ARM-USP Workshop "Comparability in Cell & Gene Therapies"

Final Report & Summary

ARM CMC Workshop Series

May 31 2019

Rockville Maryland, USA

Alliance for Regenerative Medicine

ARM-USP CMC Workshop

"Comparability in Cell & Gene Therapies"

Workshop Executive Summary

Workshop Overview:

On May 31, 2019 the Alliance for Regenerative Medicine (ARM) and the US Pharmacopeia (USP) co-hosted an educational workshop titled "Comparability in Cell and Gene Therapies". This workshop is part of a series of educational resources generated by ARM and USP to assist in navigating key CMC questions for the cell and gene therapy industry (CGTX). This specific workshop was convened in response to a running series of challenges in understanding comparability for next generation therapeutics, primarily cell-based therapies, gene therapies, and gene-modified cell therapies. The workshop represented perspectives from across a broad spectrum of industry stakeholders, including therapeutic developers, tool and service providers, and regulatory bodies. As a group, these participants sought to discuss, and where possible, address uncertainties in Comparability including planning comparability studies during developmental transitions, CMC scale up/out, and when preclinical data and/or real-world evidence may play a role in determining comparability. The summary provided below covers the principal discussion topics, potential exercises to be utilized, and key discussion findings from the workshop.

The workshop was divided into three general phases of content and discussion, including two sessions in the morning and one in the afternoon. The morning session encompassed a series of informational presentations, including talks given by FDA and EMA representatives on regulatory considerations in Comparability. The remainder of the morning was dedicated to a series of

thought exercises, intended to highlight key areas of confusion in evaluating comparability and where possible, provide insights for use by attendees. The workshop wrapped up in the afternoon with a series of three breakout sessions covering specific topics relating to Comparability, and final summary discussion before the workshop adjourned.

Morning Session 1 – Industry & Regulatory Perspectives:

Presenters (slides available at end of report):

Dr. Zenobia Taraporewala (CMC Reviewer and Acting GT Team Lead, CBER, FDA)

Dr. Margarida Menezes-Ferreira (Sr. Assessor Infarmed, Member of CAT, EMA)

Fouad Atouf (VP Global Biologics, USP)

Michael Lehmicke (Dir. Science & Industry Affairs, ARM)

At the start of the workshop, a series of presentations were given to set the groundwork for the day's discussions. Both ARM and USP presented on their current interests in CGTx, and in particular efforts around CMC, characterization, and comparability. ARM, through its Science and Technology committee, is committed to generating resources and convening the industry in order to address manufacturing hurdles, market access barriers, and clear CMC regulatory policies. The USP, as an international leader in the development and maintenance of reference and documentary standards, is focused on developing materials for use throughout CGTx lifecycle. Through their Biologics division, USP is interested in the potential impact commercial quality standards may have on easing the burden associated with testing and characterization, as a way to decrease overall costs and improve product accessibility.

Following the talks from ARM and USP, perspectives on comparability were presented by representatives of US and EU regulatory agencies. A summary of their talks and key points is included below. Both speakers recommend utilizing existing guidance's, such as FDA (ICH) Q5E, in order to help in defining and developing both the manufacturing process and the comparability tools. They both encourage sponsors to be proactive and consider comparability planning well in advance of late-phase clinical studies.

Dr. Zenobia Taraporewala, "Comparability Studies for Cell & Gene Therapy Products"

Please note that the statements below were recorded by ARM-USP staff, and any information captured should not be considered binding or on behalf of FDA.

In her talk, Dr. Taraporewala provided valuable insight into how FDA views comparability in a CGTx product, and on what is expected from sponsor submitted product comparability plans. Dr. Taraporewala also stressed the importance of wide data collection during both preclinical development and clinical trials, and she suggested development of a comparability plan as early as possible in product development - preferably before a Ph1 trial. Dr. Taraporewala highlighted the need for clear comparability, and in general CMC preparation, for CGTx sponsors seeking expedited approval pathways so as to avoid substantial late-clinical / post-approval pitfalls.

In addition, Dr. Taraporewala mentioned key considerations for product sponsors as relates to comparability planning:

1. Provide well-qualified assays that measure critical quality attributes (CQAs)
    a. Assays should be well controlled and should be orthogonal.
    b. There should exist an in-vitro biologic potency assay when possible
    c. Assays should utilize current technologies and relate to latest generation of a product

2. Possess a clear understanding and definition of product CQA and how they are impacted during manufacture
3. Show clear and robust methods to appropriately monitor and control process parameters
4. Generation of a reliable body of historical, statistically robust data on a process change
5. Lock a defined manufacturing process with limited risk for major changes before Ph3 clinical studies
6. A side by side analysis is preferred to demonstrate comparability to earlier processes and products. Just because A=B and B=C doesn't necessarily mean A=C.
7. Consider which ancillary material quality attributes may be relevant to determining comparability
8. Keep in mind the phase of development during which a change could be expected; for instance, when considering a change in a BLA product, FDA expects significantly higher proof of comparability if no additional clinical trials are planned
9. Seek alignment from OTAT at FDA early on

Dr. Taraporewala also shared a set of general Agency expectations regarding comparability plans:

1. Describe the change in the manufacturing process and the rationale for the change.
2. Describe your risk assessment and the findings from the process
3. Do you intend to look at stability? What does your toolbox look like?
4. What is the validation status of the assays? Is there a reference standard, and if so, what is its source?
5. What is the rationale behind your statistical analysis approach?

    a. *Ex. In some cases, a sponsor presents a simple mean or range such as +/- 3 SD's. However, it is key to make your approach scientifically meaningful*
6. Describe the comparability study design and explain the underlying assumptions and risk assessment informing the plan
    a. *Ex. Sometimes a sponsor says A=B and B=C so A=C – but this doesn't always work. It's a good idea to do a side-by-side analysis for comparability of CQA's*
7. Determine clear methods for determining the impact of a process change – is it a minor or major change? Is it early or late stage?

