et al., directly in line with the paper of Swartz and Krull [22], are identifying four tailored and structured transfer strategies, in the Stimuli article of 2009 presenting the basis of a new USP General Information Chapter [12]:

1. comparative testing,
2. method covalidation,
3. method verification or revalidation,
4. transfer waiver.

2.2.1. Comparative testing

In this strategy, as already underlined in the presentation of our historical approach, the statistical design, evaluation and decision procedure are essential stakes of risk management. Among the numerous papers on that topic, one may emphasize the well documented overviews of the state of the art proposed in 2009 by Rozet et al. on one hand [24] and by Liu et al. on the other hand [25]. These papers are providing in particular information and references about the three most common approaches used for the evaluation of tech transfers throughout the industry: the descriptive approach, the equivalence approach and the total error approach [26]. The equivalence and the total error approaches are standing out for low false acceptance rates (and then a good control of the consumer's risk).

2.2.2. Covalidation

Covalidation consists in involving the receiving lab(s) in the method validation, producing experimental results for critical topics (specificity, linearity, accuracy and precision). In general, in the analytical transfer framework, key items of the covalidation, homogeneously with the requirements of method verification, lie in:

- the determination, from an inter-laboratory trial, of method intermediate precision at the sending and receiving laboratory(ies),
- the assessment of the method specificity at the receiving laboratory(ies).

For impurity methods, LoD/LoQ validation is recommended additionally. As such, by design, the "hand-over" approach between the Analytical Development and QC laboratories, presented previously in the framework of method validation, has clear similarities with the covalidation strategy.

2.2.3. Method revalidation or verification

Method revalidation or verification consists in ensuring that the analytical procedure maintains its performance characteristics at the receiving laboratory(ies). The degree of revalidation (or revalidation items) may depend on the nature of the method. In the changing industry model with the increased outsourcing of R&D activities (alliances, outsourcing, etc.), method revalidation may constitute, in some cases, an efficient approach when the transfer is performed from the Analytical Development laboratory of an external partner who does not share exactly the same environment (validation standards, analytical "culture" or "traditions", equipments).

2.2.4. Transfer waiver

This last approach may be a useful strategy in very specific situations where an inter-laboratory trial is not really justified after the risk assessment (use or experience of same or equivalent method at the receiving laboratory, new product with a composition/concentration comparable to that of an existing one, move of the personnel in charge of the development and validation to the receiving laboratory).

3. Recent enhancements and simplifications proposed to sanofi-aventis R&D historical approach

Recent adaptations in the company transfer policy are especially aimed at introducing improvements in a risk management perspective: increasing the flexibility and the reliability of the process, and proposing, as far as possible, practical simplifications to the historical comparative testing approach.

This section presents a description of the transfer strategies introduced in complement to the historical approach, followed by an overview of the updated internal procedure in the case of comparative testing, and concludes with practical simplifications and adjustments to the comparative testing strategy.

3.1. A versatile panel of transfer strategies

Recognized as interesting for dealing with specific situations or methods, the method covalidation, the method verification or revalidation and the transfer waiver strategies have been included as complementary options in the policy. According to the classification of the analytical procedures into three categories (see Table 2), a preferred transfer strategy is suggested; of course, in accordance to the aforementioned ICH Q9 principles, use of an alternative strategy may be justified from evaluation on case-by-case basis. Typically, an analytical method measuring a product "critical quality attribute" (according the Quality by Design principles) will generally fall in the first category.

It should be noted that the option 3 (method revalidation) in general not the most effective economically, is envisaged as the last option in case where the other are not possible.

3.2. Overview of the updated transfer procedure

Generally speaking, as recommended in the ISPE Good Practice Guide [11], the proposed procedure aims at passing the documented knowledge and experience gained during development to a new responsible and authorized party. It embodies both the transfer of documentation and the demonstrated ability of the receiving unit to effectively perform the critical elements of transferred technology, with the concern to satisfy all parties and regulatory bodies.

Practically, the procedure is made of five steps of which the duration is adjusted case-by-case, according to the context and constraints:

1. a preparatory phase,
2. the training of the receiving lab(s),
3. the development of the transfer protocol including the written version of the methods to be transferred,
4. the realization of the inter-laboratory study (with statistical evaluation of the results when necessary),
5. the writing of the analytical transfer report.

Further description of each step is proposed hereafter.

