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EACH LIFE IS UNIQUE

COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES

PH. EUR. 5.27.

10 April 2024

Introduction - Kamada

Kamada is a growing commercial-stage global biopharmaceutical company with a portfolio of marketed products indicated for rare and serious conditions. The company is a leader in the specialty plasma-derived field, focused on diseases with limited treatment alternatives.

קמהדע היא חברת ביו-פרמצבטיקה גלובלית מסחרית צומחת, עם פורטפוליו של מוצרים המיועדים למצבים נדירים וחמורים. החברה מובילה בתחום מוצרי הפלסמה הייחודיים ומתמקדת במחלות עם חלופות טיפול מוגבלות.

- **6 FDA-approved products** with global commercial network selling in over 30 countries

CYTOGAM (Cytomegalovirus Immune Globulin Intravenous (Human) [CMV-IVIG]) – Cytogam

GLASSIA® ALPHA1-ANTITRYPSIN (HUMAN) 2% – Glassia

HEPAGAM B® Hepatitis B Immune Globulin Intravenous (Human) – HepaGam B

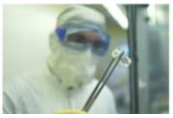
KamRho-D I.M. Rho(D) Immune Globulin (Human) – KAM-RHO D I.M

KamRho D I.V Rho(D) Immune Globulin (Human) – KAM-RHO D I.V

KamRAB Human Rabies Immunoglobulin – KamRAB

VARIZIG® VARICELLA ZOSTER IMMUNE GLOBULIN (HUMAN) – Varizig

WINRHO® SDF Rho(D) Immune Globulin Intravenous (Human) – WinRho



QC lab. Kamada

AerobiKA – AEROBIKA

BRAMITOB – BRAMITOB

FOSTER – FOSTER

Gammaplex – Gammaplex

Intratect – INTRATECT

IXIARO – IXIARO

Lamzede – LAMZEDE

Provocholine – Provocholine

Ruconest – Ruconest

Rupafin – RUPAFIN

Zetascra – Zetascra

Scope - Chapter 5.27. *Comparability of alternative analytical procedures*

- A new general chapter has been published in **Supplement 11.5** of the Ph. Eur.
- The text was adopted by the European Pharmacopoeia Commission in **June 2023**.
- This chapter describes how to demonstrate the comparability of an alternative analytical procedure to a pharmacopoeial analytical procedure, in line with the requirement laid down in section **1.1.2.5 of the Ph. Eur. General Notices**, which states:

"... alternative analytical procedures may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used."

Chapter *5.27.* does not introduce any new requirements, but is published for information.
The text provides practical guidance on how to demonstrate comparability and indicates that this comparability must be maintained over the lifecycle of both analytical procedures.

The EDQM performed a webinar on **17 January 2024** to present the new general chapter to its stakeholders in detail and provide an opportunity to answer any related questions.

-הפרק פורסם ביוני 2023.

-הפרק מדבר על

דרישות להצגת השוואה

בין שיטה אלטרנטיבית לשיטה פרמקופאלית.

הפרק רלונטי עבור:

- שיפור שיטות אנליטיות קיימות
- שיטות בהעברת תהליכים/שיטות (TT) בין מעבדות/אתרים
- שיטות אנליטיות לפיתוח מוצר חדש

Introduction

5.27. COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES

This general chapter is published for information. It describes how the comparability of an alternative analytical procedure to a pharmacopoeial analytical procedure may be demonstrated. Other approaches to demonstrating comparability may also be appropriate. The use of an alternative procedure is subject to authorisation by the competent authority. The final responsibility for the demonstration of comparability lies with the user and the successful outcome of the process needs to be demonstrated and documented to the satisfaction of the competent authority. Comparability must be maintained over the lifecycle of both the pharmacopoeial and alternative analytical procedure.

חשיבות הפרק:

מאפשר להשתמש בשיטות אלטרנטיביות

- משמש כפרק נותן מידע, לא מחייב
- נותן סקירה של תנאים מקדימים שצריכים להתקיים
- נותן תכולה של מחקר השוואתי: תכנון, תנאי קבלה ופיענוח הנתונים

Introduction

INTRODUCTION

The tests and assays described in monographs are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, alternative analytical procedures may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official analytical procedures (i.e. pharmacopoeial procedures) were used. The aim of this chapter is to provide guidance on possible approaches to the assessment of the comparability of an alternative procedure that is used instead of a pharmacopoeial procedure. In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative.

Comparability of alternative microbiological methods is covered in general chapter *5.1.6. Alternative methods for control of microbiological quality*.

Specific guidance to facilitate the use of *in vitro* methods as substitutes for existing *in vivo* methods for testing vaccines is given in general chapter *5.2.14. Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines*.