Dr. Margarida Menezes-Ferreira, "CAT Comparability Perspectives"

Please note that the statements below were recorded by ARM-USP staff, and any information capture should not be considered binding or on behalf of CAT or EMA.

During her presentation, Dr. Menezes-Ferreira highlighted the rising need for clear understanding of regulatory requirements due to the rapid increase in CGTx products under regulatory review. In addition, she strongly reaffirmed the critical role of statistical analysis and generation of sufficient and robust data sets to perform comparability studies. Emphasis was placed on the importance of sufficient statistics provided to demonstrate equality or superiority in a post-change product. In addition, Dr. Menezes-Ferreira made the point that not all comparability requirements are necessarily regulatory requirements – sponsors may need to be responsible for comparability beyond regulatory requirements.

During her presentation, Dr. Menezes-Ferreira also introduced some key concepts for consideration by sponsors.

1. For comparability, analytical methods of comparison on critical, and all analytical methods should be validated and very robust.

2. When possible, side-by-side comparability is strongly preferred
3. An understanding of CQA and associated critical processing steps is integral to comparability planning
4. Comparability should not be mixed with, or confused with, similarity.
5. Split samples are recommended when you move the samples to different locations.
    a. *Reference standards can be crucial for this process*
6. When considering sponsorship int EU, review the three existing guidelines for comparability
    1. *Guideline on Comparability Of Biotechnology-Derived Medicinal Products After A Change In The Manufacturing Process Non-Clinical And Clinical Issues (EMEA/CHMP/BMWP/101695/2006)*
    2. *Guideline on Comparability Of Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Quality Issues (EMEA/CHMP/BWP/3207/00/ Rev 1)*
    3. *Comparability of Biotechnological/Biological Products Subject To Changes In Their Manufacturing Process (EMEA/CPMP/ICH/5721/03)*
7. For a cell-based product sponsor, potency testing is a key attribute, and should be correlated to or cross-referenced to a validated functional assay.
8. For gene therapy product sponsors, all starting materials must be qualified, and must undergo extensive characterization during manufacture and as part of any process change
9. In the EU, "cell stock" management is a key aspect of a manufacturing program. Sponsors need to be prepared to utilize multiple cell stocks over the course of time and should be prepared to show comparability between stocks.
10. EU clinical trials are approved on a nation by nation basis. We seek harmonization, but each country decides on their own what the trial should look like. In all cases, the safety of the patient is paramount. As

we consider comparability, if, for example, you are at phase 3 and are close to authorization but then engage in a process change, we cannot say that your comparability equals consistency in quality. We would still require proof of comparability, though other questions may not need to be answered in clinical trials.

Morning Session 2 – Group Thought Exercises:

Session Leaders:

Keith Wannacott, Pfizer

Mike Lehmicke, ARM

Natalie Ward, C&GT Catapult

Adam Roose, ARM

Jim Richardson, USP

The insights provided by the FDA and EMA-CAT representatives prepared the field for the comparability thought exercises that followed. The purpose of this activity was to identify CQAs of therapeutic products and then perform theoretical risk assessments under various circumstances. The attendees divided into two groups, with each group performing the same brainstorming exercises. Participants generated a list of general product attributes, which were then qualified a 'critical' for either autologous or allogeneic cell therapy, or as an attribute of a gene therapy. Each CQA was then weighed according to their impact on safety, quality, and efficacy. Within Group A, there were interesting insights into evaluating CQA, including the consensus that CQA ranking and the relative assigned importance depends entirely on the type of product under development. It was agreed to focus the discussion on an ex vivo gene modified autologous cell therapy. In Group B, a similar comment was found: "with regard to correlation of assay to clinical outcomes, it depends on the product: for an engineered T-cell, it could be persistence, but for an

adeno-associated virus (AAV) product, it is predictability of infectivity of the target cell and ability to express a functional protein—the questions can be different. What applies for one product may not apply to another product".

Despite this apparent subjectivity, several quality attributes were agreed as critical. For Group A they identified dose strength, viability, potency, engraftment, vector copy number, cell purity, residual cytokines and identity. For Group B viability, titer, assay, cell count, cytotoxicity, potency, cytokine secretion, impurity profile, identity, sterility, endotoxin, mycoplasma, phenotypic markers, pH, appearance, osmolarity/osmolality, growth/doubling time, transduction efficiency, and yield reached participants' consensus. The overall risk of the CQA was determined by multiplying the weights which were agreed after a thorough discussion. Thus, group A identified cell identity and vector copy as the ones with the highest associated risk, meanwhile group B focused on viability, potency and endotoxin.