Although not intrinsic components of the transfer, two additional and crucial stages embedded in the process should be mentioned here:

- the final validation of the methods transferred at the sending site, concluding the preparatory phase,
- the writing of the monograph to be registered at the very end.

The writing of the monograph to be registered is concluding the transfer process, when receiving units have passed all acceptance criteria. This final monograph takes into account the last comments on the methods, without impact on their validation and transfer; moreover, the very knowledgeable hindsight on the method performances gained from the comparative study (cf. assessment of method precision at the different levels that are repeatability, intermediate precision, and possibly reproducibility when the number of laboratories is sufficient) is taken into account for establishing practical aspects of the monograph and supporting the specifications.

3.2.1. Preparatory phase

This initiation phase is started by the constitution of the analytical transfer team with a leader from the sending laboratory and representative(s) from the receiving laboratories and from the other concerned disciplines (statistics and quality assurance).

The first meetings of the team, taking place before the final validation of the method, are aimed at:

- listing the methods to be transferred,
- clarifying the transfer approach for each of them and identifying, through the acquired knowledge and an adequate risk assessment, the ones of which the transfer will require a formal comparative study with statistical design and analysis,
- running a desk review for each of them.

During this desk review, the discussed items include:

- Method: safety concerns, system suitability tests (and guidance when failed), preparation of samples (dissolution), number of injections, calculations, preliminary validation data, typical chromatograms, integration, preliminary validation data (important information if ever there is one).
- Materials: reagents (quantity and quality).

Table 2
Guide to transfer strategy depending on method category.

Category of methods	Preferred transfer strategy
Methods developed specifically for the API or drug product, and that are considered *critical*: *Assay*, *related substances and degradation products methods*; *in some cases, water content*, *dissolution*	Option 1: comparative testing with comparison based on formal equivalence approach[a]
Methods developed specifically for the API or drug product, and that are considered *less critical*: *GC*, *water content*, *dissolution*, *particle size distribution i.e.*	Option 2: covalidation, with comparison based on descriptive statistics only[b]
Compendial methods (Pharmacopeial): *Appearance*, *pH*, *particulate matter i.e.*	Option 4: transfer "waiver"[c]

[a] Options 2 or 4 could be applied in some cases when justified.
[b] Options 1 or 4 could be applied in some cases when justified.
[c] Even if there is a transfer "waiver", the method of the monograph is applied by the receiving site on one (or two) batch(es).

- Equipment: safety concerns to be added, apparatus availability, devices, glassware, etc.
- Product: batches, reference substances (availability, quantity, stability, etc.).
- Documentation: documents to be sent to the receiving laboratories.

This preparatory phase should give the opportunity to the receiving laboratories to make comments, suggestions for issue resolution or improvements before method validation. Possible changes in the method may be decided for the routine adaptation and the suitability of the method to an industrial environment.

However, depending on the circumstances of the development, one cannot exclude that the preparatory phase follows method validation in some cases.

3.2.2. Method validation at the sending site

Once the transfer strategy is defined, the methods are validated at the sending laboratory to fulfill the ICH requirements in the view of registration.

This step, which is not strictly part of the transfer operation, is a key milestone in the process for getting a reliable view on the performances of the analytical method (in particular, precision, accuracy – according to ICH definition – and robustness) and for the establishment of the transfer protocol.

For very critical methods submitted to the option 1 (equivalence-based comparative testing), the final validation takes the original form of a significant intermediate precision study, involving both the Analytical Development laboratory (the formal sending laboratory, developer of the analytical method and responsible of the transfer to Manufacturing sites) and the GMP Quality Control laboratory, co-located in the same facilities at the R&D site. After a preparatory phase and a training phase very similar to those described in this paper for the tech transfer, a comparative/collaborative study is conducted by both laboratories with the experimental design described in Table 3. It should be underlined that the proximity of these laboratories (often located in the same building), the day-to-day collaboration of their teams, the homogeneity of their equipments (sometimes even sharing the same apparatuses!) and reagents are making them not more heterogeneous than some laboratories may be inside.

This key co-validation work, referred internally as the "hand-over" study and supported by this bicephalous organization of analytical activities within the R&D, provides sound information that is leveraged in the design of the comparative study.