שיטות אלטרנטיביות ניתנות לשימוש בתנאי שהן מאפשרות קביעת החלטה חד משמעית בדומה לזו שהייתה מתקבלת בשימוש בשיטה פרמקופאלית.

השוואת שיטות מיקרו': 5.1.6

השוואת שיטות in vitro לשיטות in vivo: 5.2.14

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Preliminary conditions

PRELIMINARY CONDITIONS FOR THE COMPARABILITY STUDY

The scope and extent of the comparability study should be laid out in the study protocol, together with the relevant justification(s). Prior to the comparison of analytical data, the alternative procedure is validated for its intended purpose in accordance with accepted scientific practice, current recommendations on analytical validation and guidelines that are relevant with regard to setting appropriate specification limits. In specific cases where the alternative procedure is an established analytical procedure described in a Ph. Eur. general chapter (e.g. multi-product analytical procedures), validation may consist only of the application of the provisions given in the respective general chapter.

Demonstration that the alternative procedure meets its performance criteria during validation is not sufficient to imply comparability with the pharmacopoeial procedure. The performance of both procedures must be assessed and compared. Therefore, it is required that the pharmacopoeial procedure is implemented as defined in general chapter *5.26. Implementation of pharmacopoeial procedures*, including verification experiments if appropriate.

It is recommended to perform a comparability assessment of the data generated during implementation of the pharmacopoeial procedure and during the validation studies on the alternative procedure. In particular, depending on the intended purpose of the test, analytical procedure performance characteristics (APPCs) such as specificity/selectivity, sensitivity (at the lower range limit), linearity and range should be assessed to ensure that the alternative procedure is at least as capable as the pharmacopoeial procedure. The outcome of the comparability assessment may form the basis for the design of the comparability study (see *Study design*).

Although validation data for the pharmacopoeial procedure are not available in the public domain, the required level of performance of the pharmacopoeial procedure may typically be inferred from suitability test criteria or acceptance criteria given in the monograph.

תנאים מקדימים למחקר השוואה:

- פרוטוקול הכולל היקף המחקר והצדקות
- שיטה ולידית
- השוואה של ביצוע (performance) של 2 השיטות
- השוואת נתונים קיימים עבור 2 השיטות
- השוואת יכולות (capability) של 2 השיטות

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Comparability study

COMPARABILITY STUDY

The purpose of the comparability study is to evaluate whether the results and performance of an alternative analytical procedure are comparable to those of the pharmacopoeial analytical procedure. This evaluation typically involves a comparability testing study that generates comparative data for the relevant APPCs of the two procedures. In the case of quantitative tests, the accuracy and precision of these comparative data across the measurement range may be evaluated. Other APPCs, e.g. specificity/selectivity, may also be evaluated as part of the comparability study, depending on the intended use of the procedure. If data from two analytical procedures cannot be statistically compared, the conclusion on comparability is based on evidence that the results of the alternative procedure lead to the same unequivocal decision that would be made with the pharmacopoeial procedure, which is also the ultimate goal of the comparability study.

The study protocol contains the tests and the method for statistical evaluation that will be used to compare the performance of the analytical procedures, in terms of relevant APPCs, together with the corresponding acceptance criteria that will be used to conclude on the comparability. The study protocol is established on the basis of the study design and should also address the possibility of performing additional experiments, in the case where equivalence of the two procedures is not demonstrated with the chosen sample size (see also *Step 3. Example statistical analysis: equivalence testing*). The results, as well as other relevant information, are summarised in a study report.

For quantitative results, the two one-sided t-tests (TOST) method could be considered for the comparison of the two group means. For results spreading over a wider range than those obtained at a single level, a regression approach (e.g. Deming regression, bivariate least squares regression) may be considered instead. For qualitative results (e.g. pass/fail) and limit tests, results could be summarised using a contingency table prior to assessing the agreement between the analytical procedures. The reported results should be compared in order to ensure that when samples close to the specification limit are analysed, results obtained with both analytical procedures would lead to the same unequivocal decision.

מחקר השוואה:

- מטרה: להשוות תוצאות וביצוע
- Accuracy and Precision
- השוואת נתונים ע"י כלים סטטיסטיים (TOST)
- הוכחה שהתוצאה של שיטה אלטרנטיבית קובעת החלטה חד משמעית בדומה לזו שמתקבלת בשיטה פרמקופאלית.
- יש אפשרות לבצע ניסיונות נוספים אם לא הוכח דמיון על סמך גודל המדגם שנבחר.

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Study design

Study design

To enable the use of the equivalence testing approaches proposed in this chapter, it is recommended that the same experiments – where feasible, using the same samples – are performed for the pharmacopoeial procedure and the alternative procedure in a head-to-head testing format. The sample preparations may or may not be the same, depending on the nature of the comparison and/or the analytical procedures used.