Besides identifying and ranking key CQAs, the debates held during the morning thought exercises resulted in notable recommendations about comparability for the companies developing cell and gene therapies. Group B worked to generate a short list covering recommended actions for a prospective sponsor to follow as they generate a comparability plan:

1) Understand the product: What is critical and what is important? Has the product changed? Then you try to understand the quality attributes of the product.
2) Identify what is the change, and what is the potential for the change to have an impact? Discussed specific changes, but also cumulative changes. It is rare to change sites and have everything stay the same. Other things are changing.

3) Define the potential to change: how to execute the study to assess the change? What are the ways to assess the change?
4) Conduct the final analysis: run study, get data, analyze it, and make decisions. Are the data what was expected? If not, is that relevant?

Afternoon Session 1 – Breakout Discussions:

Session Leaders:

Nimi Chhina, BioMarin

Dan Leblanc, Flexion Therapeutics

Kanti Thirumoothry, Kite Pharma

Steve Rabin, Iovance Biotherapeutics

Dawn Henke, Standards Coordinating Body

Rebecca Potts, USP

In the afternoon, breakout sessions provided attendees a unique opportunity to participate in three sessions:

1. *"Developing a Comparability Plan for A-Gene AAV Gene Therapy"*
2. *"Understanding the Development and Use of Reference Standards in Comparability Planning"*
3. *"Determining Comparability between Analytical Methods for Potency and Characterization in a Development Phase-dependent Manner"*

During the session on 'AAV Gene Therapy', it was recognized that the process of constructing a comparability plan starts with the scientific risk assessment of the proposed change. The approach to the plan should look at the entire system holistically and, due to existing guidance's that specialize on post-approval changes, focus should be put on the pre-approval stage. Moreover, attendees suggested that strong emphasis should be allocated to gather data to support the rationale of the change and its characterization. In those lines,

it was mentioned that a minor change may need some limited data while a major one will likely require a formal comparability study.

In the breakout session focused on 'Development and Use of Standards,' the important role that Reference Standards (RSs) play in all phases of a cell/gene therapy development process was discussed in detail. The group noted that many of the RSs currently used by developers are product specific internal reference standards. While this is sufficient to support an individual application, there remains an urgent need for new documentary and physical reference standards that cover areas such as vector copy number (VCN), rapid microbial methods and viability, as well as standards for flow cytometry using cell markers (e.g., CD25, CD45, etc.). The best approach, participants believed, would be that these RSs were intended for individual assays and not product-specific. In this regard, USP and ARM are interested in working together in the near future to ultimately provide new useful standards for the development of groundbreaking cell and gene therapies.

In the third session, covering the 'Determination of Analytical Methods through Development', there was lively discussion exploring analytical methods to determine comparability. Reducing assay variability was seen as critical by the experts to ensure that comparable products are being made. The group further determined that keeping retain samples (ex. "at least 10 vials per lot") from past processes is another key step for a sponsor to take; these retains have allowed members to perform comparability studies when a process changes or a product moves between sites. If it is impractical to keep retains then it is advisable to obtain as much data as possible from each lot and maintain this data in a secure format. Developers were also reminded to consider leachables and extractables from the container-closure if it differs from the original container.

Summary:

Overall, the first workshop on CGTx CMC organized by ARM and USP saw more than 120 experts actively engaging in debates relating to different aspects of comparability for cell and gene therapeutic products. These discussions understandably highlighted significant challenges, and it was recognized that future educational efforts around comparability would benefit from a more-narrow focus. With this in mind, and as CGTx is a relatively new field that therefore presents many challenges, the group did well to focus on broad questions. Many of the issues that were discussed are in fact product-related, and the morning presentations provided valuable information about the efforts which both FDA and EMA have been making to assist the industry in overcoming hurdles related to comparability. The thought exercises and breakout sessions utilized the knowledge and expertise of the participants to identify 22 different CQAs and discuss processes to evaluate them. Additional discussions related to understanding the development and use of RSs and determining comparability through analytical methods. It is ARM's and USP's combined mission to keep advancing the understanding of this exciting area of healthcare by facilitating opportunities to inform and discuss with the overall goal of streamlining and expediting development of much needed treatments.

