ENDLESS BREAKTHROUGH POSSIBILITIES

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About ADRES

- Forefront of biotech innovation
- RA, QA, and CMC consulting and execution services.
- Complex regulatory challenges
- Worldwide work with the FDA and EMA
- Endless breakthrough opportunities for startups in European markets aiming to the U.S
- Your vision becomes a global reality

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April 08, 2024

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אני רבקה זייבל, מייסדת נשיאה ובעלים של חברת אדרס. היום מלאו 36 שנה מאז התחלתי את דרכי בתעשית הביוטק. 21 שנה של עבודה בחברת ביוטכנולוגיה כללית ו15 שנה מאז הקמתי את חברת אדרס.
שמחה להשתתף בוובינר זה של ה-PDA, אדרס נמצאת בחזית של הפיתוח והחדשנות, מספקת שרותי איכות, רגולציה, פיתוח תהליכי ייצור, קליניקה ופרה קליניקה, ומלווה חברות מהרעיון עד למוצר בשוק. לאחרונה פתחנו קהילת וואטסאפ לטובת התעשיה הישראלית ובסוף יוני, יחד עם חברת סיניי אנחנו נקיים קורס תאורטי ומעשי בנושא ייצור בתנאים אספטיים.
אשמח לפגוש אתכם גם בקהילה וגם בקורס.

April 11, 2024

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Your gateway to mastering aseptic operations: An exclusive course for pharmaceutical and biotech professionals.

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- Interactive tours of Grade A, B, and C manufacturing facilities
- Lectures by Mrs. Rachel Shimonovitz, Head of GMP Inspectorate, MOH
- Roundtable and Q&A - With Dr. Ofra Axelrod, Head of ISCP, MOH
- Insightful case studies
- Practical and hands-on demonstrations of aseptic techniques and gowning procedures
- Regulatory insights

26-27 June 2024
08:30-17:30 | Scinai Facilities
Register Here
adres.bio/lp-scinai-course

Points to Consider in Comparability of Biologics

Presented by:
Mrs. Rivka Zaibel
President and Founder Of ADRES

April 08, 2024

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List of Guidelines

- Guidance for Industry Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, June 2005
- EMA GUIDELINE ON COMPARABILITY OF BIOTECHNOLOGY-DERIVED MEDICINAL PRODUCTS AFTER A CHANGE IN THE MANUFACTURING PROCESS NON-CLINICAL AND CLINICAL ISSUES , November 2007
- EMA Questions and answers, comparability considerations for Advance Therapy Medicinal Products, December 2019
- FDA Comparability Protocols for Post approval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA, October 2022
- Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products Draft Guidance for Industry July 2023

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Introduction

ICH Q5E is the basis for comparability guidelines by EMA and by the FDA. While the implementation of comparability guideline was adopted by EMA both for changes in the manufacturing by the innovator as well as for changes to new facility and for biosimilar products, FDA comparability guideline was adopted only for changes by the innovator either at the same facility or transfer to new facilities.

In 2019, EMA published questions and answers related to comparability of ATMPs and FDA published in 2023 a specific comparability guideline for cell and gene therapy (CGT) which supports the guideline of post approval changes to CGT.

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Introduction

ICH Q5E

- Provides the principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product.
- The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, **but that they are highly similar, and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product**.
- A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. **If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted**.

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Introduction

What needs to be considered prior to initiation of a change?

- Impact of the change on product quality
- Impact of the change on product safety
- Impact of the change on product effectiveness

To evaluate the impact, a risk assessment should be performed for all types of manufacturing changes, and based on the results of the risk assessment, comparability studies should be performed. The scope of comparability during the investigational phase is dictated by the clinical phase, the analytical data and preclinical data already available and the outcome of the risk assessment.

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Introduction

Factors such as product and process knowledge, qualification/validation of methods, and the stage of clinical development should be considered when assessing the risk of the manufacturing change.

If multiple changes are considered prior to BLA/MAA submission, a comprehensive comparability study should be developed, and it is recommended to consult with the regulatory authorities prior to the execution of the study.

If post approval changes are planned, it is highly recommended to submit with the BLA/MAA a comparability protocol by which changes will be managed post approval.

For CGT the guideline emphasizes the importance of acceptance criterion for potency in comparability studies and interpretation of potency values not only from a quality perspective but also from a safety point of view.