Each laboratory is performing four series of three independent determinations (with independent preparations of test and standard solution for each determination) on homogeneous samples from a same batch. At each laboratory, the four series are performed by at least two different operators and on at least two different apparatuses; the suitability tests described in the procedure should be achieved. For assay methods, the test solutions are prepared at the nominal concentrations. For impurity methods, the tests solutions should contain a quantifiable amount of impurities for allowing statistical analysis; if such a batch is not available (very pure batches), spiked solutions (with, in general, a content equal or close to the specification limit) or stressed samples may be used.

Statistical analysis of the experimental results is including two steps:

- Analysis of the Quality Control laboratory results using a one-way nested ANOVA model for estimating the within and between-series variance components [18,19], the intermediate precision CV q_0 at that laboratory, with 95% one-sided upper confidence limit calculated with the Graybill–Wang method [20].
- Analysis of the inter-laboratory results using a two-way nested ANOVA [4] for estimating:
  - the mean bias of the Quality Control laboratory to the Analytical Development laboratory with a 90% confidence interval, noted $b_0 \pm \mathrm{CI}(b_0)$,
  - the CV of reproducibility (for method robustness purpose), including between-labs, between-series and repeatability components of variability [18,19], with its 95% one-sided upper confidence limit calculated with the Graybill–Wang method [20] (NB: in the case where the number of receiving laboratories involved in the inter-laboratory study is small, the estimate of the CV of reproducibility is obviously poorly precise (large confidence interval)).

From this information, the estimates q_0 and b_0 are used for acknowledging the handover of the methods at the Quality Control laboratory; considering the context (cf. proximity of both laboratories) and the very limited risks of failure, the selected decision procedure is reduced to the simple comparison of point estimates of the QC laboratory CV and bias to predefined acceptance limits ("descriptive" analysis).

The results of this study are also involved in the assessment of the method accuracy, just as in confirming the adequacy of the specification limits in force and envisaging any adjustment if needed according to the revealed method performances.

3.2.3. Training of the receiving lab(s)

A technical training on methods is organized for the receiving lab(s), with observation and then, execution of the test procedure. This is an essential part of the whole process. The receiving lab(s) readiness is focused on technical aspects of the execution of the method at the site. In order to facilitate and/or improve the efficiency of the transfer or to prevent any difficulties during the inter-laboratory study, technical training is including the analysis of well known batches.

At this step, if available, the analysis of poor batches or stressed samples may be judicious, as a preliminary qualitative verification

Table 3
Intermediate precision (or "hand-over") study design.

R&D Analytical Development laboratory				R&D Quality Control laboratory (RQC)[a]			
Series 1	Series 2	Series 3	Series 4	Series 1	Series 2	Series 3	Series 4
x	x	x	X	x	x	x	x
x	x	x	x	x	x	x	x
x	x	x	X	x	x	x	x

[a] Laboratory located at the same R&D facilities than the Analytical Development laboratory.

of the capacity of the receiving laboratory to differentiate between good and poor batches. A clear and documented status on results found during the technical training should be done before deciding to launch the formal inter-laboratory study.

3.2.4. Development of the transfer protocol

The transfer protocol is prepared by the sending laboratory and preapproved by all the parties; it should make provision for:

- responsibilities,
- detailed analytical procedures to be transferred,
- samples to be used (test and reference materials),
- instruments to be used (including columns), and justification of equivalence when differing between sending and receiving laboratories,
- description of analytical methods,
- conclusion on the training phase,
- study design (inter-laboratory study design in case of comparative testing, items of focus, in case of method revalidation or covalidation), including experimental design and sample size (with explicit requirements on injections sequences and calculations),
- analytical results reporting rules (number of decimal figures),
- statistical analysis and decision procedures,
- acceptance criteria, chosen to ensure adequate performance in routine use,
- time schedule.

Whatever the strategy (comparative testing, co-validation and verification or revalidation strategies), the core inter-laboratory study experiments are focused on a single batch, just as done for the method validation (cf. related precision and accuracy items in particular) according to the regulation in force in that area.