Comparability Studies for Cell and Gene Therapy Products

A Regulatory Perspective

Zenobia Taraporewala
FDA/CBER
Office of Tissues and Advanced Therapies

Comparability Workshop USP ARM; May 31st 2019

Overview

Comparability studies of CGTPs

- **Introduction**
- **Key considerations**
- **Challenges**
- **Summary**

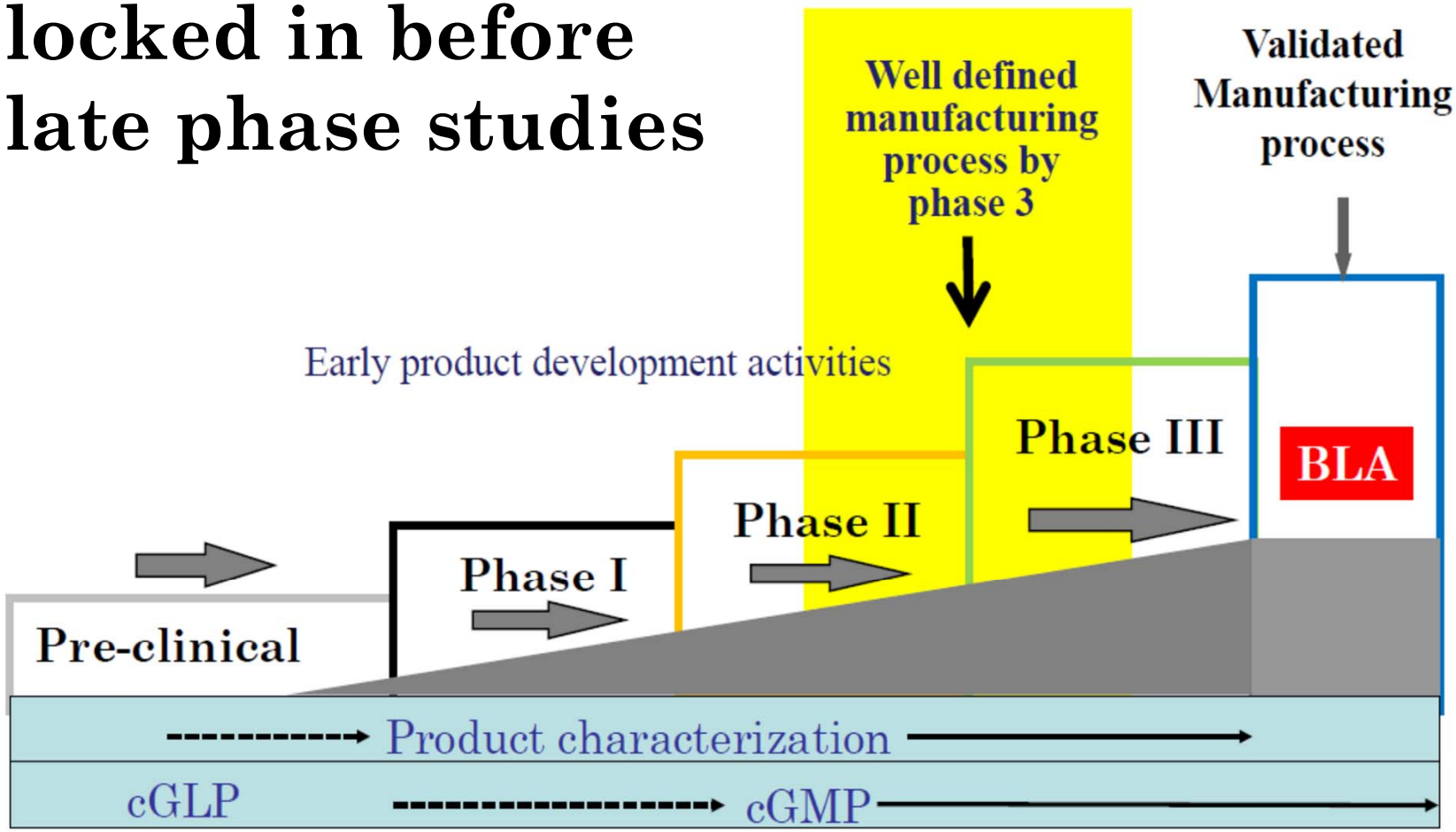
Introduction

For most programs, it is anticipated that manufacturing changes will be made throughout development; commonly to support product needs for late phase trials and/or commercialization

For example:

- *Manufacturing site (adding new sites)*
- *Scale/platform: upstream/downstream processing*
- *Formulation, storage conditions*
- *Automation to expand market and fulfill business needs*
- *Changes made to improve product stability*
- *Complying with changes in regulatory requirements*
- *Change in suppliers/source of reagents/critical starting material (cell banks)*

A well defined manufacturing process should be locked in before late phase studies



Guidance

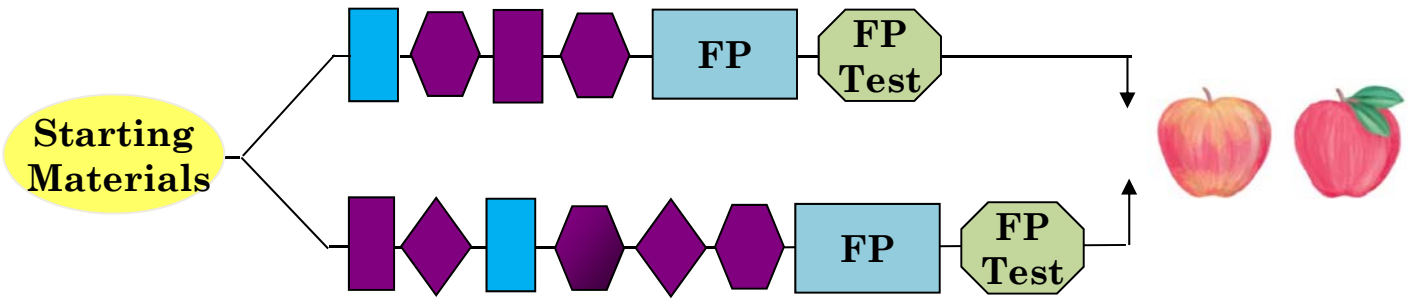
FDA (ICH) Guidance: Q5E Comparability of Biotechnological or Biological Products Subject to Changes in Their Manufacturing Process (2005):

When changes are made to the manufacturing process, the sponsor generally ***evaluates the relevant quality attributes of the product*** *to demonstrate that* ***modifications did not occur that would adversely impact the safety and efficacy of the drug product.***

Determinations of product ***comparability can be based solely on quality considerations if*** *the manufacturer can provide* ***assurance of comparability through analytical studies.***

Additional evidence from nonclinical or clinical studies *is considered appropriate* ***when quality data are insufficient*** *to establish comparability.*

What are Comparable Products?