Although Q5E does not apply to ATMPs/CGT, the principles of ICH Q5E may be applied to ATMPs/CGTs.

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Comparability Exercise

- The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.
- The comparability exercise composes of:
  - Comparability Protocol, in which the current status and the status after change are described in detail: list of all current process steps, for each process step identify changes being suggested in the equipment, raw materials, process controls, etc.; analytical tools to evaluate the change are listed; the studies to be conducted (quality comparability, characterization, pre-clinical and/or clinical studies); acceptance criteria
  - Risk assessment related to the change
  - Reports of all studies conducted as part of the comparability exercise
  - Comparability Report

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Comparability Exercise

- It is usually expected that 3 pre-determined batches from the current process are compared to 3 batches from the new process. The comparability should include stability comparison.
- Statistical tools need to be used in order to prove comparability
- Acceptance criteria should be pre-defined
- The protocol should include provisions for additional tests or studies in case acceptance criteria are not met.

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Comparability Exercise

- Comparability assessment always include analytical studies to address structural and functional characterization as well as safety of the product
- Based on the basic comparability assessment, nonclinical PK/PD studies are required
- As it is known that for biological products, animal studies do not predict the outcome in human, sometimes PK/PD human studies are required
- Rarely, clinical efficacy, safety and immunogenicity studies will be required
- If changes are introduced prior to the chronic toxicity studies, the results of the chronic toxicity studies with the post changes product can justify using the post changes product in human studies.

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Comparability Exercise – Selection of analytical panel

API analysis	Formulation/process related
SEC/cGE	Detergents
IEX/cIEF	Leachables
RP/HIC	Extractables
Peptide Mapping	
Potency	
Glycosylation pattern	
Host cell related species	**Characterization methods**
HCP ELISA/MS	Molecular Weight MS
Media component analysis	Amino Acid Analysis
	NMR
	CD

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Comparability Exercise – Selection of analytical panel

- Based on the characteristics of the product select the appropriate analytical methods to identify differences in the quality attributes and characterization of the pre and post changes product.
- Characterization methods should be qualified
- Release testing methods should be validated (qualified if the change is incorporated in development phases)

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Comparability Exercise – Interpretation of results

- The following represents potential source for heterogeneity/changes observed during the comparability studies:
  - Source of raw materials
  - Product contact materials (stainless steel vs. single use equipment)
  - Scale up
  - Adaptation of process steps as result of tech transfer
  - Adaptation of analytical methods as result of tech transfer

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Comparability Exercise – Interpretation of results

- When heterogeneity is observed, it is important to understand whether those changes were already observed in earlier batches (mainly during clinical development)
- Use more sensitive assays in order to understand whether this variability/heterogeneity is observed also in the current process
- Based on phase of development and criticality of heterogeneity, need to decide whether additional analytical methods or animal safety studies are needed

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Examples of comparability studies

- Change of CMO/manufacturing facility:
  - Post phase 1 or phase 2 clinical studies
  - Prior to phase 3 clinical study
  - Change in expression system prior to pivotal study
- What needs to be compared:
  - Process steps
  - Process equipment
  - Process scale
  - Expression system
  - Stability profile

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Examples of comparability studies

- Change of QC/Analytical laboratory:
  - Prior to Phase 2 and Phase 3
- What needs to be compared:
  - Analytical equipment
  - Method performance

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Examples of comparability studies

- Change of API source:
  - New API supplier same expression system
- What needs to be compared:
  - Proof of concept studies
  - Certificate of analysis
  - Analytical methods
  - Manufacturing process (to the extent possible)
  - Toxicity studies
  - Stability profile

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Examples from actual comparability studies

Change of CDMO resulted in:

- Change of expression system
- Change of process steps
- New Isoform not seen in the past

- All that resulted in an intensive investigation, following which, new process parameters and acceptance criteria were established to control the formation and level of the new isoform

Analytical method transfer to new CDMO:

- Fail to obtain same results
- Resulted in change of sample preparation and column

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Examples from actual comparability studies

Change of CDMO resulted in:

- Change of process steps
- Modification of glycosylation pattern

- Comparative PK/PD study was conducted in order to proceed with the post change product to phase 2 clinical study

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Recommendation

- Meet with the authorities and discuss the comparability exercise prior to initiating it.
- For the meeting provide a detailed protocol

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Thank you!

We invite you for a free "Pick Our Brain" consulting meeting.

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