The choice of samples for comparative testing requires careful consideration. It is preferable to test the same homogeneous, authentic (i.e. non-spiked) sample with both procedures. If authentic samples are not available, samples can be synthesised e.g. by spiking with analytes or by undergoing forced degradation under controlled conditions. It is important that the sample chosen is representative of the material that may be tested in routine use of the procedure. The following should be taken into consideration when selecting representative samples.

- The expected variability of the quantity values of the product attribute being tested, e.g. concentration, should be covered. It may also be beneficial to consider including samples known to be close to the specification limit, if available.
- Any expected variability of the sample matrix should be considered.
- For procedures that generate multiple results, e.g. an impurities determination, the choice of samples should allow comparative testing of all relevant individual results to ensure that, with regard to its intended use, the alternative procedure is comparable to the pharmacopoeial procedure.
- Samples that contain components of interest at or near the reporting threshold may be included in the study.

These considerations may contribute to deciding whether a single batch is appropriate for the comparability study or whether multiple batches of the test article are required to achieve samples representative of the manufacturing variability. This will have an impact on the study design chosen for the comparability study in terms of the sample size and experiments selected. Statistical approaches to selection of sample size may be used. The statistical approach chosen for the evaluation of the data may also determine the appropriate sample size at the study design step.

תכנון מחקר:

השוואת נתונים ע"י כלים סטטיסטיים equivalence testing

- Head-to-head testing format
- אותם ניסיונות
- אותן דוגמאות:
  - דוגמאות אוטנטיות
  - דוגמאות המייצגות את אלה שיבדקו ברוטינה
  - דוגמאות בעלות כמות (ריכוז) מייצג
  - דוגמאות עם ערך הקרוב לגבול הספסיפיקציה
  - דוגמאות עם שונות במטריקס
- השואה של תוצאות אינדיווידואליות

נתונים אלה יתמכו בהחלטה על כמות האצוות וגודל המדגם

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Study design

Precision experiments carried out during validation of the alternative procedure may also be suitable for comparative testing, provided that the same sample(s) are analysed using the pharmacopoeial procedure. If it is known that intermediate precision factors do not significantly contribute to the variability of the procedure, then a repeatability experiment to determine precision for the comparative testing would be sufficient.

Ph. Eur. reference standards are appropriate for the purposes of the pharmacopoeial procedure, according to the use described in the monograph; they are not necessarily suitable for other purposes. It is the responsibility of the user to establish a reference standard for the alternative procedure, taking due account of general chapter *5.12. Reference standards*. Depending on the intended purpose of the procedures, useful comparability information for certain APPCs may be generated in the comparability study by analysing the Ph. Eur. reference standard using the alternative procedure.

תכנון מחקר (המשך):

- ניתן להשתמש בנתונים מהולידציה (Precision-repeatability)
- יש למצוא סטנדרט מתאים לשיטה

Acceptance criteria

Acceptance criteria for comparability

For the evaluation, it is important to emphasise that 'comparability' does not imply 'equality'; rather, it should be understood to mean that the alternative procedure is sufficiently similar to the pharmacopoeial procedure and therefore meets the acceptance criteria of the comparability study. The definition of 'comparable' is to be decided beforehand in the study design. As a common example, to be considered comparable, it may be decided that the means of two procedures can differ with an acceptable confidence level by no more than an amount deemed practically important. This acceptance criterion is commonly called the equivalence margin.

One of the most difficult aspects of comparability studies is assigning a value to the equivalence margin, and typically a combination of scientific knowledge and statistical expertise is applied to determine a suitable value. This acceptance criterion is defined and justified by the user prior to running the study. Compliance with the pre-defined equivalence margins indicates that the alternative analytical procedure may be used instead of the pharmacopoeial procedure (see Figure 5.27.-1).

תנאי קבלה:

- **הגדרה של "comparable" צריכה להיקבע בפרוטוקול**
- **קביעת equivalence margin**
- **קביעת ערך ל- equivalence margin ע"י מידע מדעי וחישובים סטטיסטיים**

Data evaluation

DATA EVALUATION

The TOST method for the statistical evaluation of quantitative data is presented in this chapter. This method involves comparison of the means and standard deviations obtained for the two procedures. Other approaches to the evaluation of analytical procedure comparability, including other valid statistical methods, may be used.

ניתוח נתונים:

- **ניתוח סטטיסטי (TOST)**
- **שיטות סטטיסטיות אחרות**

Statistical evaluation

Statistical evaluation of results

The purpose of the statistical evaluation is to demonstrate that the performance of the two analytical procedures is equivalent. Although other statistical methods may be employed, a commonly used statistical approach for this is to compare the mean results obtained with the two procedures by calculating the mean difference between results and associated confidence limits. Equivalence of the mean results is demonstrated if the confidence limits are within the equivalence margins defined in the study protocol. Before these calculations are carried out, the data should be described and relevant assumptions made (e.g. distribution of results, assumption of normality).