- **Highly similar quality attributes before and after change**
- **No adverse impact on the quality, safety or efficacy**

Process and Product knowledge

CQAs CPPs and (C)MAs

Critical Quality Attribute

- **CQA:** A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

  - Pharmaceutical Development ICH Q8(R2)

Critical Process Parameter

- **CPP:** A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

  - Pharmaceutical Development ICH Q8(R2)

(Critical) Material Attribute

- **(C)MA: A physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.** .....*understanding starting material attributes may be valuable (and critical) when demonstrating product comparability of cell-based GT products*

Establishing Product Comparability
What are the Expectations?

Expectations

- Statistically robust and comprehensive data
  - Side-by-side analysis of multiple lots (pre and post change): Developmental, engineering, clinical
  - Comparison to historical data (manufacturing clinical lots) may be acceptable during early development, if justified
  - Acceptance criteria with predefined variability (comparability criteria): Consider criticality of the product attribute, sensitivity of the analytical assay, past manufacturing experience/data, sources of variability
- Well-developed (and validated, when possible) assays should be used
  - Assays that measure CQAs
- Comparability protocol should be developed and discussed with FDA prior to comparability demonstration

ICH Q5E Guidance on Comparability Protocols

Gain Agency Feedback on the Comparability Plan

What information to submit to FDA?

- Describe the change and the rationale for the change
- Provide updates on the current process and product knowledge:
  - CQAs, CPPs (and CMAs)
- Describe the risk assessment performed and the findings
  - Change in critical starting material, process, product, stability?
- Updates on the adequacy of the analytical tool box to assess the change:
  - Release testing, characterization testing. Validation status of the assays. Reference lot?
- Indicate the number of lots and describe the related information about the lots (manufacturer? process? clinical lot/engineering lot? etc.) that will be used to demonstrate comparability.
- Describe the statistical approach
- Define the comparability criteria

Key Considerations for Comparability Studies

1. Risk assessment and mitigation plan

What impact does the manufacturing change have on product quality and any mitigation strategy?

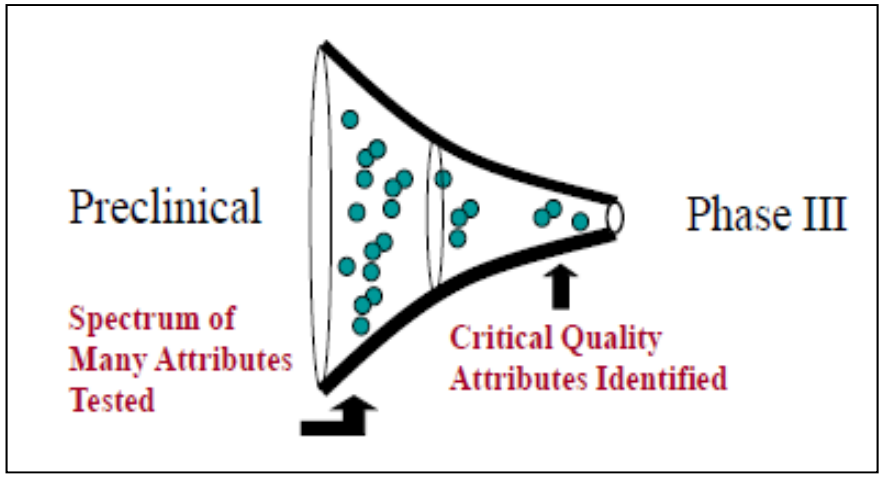
Is it a minor or major change?
- *Major changes will likely require comprehensive comparability studies.*

Consider the stage of product development: early vs late vs post-approval.

- If manufacturing changes are introduced in late stages of development with no additional clinical studies planned to support the BLA, the expected level of comparability demonstration will be significantly higher.
- If analytical comparability study data are not sufficient to establish comparability, additional pre-clinical and/or clinical studies may be required to demonstrate comparability of product safety and efficacy.

Key Considerations for Comparability Studies

2. Knowledge of CQAs of the product under study is critical to establishing comparability



Evaluate many attributes early during development and prune during lifecycle to those that can discern process-related changes in product safety, quality and efficacy.

Key Considerations for Comparability Studies

3. Adequacy of the analytical tool box

Well-controlled, sensitive and quantitative assays are crucial when product comparability has to be demonstrated using analytical methods (*particularly for complex biologics*).

<u>Assays used in comparability study of CGTPs should:</u>

- Be qualified and controlled
- Be orthogonal (different assays should be used to measure a CQA)
- Include a biological potency assay
- Include product characterization assays [can be valuable in identifying changes in product attributes not otherwise monitored for release testing]
- Include assays that use current technology to allow greater understanding of the product characteristics and reduce the risk of the "unknown" change.