Although diverging from the recommendations of the ISPE guideline [11], the option of focusing on a single batch is generally considered in first intention by most of the authors [8,13,25–31], considering its intrinsic focus on method variability with the exclusion of the production process variability. It is generally admitted that multiple analyses on a same batch are better than a few analyses on three batches for obtaining relevant statistical estimates of method precision and accuracy at the receiving laboratories, a reliable assessment of the performances of involved laboratories being a necessary condition to conclude to similarity with controlled risks. Otherwise, the batch should obviously be chosen for its representativeness of the product quality resulting from the process in force [8]; the usage of the most "perfect" batches is not advised. For related substances methods, the use of spiked samples (with amounts close to the specification limit) or stressed samples constitutes effective approaches; as much as possible, the sending laboratory will provide the samples to be tested at all the laboratories. In addition, for these related substance methods, the receiving site should evaluate the equipment sensitivity via the Limit of Detection (LoD) and Limit of Quantification (LoQ), which should be lower or equal to the reporting limit. Nevertheless, it should be noted that the sensitivity of the analytical method is generally monitored in routine analysis of batches through a suitability parameter lying on the simultaneous analysis of a sample at the LoQ level.

In order to reinforce the evaluation of the receiving site to handle the methods, it is proposed that, after passing the acceptance criteria of the inter-laboratory study conducted on one batch, the receiving site analyzes, according to the monograph, at least one more batch as different as possible from the batch used for the inter-laboratory study; tests realized in the framework of stability studies (cf. batch stored in accelerated conditions in particular) may be an excellent opportunity to perform such a verification, while using data available at the sending laboratory for other purpose. Acceptance criterion for this complementary verification may consist simply in compliance of the batch to the specifications or may be deduced from method reproducibility characteristics derived from the inter-laboratory study or other historical data.

3.2.5. Realization of the inter-laboratory study and statistical evaluation of results

The involved laboratories should try to perform the inter-laboratory study on the same period. Ideally, at each site, the test series have to be performed by at least two trained technicians, preferably using at least two different pieces of equipment at each site to enable some view on operator-to-operator and equipment-to-equipment sources of variability.

For all the tests, the laboratories should pass all suitability tests described in the procedure (in general: blank analysis, retention time, system precision and, in addition, for critical methods: specific chromatographic parameters, S/N ratio at reporting limit, etc.). In passing, one may point out that the verification of suitability tests by participating laboratories should also be included as prerequisite when using the covalidation approach.

For each parameter, results are reported as much as possible with a well-chosen number of decimal figures [9] and quality controlled at each site; these experimental results are collected by the sending site for statistical analysis (ideally, an adequate data entry template may be provided to each site by the sending laboratory).

Statistical analysis is conducted and results are interpreted according to the transfer protocol (comparison to the pre-established acceptance criteria).

3.2.6. Writing of the analytical transfer report

The final report, including:

- a presentation and a detailed review of the results (suitability tests, individual results),
- the main conclusions of the statistical analysis,
- the reporting of deviations with assessment of their impact, should conclude clearly on the accreditation or not of the receiving lab(s).

In case of failure of the acceptance criteria during the transfer process, results and conclusions of investigations should be appropriately documented, just as the rationale to perform further experiments when needed.

In the case where the acceptance criteria are just passed, provision for a surveillance period at the receiving lab(s) is advisable (cf.

Table 4
Predefined acceptance criteria for assay methods.

Assay	Specification limits	Transfer acceptance criteria	
		Q^* (%)	B^* (%)
Active Principal Ingredient[a]	(100) ± 1.0%	0.7	0.6
	(100) ± 1.5%	1.1	0.8
	(100) ± 2.0%	1.5	1.1
Drug product	(100) ± 5.0%	3.0	2.5
	(100) ± 10.0%	6.0	6.0

[a] For the API case, this formulation of specification limits is assuming the absence of impurities produced by the synthesis process; in the presence of impurities, the lower limit should be corrected with the total sum of impurities.

in particular, careful monitoring of suitability parameters, response factors, etc. in routine use). Evaluation of stability results generated by the receiving laboratory is in general a good approach to provide assurance about its appropriate mastery of the method [10].

After transfer completion, a conclusion meeting involving sending and receiving laboratories is organized with two main goals:

- a retrospective review of the transfer operation, with identification of possible ways of improvements and lessons learned,
- the development of a common monograph, constituting the first version of registration procedures, taking into account all the information generated during the transfer operation on method performances.

3.3. Practical simplifications and adjustments of the comparative testing strategy

For assay and impurity methods, the proposed simplifications to the historical approach consisting mainly of:

- a set of "standard" acceptance criteria,
- a "generic" inter-laboratory study design, made of 6 series of 2 determinations per laboratory.

The other fundamentals of the transfer process (steps, actors, statistical analysis and decision procedure) remain basically unchanged.