Step 1. Data description

A graphical representation may be used to describe the data efficiently. Basic statistics may also be reported (e.g. minimum, maximum, mean and standard deviation). The graphical representation should be used to:

- assess the distribution of the data;
- gain insight into the mathematical sign and magnitude of the difference between the means of the results of the alternative procedure and the pharmacopoeial procedure; this can be complemented with expert knowledge and historical data.

Step 2. Statistical assumptions

Statistical assumptions related to the study design and/or data distribution should be verified. Normality of results is a typical assumption that may be tested using graphical representations or statistical tests. Prior knowledge (e.g. from scientific literature or existing data) may also be used. A data transformation (e.g. logarithm) may be performed to attain normality of the data to be analysed.

The experimental variance of the alternative procedure should be similar to that of the pharmacopoeial procedure when implemented in the laboratory; a much lower variance (better precision) of the alternative procedure may be acceptable. A descriptive plot or a statistical test may be used to demonstrate that the variability of the alternative procedure is equivalent to or better than that of the pharmacopoeial procedure.

Step 3. Example statistical analysis: equivalence testing

When using a statistical test for equivalence of means, the mean difference between the results of the two procedures and the associated confidence limits should be calculated. Pairing of results and/or differences in experimental variances (i.e. better precision of the alternative method) should be taken into account as part of the statistical analysis, as applicable.

The confidence limits should be compared to the equivalence margins defined in the study protocol, leading to different possible outcomes, some of which are described below and shown in Figure 5.27.-1.

ניתוח נתונים:

-מטרה של ניתוח סטטיסטי

-הגישה המקובלת

-הצגת הנתונים

-הנחות סטטיסטיות

דוגמא: equivalence testing

Statistical evaluation

- Case 1: there is little difference between the mean results of the two procedures, and the confidence interval is within the equivalence margins. Equivalence is accepted.
- Case 2: despite a greater difference between the mean results of the two procedures than in Case 1, the confidence interval is within the equivalence margins. Equivalence is accepted since the mean difference is deemed to be practically acceptable.
- Case 3: there is little difference between the mean results of the two procedures, but the confidence interval extends beyond the upper equivalence margin. With the current set of data, equivalence is rejected.
- Case 4: there is a large difference between the mean results of the two procedures, and the confidence interval extends beyond the lower equivalence margin. With the current set of data, equivalence is rejected.
- Case 5: the difference between the mean results of the two procedures is above the upper equivalence margin. Equivalence is rejected.
- Case 6: the difference between the mean results of the two procedures is above the upper equivalence margin, and the confidence interval lies outside of the equivalence margin range. Equivalence is rejected.

Note. The equivalence testing approach may also be used for biological assays. In cases where results follow a log-normal distribution, the various outcomes shown in Figure 5.27.-1 are applicable to log-transformed results and equivalence margins.

Where bias and/or variability between the results of two procedures is observed, leading to the equivalence being rejected, the likelihood of subsequently demonstrating equivalence between the two procedures can be improved by identifying the source of the bias and/or variability and taking steps to reduce it prior to pursuing the assessment.

When the equivalence as part of the comparability study is accepted, the alternative procedure may be considered statistically equivalent to the pharmacopoeial procedure.

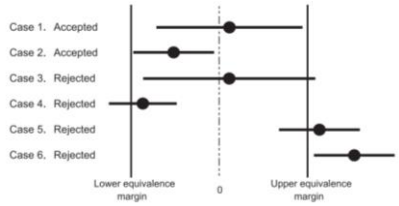

Figure 5.27.-1. – Some possible outcomes of an equivalence test. The dot represents the mean difference and the horizontal bar represents the confidence interval. The vertical bars represent the pre-defined equivalence margins

ניתוח נתונים (המשך):

-דוגמאות למקרים שונים

-גישת ה- equivalence testing

יכולה להתאים גם לשיטות

ביולוגיות כאשר מתקיים פיזור

נורמלי של התוצאות ב- log.

- **כאשר יש bias או הבדל בין התוצאות שגורם ל equivalence rejection**

ניתן לשפר את ההשואה ע"י גילוי המקור להבדלים וניסיון לצמצם אותם.

Summary

חשיבות הפרק:

מאפשר להשתמש בשיטות אלטרנטיביות במקום שיטות פרמקופאליות

- **משמש כפרק נותן - מידע, לא מחייב**
- **נותן מתווה איך לבצע מחקר השוואתי**

THANK YOU

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11 April 2024

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