Key Considerations for Comparability Studies

4. Adequacy of manufacturing data

- Depends on the stage of clinical development
- Comparability plan should have preset acceptance criteria for testing product attributes
  - Not necessarily lot release criteria
  - Justification/rationale
- Manufacturing history should be leveraged
  - Consider in-process testing data, product characterization data and lot release data
  - Development lots, engineering lots, pharm-tox lots, **clinical lots**
- Split manufacturing when processing patient-specific starting material (highly variable)
  - At different sites or with different processes
- Appropriate and robust statistical analysis with rationale for approach, *when possible*.

Analytical Comparability Studies:
Points to Note

- Demonstrate that data generated with pre-change product are relevant to post-change product
- Analyze attributes likely to be affected
  - Risk assessment
  - Prospective protocol
  - Acceptance criteria with predefined variability (comparability criteria set using the statistical approach) based on lots shown to be safe and effective
  - Side-by-side comparison of retained samples or split manufacturing
- Evaluate effect at multiple stages of the manufacturing process
- May need to assess impact on product stability
- May require additional nonclinical or clinical studies
- Major manufacturing changes are not recommended during Phase 3 or registration studies

Common Challenges for Comparability of CGTPs

- **Limited lots** (manufacturing history):
  - Comparability studies are not statistically powered
  - Not enough retention/test samples available
- **Limited assay development** (potency, purity):
  - Assays not qualified; reference standards not established or adequately characterized.
- **Limited product characterization:** CQAs not known
- **Limited knowledge of product- and process-related impurities**
- **Limited understanding of the MA** (of critical starting material): E.g., patient-specific or donor-derived PBMCs for CAR-T manufacturing
- **Limited in-process testing:** Process variables and CPPs not known
- **Limited product stability data collected:** Limited product attributes tested in stability plan.

Common Challenges for Comparability of CGTPs

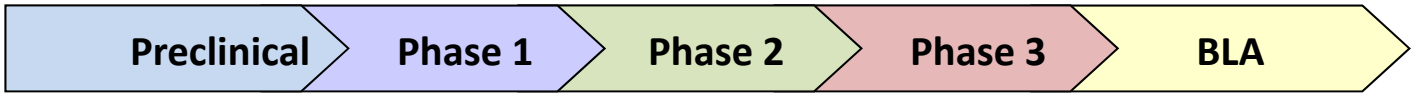
Expedited programs:

- Breakthrough (BT)
- Regenerative Medicine Advanced Therapy (RMAT)
- Fast Track
- Accelerated Approval
- Priority Review

Expedited programs often have faster, and therefore compressed timelines for clinical development…….but commonly, the CMC development is lagging.

Comparability Studies
Expedited Programs

When a clinical program advances rapidly the timelines from early to late development may be compressed



<u>Planning</u> for commercial scale manufacturing including comparability studies (when needed) should be conducted early (Phase I/II).

Challenges for CGTPs on Expedited Programs

- Limited manufacturing experience
- Limited process knowledge and variables
- Inadequate analytical development and
- Lack of comprehensive product characterization

In this scenario, there are challenges in:

- Assessing the risk to product quality and safety due to the manufacturing change(s)
- Designing robust and statistically sound comparability studies
- Meeting the product needs of a late phase trial and/or licensure due to manufacturing programs that are slowed.

Summary

Key Considerations:

- Understand critical process parameters and critical quality attributes early in development
- Understand the risk (safety and efficacy) and develop a risk assessment and mitigation plan; develop a comparability strategy accordingly
- Build a robust analytical tool box for product characterization and testing early

Gain alignment from the agency on comparability plans for seamless early to late phase transition (even more so for products in expedited programs!).

Seek OTAT advice early !

Contact Information

Zenobia Taraporewala

- Email: Zenobia.Taraporewala@fda.hhs.gov

Regulatory Questions:
OTAT Main Line: 240-402-8190

- OTATRPMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov

CBER:

- Website http://www.fda.gov/BiologicsBloodVaccines/default.htm
- Phone: 1-800-835-4709 or 240-402-8010
- Consumer Affairs Branch: ocod@fda.hhs.gov
- Manufacturing Assistance and Technical Training Branch: industry.biologics@fda.hhs.gov
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OTAT Learn Webinar Series:
http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Thank You

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Alliance for Regenerative Medicine

ARM Comparability Workshop

May 31 2019, USP Rockville MD (teleconference)

CAT COMPARABILITY PERSPECTIVES

Margarida Menezes Ferreira
Senior Assessor at INFARMED
PT expert at BWP/CHMP - EMA
member of the CAT - EMA
(margarida.menezes@infarmed.pt)

"I attend this conference as an individual expert and do not represent the CAT. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CAT or reflecting the position of the CAT"

ADVANCED THERAPY MEDICINAL PRODUCTS

Directive 2009/120/EC, Annex I Part IV and Regulation 1394/2007/EC

Defined as BIOLOGICAL MEDICINAL PRODUCTS …
Directive 2003/63 Part I, paragraph 3.2 annex 1

Cell based Medicinal Products

Somatic Cell Therapy

Tissue Engineered Products

Gene Therapy Medicinal Products

Gene Therapy

Genetically Modified Cells

Market Authorisation Applications

CAT 2009-2019

APPROVED AND LATER WITHDRAWN:

ChondroCelect - for cartilage repair, 2009 *(withdrawn 06/2016)