If the application of the recommended acceptance criteria does not involve formal prerequisites in general, the choice has been done to condition the use of the proposed "generic" design to the results of the method validation (intermediate precision study) for concerns of power of the equivalence tests in the transfer study.

3.3.1. Predefined acceptance criteria for the assay methods

The definition of predefined criteria remains merely based on the methodology published in 2001 [4] and recalled previously.

Otherwise, in the routine application of API and DP assay methods, the authors have summarized in Table 4, from the company experience, the five sets of specification limits of current usage.

For the record, the specification limits for the API are derived from an assessment of the overall method variability pre-existing at the time of the transfer and the process limits in the presence of impurities, whereas the ones relating to the DP correspond to standard practices.

For these different sets of specifications, the corresponding sets of acceptance criteria (Q^*, B^*) have been determined using the simulation programs. For the record, the median value of 0.5 was used for the ratio of repeatability CV to total CV. On our internal hindsight of analytical methods for the API and the DP, this choice covers most of the situations, while remaining rather an unfavourable case in general; this experience is reported by other authors [24]. Criteria presented in Table 4 have been deduced from the contourplots of probabilities of passing the release test (considering the difference in incurred patient risk for the API and the DP, a higher probability requirement is selected for the choice of criteria for the DP – 80% probability to meet specifications for the DP instead of 70% for the API).

Table 5
Proposed acceptance criteria for impurity methods.

Amount of impurity (%)	Q^* (%)	B^* (%)
0.15–0.30	20	60
0.31–0.50	15	50
0.51–0.80	10	40
>0.80	10	30

These acceptance criteria are chosen to ensure a satisfactory initial mastery of the method, knowing furthermore for a fact that the performances of the receiving laboratory will improve with gained experience of the method from routine use.

These proposed criteria for assay methods may be collated to the transfer criteria suggested in the literature. If some authors are sticking to recommend a case-by-case selection of the criteria [30] with more or less details on the supportive historical data [32], several publications/guidelines are attempting to provide generic figures for the most current situations.

The ISPE guideline recommends an acceptance criterion for the bias of 2% between the sending and the receiving laboratories with no distinction between API and dosage forms [11]. There is no explicit mention in the guideline about the acceptance criterion on the intermediate precision despite the recommendation of the guideline to compare both mean and variability. This choice is confirmed also as a standard industry practice at the time of the 2003 PhRMA workshop on Acceptable Analytical Practices [31].

Otherwise, a criterion of 2.0% is also recommended for the intermediate precision CV by some authors [28].

For drug substances, Brutsche [33] is proposing the following criteria: 1.0% for the bias and 2.0% for the intermediate precision; for drug products, a 2.0% criterion is recommended for both items.

Several authors are stating the inappropriateness of the typical 2.0% criterion for the bias in the case of the API. If this criterion is considered as acceptable by Ermer and Miller [27] for the assay of a DP with a specification range of [95%; 105%] in the case of a technology transfer study of common design and simple comparison of means, the acceptance criterion of 1.15% is proposed for the API with a specification range of [98%; 102%]; this criterion is similar to the 1.1% one proposed in this paper.

In the same situation, Chatfield and Borman [15] are recommending a tighter acceptance criterion of 0.5% for the bias with an approach focusing more on the producer's risk when process batch data is close to or overlaps specification limits.

At last, it may be noted that the predefined acceptance criteria Q^* on the intermediate precision CV remain compatible with the system precision suitability criterion defined by the European Pharmacopeia [34] (0.64% for a specification range of [98.5%; 101.5%], 0.85% for [98.0%; 102.0%] for a precision calculated on 6 injections) as greater than the latter.

3.3.2. Predefined acceptance criteria for impurity methods

The proposed criteria for the intermediate precision CV and the bias (Q^* and B^*) are depending on the actual amount of impurity in the investigated samples, are presented in Table 5; of course, appropriate scientific judgement may justify adaptations of these criteria on a case-by-case basis.