MACI - for cartilage repair, 2012 *(closure of EU manufacturing site 09/2014)

Provenge advanced prostate cancer, 2013 *(withdrawn 05/2015)

Glybera - LPL deficiency, 2013 ..... withdrawn 10/2017

APPROVED :

Holoclar - limbal stem cell deficiency, 2015

Imlygic - advanced melanoma, 2015

Strimvelis - ADA-SCID, 2016

Zalmoxis - high-risk haematological malignancies (adjunctive to HSCT), 2016

Spherox - for cartilage repair < 10 cm^2, 2017

Alofisel - complex anal fistulas in Crohn's disease, 2018

Kymriah - children + adult <25yo ALL and adult DLBCL, 08/2018

Yescarta - adult DLBCL and PMBCL, 08/2018

Luxturna - children and adult retinal dystrophy biallelic RPE65 mutations, 09/2018

Zynteglo – β Thalassemia - non β0/β0, 03/2019 ..

Scientific challenges of PRIME candidates

areas - scientific advice requests (data up to July 2018)

Critical areas
Number of question > 7

API/ Substance

Areas	Raw materials	Orphan similarity	Cell banks	**Starting materials**	GMP/ site
# Q	**2**	**2**	**4**	**8**	**6**

Process

Areas	Process development	**Comparability**	Change management	**Validation**
# Q	**4**	**22**	**2**	**8**

Control

Areas	Potency assay	**Analytical control strategy**	**Specifications**	Adventitious agents	**Stability**	Product-rel. impurities
# Q	**6**	**14**	**7**	**3**	**9**	**5**

towards consistency at MA

Changes throughout development

From process characterisation to process validation

Not applicable to ATMP but …

Improvements acceptable based on COMPARABILITY
to ensure validity of previous safety and efficacy claims

COMPARABILITY

Comparability is an essential part of the evolving process to ensure that data gathered is valid through development, for marketing authorization and beyond.

Understand critical process steps and set predefined acceptable ranges required –level of variability to be acceptable.

Meaningful set of QA and methods should be identified to be suitable for control (assay accuracy and precision) and comparability.

Comparability supporting manufacturing changes should not be confounded with similarity.

Analytical considerations

- ✓ Side by side comparability exercise of statistically significant number of batches if possible
- ✓ Statistical methods should be valid for the sample size
- ✓ limited sample sizes pre-post change mandates robust analytical method and side by side testing
- ✓ Comparability of analytical methods in time
- ✓ Equivalent analytical methods if different location
- ✓ Split samples when possible
- ✓ Standards?

Considerations on statistical methodologies for comparability

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development **Draft** EMA/CHMP/138502/2017

- ✓ Small/uneven number of batches from pre and post-change process / non-random sampling – questions representativeness
- ✓ Two unknown distributions pre and post-change to be compared
- ✓ Comparability of statistically significant number of batches taken in consideration the variability of the method (min- max suitable for specs – not adequate for comparability with low numbers in post change)
- ✓ Appropriate statistical method to be defined – non inferiority, data distribution, metrics for the difference measurement (difference of means) and distribution of the metric itself (normal?) – statistical interval (tolerance interval) possible?
- ✓ Side-by side comparability in the same assay run generally considered adequate for low number as in earlier development phases
- ✓ Inferential statistics possible for later development – for higher number of batches

COMPARABILITY

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS
EMEA/CHMP/410869/2006

GUIDELINE ON GENE THERAPY MEDICINAL PRODUCTS rev 1
EMA/CAT/143641/2017

Guideline on quality, non-clinical and clinical aspects of 5 medicinal products containing genetically modified cells – draft
EMA/CAT/GTWP/671639/2008 Rev. 1

- **ICH Q5E guidance to be considered relevant**
- **Critical steps identified during development** – needed for comparability
- **analytical tools** for comparability **should be established through product development.**
- Develop comparability tools **as early as possible**
- During the **pivotal clinical studies changes should not be introduced** to the manufacturing process and the final product.

ICHQ5E – general principles apply to ATMP

ICH Q5E on comparability is broadly applicable

- **comparability exercise should start with quality data and then continue as appropriate with non-clinical and clinical studies.**

- **extent of studies will depend on:**
  - **the production step where the changes are introduced;**
  - **potential impact on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g. product related substances / impurities)**
  - **suitability of analytical techniques to detect potential product modifications and results**

- **Differences in quality attributes impact on safety and efficacy, based on nonclinical and clinical experience**

ICHQ5E – **general methodology** apply to ATMP

Comparability exercise includes:

- • demonstration of compliance with approved specifications;
- Extended characterisation;
- assessing critical control points in the manufacturing process that affect product characteristics (e.g., intermediate, drug substance, and drug product);
- need for stability data, namely from accelerated or stress conditions, to identify differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;

historical data to provide insight into potential "drift" of quality attributes with respect to safety and efficacy

- Consider nonclinical or clinical characteristics of the drug product and its therapeutic indications

Cell based Medicinal Products :

somatic cell therapy

tissue engineered

ICHQ5E scenarios - too strict for CELL BASED MP?

- **HIGH SIMILARITY** based on quality attributes almost impossible

- **ANALYTICAL PROCEDURES** used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product.
  Potency often based on surrogate markers and combined testing approaches - difficult to interpret in terms of comparability.