For impurity amounts lower than 0.15%, one may suggest a Q^* acceptance limit for the intermediate precision CV of 25% and an absolute difference (and not relative that time) of mean impurity

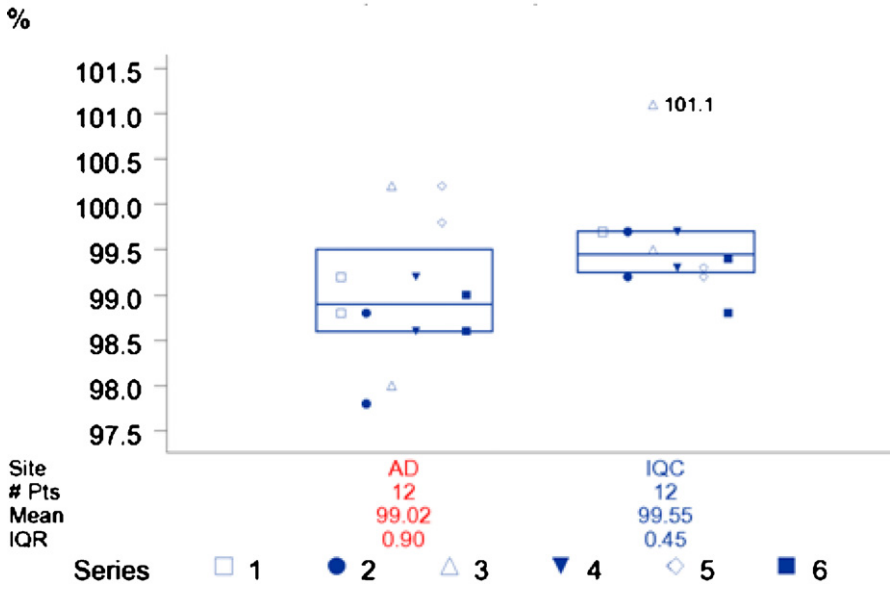

Fig. 3. Example (transfer of DP assay method): graphical representation of the inter-laboratory study results.

amounts relative to active (%) lower or equal to 0.05% between laboratories. In passing, these acceptance criteria are providing also indicative ruggedness requirements at the reporting limit (or Limit of Quantification) in the framework of method development and validation.

3.3.3. Generic study design

The proposed generic design for the inter-laboratory study is made of 6 series of 2 determinations per laboratory; the series are shared by at least two technicians and performed on at least two different equipments. This generic study design is close to the minimal design recommended in the founding paper (5 series of 3 determinations); with 2 determinations, each series correspond to the routine release protocol.

With this design, simulations (performed with the median value of 0.5 for the ratio of repeatability CV to total CV) are showing that the power of the equivalence test on the intermediate precision CV is greater than 80% for a true CV up to about $0.4 \cdot Q^*$. Otherwise, further simulations (with same assumption on the ratio of repeatability CV to total CV) are showing that the power of the equivalence test on the bias remains close to 80% for a true bias up to about $0.3 \cdot B^*$ and a true CV up to about $0.4 \cdot Q^*$.

As indicated before, the use of the generic design is envisaged only if, at the time of the method validation, the R&D Quality Control laboratory (RQC) has already been able to achieve good performances with the method. Otherwise, the statistician in charge of the analytical transfer performs a sample size calculation to determine a design with a sufficient power.

Practically, an informal decision rule based on the RQC laboratory performance characteristics is used to validate the applicability of the generic design. If the intermediate precision CV (q_0) and the mean bias (b_0) of the RQC laboratory are satisfying the following inequalities vis-à-vis the transfer acceptance criteria:

- $q_0/0.4 \leq Q^*$,
- $\text{Max}(|b_0 - 0.8 \times \text{CI}_{b_0}|; |b_0 + 0.8 \times \text{CI}_{b_0}|) \leq B^*$,

Table 6
Example (transfer of DP assay method): results of method hand-over.

R&D Analytical Development (AD) laboratory				R&D Quality Control (RQC)[a] laboratory			
Series 1	Series 2	Series 3	Series 4	Series 1	Series 2	Series 3	Series 4
99.2	98.8	101.0	99.2	98.6	99.0	99.2	98.8
95.8	98.8	100.2	98.6	99.8	99.0	99.2	97.8
98.8	96.4	98.0	99.2	100.2	98.6	99.2	97.0
Mean: 98.67				Mean: 98.87			
Repeatability CV (95% OUCB): 1.4% (2.4%)				Repeatability CV (95% OUCB): 0.6% (1.1%)			
Intermediate precision CV (95% OUCB): 1.5% (2.9%)				Intermediate precision CV (95% OUCB): 0.9% (2.2%)			
				Bias to AD lab: 0.2 [−0.9; 1.3]			

Table 7
Example (transfer of DP assay method): results of method transfer to Industrial Quality Control.

R&D Analytical Development (AD) laboratory						Industrial Quality Control (IQC) laboratory					
Series 1	Series 2	Series 3	Series 4	Series 5	Series 6	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6
99.2	98.8	100.2	98.6	99.8	99.0	99.7	99.7	99.5	99.7	99.2	99.4
98.8	97.8	98.0	99.2	100.2	98.6	99.7	99.2	101.1	99.3	99.3	98.8
Mean: 99.02						Mean: 99.55					
Repeatability CV (95% OUCB): 0.8% (1.4%)						Repeatability CV (95% OUCB): 0.5% (1.0%)					
Intermediate precision CV (95% OUCB): 0.8% (1.4%)						Intermediate precision CV (95% OUCB), that is: Q_s (UB(Q_s)): 0.6% (1.0%)					
						Bias to AD lab: 0.5 [0.0; 1.1]					

the generic design with 6 series of 2 determinations may be selected for the transfer inter-lab study.

Margin coefficients 0.4 (applied to q_0) and 0.8 (applied to b_0) are chosen for adjusting for the difference of design and sample size between the hand-over and the transfer studies.

3.3.4. Real example of application of the simplified strategy for a DP assay method

This section is proposing an example of application of the strategy to the analytical transfer of the drug product assay of an oncological compound in current development at sanofi-aventis.

Considering the specification limits [95.0%; 105.0%], the chosen transfer acceptance criteria are: $Q^* = 3.0\%$ and $B^* = 2.5\%$.

Results of Table 6 have been obtained during the hand-over study.

As a consequence,

- $b_0 = 0.2$ and $CI_{b_0} = 1.1$; $\text{Max}(|b_0 - 0.8 \times CI_{b_0}|; b_0 + 0.8 \times CI_{b_0}|)$ is then equal to 1.1% and clearly lower than B^* (2.5%);
- $q_0/0.4 = 0.9\%/0.4 = 2.25\%$, which is lower or equal than Q^* (3.0%).

Then, the generic design with 6 series of 2 determinations has been applied.

Finally, the results of the inter-laboratory trial of the transfer are presented in the form of a boxplot in Fig. 3. The individual adat and the results of their statistical analysis are put together in Table 7.

As a consequence, the receiving laboratory IQC is readily passing the transfer acceptance criteria with an intermediate precision CV significantly lower than 3.0% (95% one-sided upper confidence bound equal to 1.0%) and a mean bias to the sending laboratory AD, equal to 0.5%, and significantly lower than 2.5% (90% confidence interval equal to [0.0%; 1.1%]). The IQC laboratory is accredited to use the method.

4. Conclusion

The main purpose of the analytical technology transfer process is to qualify the receiving laboratory to perform an analytical procedure with controlled risks in decision making. The transfer strategies presented in the paper are forming a panel of approaches offering a good capacity to find a commensurate solution with the level of incurred risks, depending on the compound, the category of method, the criticality of related attributes and the type of the transfer. The selection of an approach should always be based on scientific knowledge and ultimately linked to the protection of the patient.

For the transfer of new and most critical methods, the comparative testing approach remains the preferred strategy. In this strategy, sound choices of:

- the statistical design, end-points and decision procedure,
- the transfer acceptance criteria on need for intended use,

are remaining the pillars of the control of risks (risks on the decision to accredit or not receiving labs, risks for a qualified receiving unit in the decisions made from the method results). Although each analytical transfer remains, to some extent, a specific case, the long term experience and collaboration between analysts and statisticians on that topic have permitted to build an approach combining sensitivity, selectivity, simplicity and efficiency.

As a final remark, if the rigorous process and methodology such as the good communication are undoubtedly increasing strongly the chances of succeeding in the transfer operations, they increase also the chances to find a well-assignable cause of failure when it occurs. Even if such a failure is in general not desirable for analytical transfer teams, it should be considered also as a real opportunity: opportunity of last improvement of the method before intensive use... and thus opportunity of increasing the reliability of the upcoming pharmaceutical routine quality control.

Acknowledgements

The authors would like to thank kindly M.A. Enault for her precious statistical programming support, T. Beltran, O. Bousquet, A. Savadogo, B. Vasselle for the materials of the presented example, all the analysts and preclinical statisticians of the company who have participated to the numerous transfer studies evoked in the article and played their part in the building of the proposed strategy.

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