- **DIFFERENCES JUSTIFIED** due to no adverse impact on safety or efficacy
  how to justify dynamic aspects that are difficult to address?

- **PRODUCT RELATED IMPURITIES -** cells of unwanted lineage, or undifferentiated, supportive cells
  how to qualify impurities as part of the comparability exercise. Should there be compliance to range or maximum limits?

- **PRODUCTS NOT HIGHLY SIMILAR = NOT COMPARABLE**
  cells will hardly be highly similar

ALWAYS NECESSARY TO CONFIRM SAFETY AND EFFICACY ?

CELL - What quality atributes for comparability ?

- potential impact of changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product related substances)

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS EMEA/CHMP/410869/2006

Variable characterisation programme

Product definition - intended function based on multiple interactions
autologous vs allogeneic / cell like or tissue like / immunoactive / proliferative / differentiated

Identity – markers, morphology, cell interactions, metabolism, matrix, scafold

Cell purity – relevant cells, ratio of viable to non viable, scenescent

Impurities : product / process **– unwanted cells, degradation products, metabolites / adventitious agents, bioactive reagents**

Potency – according to intended function – required for comparability, consistency and stability

Tumourigenicity ,
Karyology,
Genetic Stability

Product related CQA: POTENCY

consistency – release – stability – comparability

- Potency should reflect relevant biological properties – mode of action
- Potency is quantitative – sensitive to deviant analyte
- Standardisation necessary – define reference preparations for cross referencing
- Potency evolve during development – validated for commercial process
- Surrogate purity markers cross referred to functional assay can replace potency for in-process control and release

CBMP scenario: improved manufacturing process

- Introduction of changes e.g. biologically active reagents or new step

✓ Impact assessment – whether changes are at critical step

✓ Establish a comparability program applied to various batches before and after the change

✓ Extent of comparability - whether changes have impact on:

  - specifications only
  - mechanism of action
  - risk/benefit

✓ Re-validate the process using various batches from new process

✓ Bridge potency with non clinical in *vitro / in vivo* studies

✓ Bridging clinical studies depending on comparability extent

Additional considerations for autologous donor variability

- process characterisation / validation with healthy donor cells
- Phenotypic profile comensurate to donor variability
- potency very relevant to integrate intrinsic complexity (*in vitro* and/or *in vivo* assay),
- Comparability between healthy and patient starting material necessary but may come as concurrant validation / continuous verification
- Acceptability of concurrent validation with patient materials to be agreed upfront
- Accelerated stability studies could be relevant to identify differences

risk evaluation to assess impact on safety and efficacy

CBMP scenario:
periodic introduction of allogeneic new cell stock

MCB often with limited time span not covering the entire life cycle of the product

- ✓Validated process from various cell stocks
- ✓Validate the multiplicity of stocks by using the various lots generated in clinical trials
- ✓Establish a **predefined comparability program** applied to various lots originated from several stocks
- ✓Submit a PAMP – „do and tell“

Additional considerations for technology transfer
Multiple sites with same manufacturing process

- ✓ Enhanced focus on critical manufacturing steps IPC‘s, intermediates quality attributes and stability
- ✓ Manufacturing process validated for multiple sites with comparable outcome
- ✓ Side by side comparability exercise of statistically significant number of batches
- ✓ Comparability of analytical methods
- ✓ Split samples when possible

Gene Therapy Medicinal Products

Gene Therapy

Genetically Modified Cells

GTMP STARTING MATERIALS - changes

Plasmid – ex. AAV redesign – new promotor

cell substrate – cell factory change

viral vector - retroviral vector safety improvement

Human cells – expected for autologous gene therapy

Extended characterisation – gene therapy

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

16 February 2018
EMA/CAT/143641/2017
Committee for Advanced Therapies (CAT)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Genotypic and phenotypic identity,
- Ratio of infectious to non-infectious particles
- Empty to full capsid ratio
- Particle size / aggregates
- biological potency/therapeutic sequence activity,
- infectivity/transduction efficiency
- replication capacity
- …

AAV redesign …. Plasmid as starting material – new more efficient promotor and refined construct.

- same process – same AAV – same capsid
- Impact expected mostly on potency – transgene expression

- Consider also impact on:

- Genomic integrity
- Ratio virus / infectious particles
- Ratio empy/full capsid
- Agreggation
- Stability

- *Additional pharmacotox on AAV for increased expression*

13 April 2012
EMA/CAT/GTWP/671639/2008
Committee for Advanced Therapies (CAT)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

- Requirements as in the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006), PLUS
- Absence of adventitious viruses, replication-competent vector, transposase sequences (when using transposon vectors)
- release of vector from transduced cells
- transduction efficiency,
- vector copy number,
- sequence of transgene (and of other regions as needed),
- level of transgene expression,
- quality of the expressed molecule(s),
- removal or elimination of the desired nucleic acid sequences when appropriate for transient genetic modification.

Retroviral Vector Starting Material

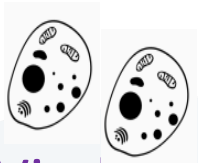
for transduction of patient cells

- Process :

Sequence integrity, copy number of gag / pol / env and genetic stability of packaging / producer cells + Vector titer

- Viral vector:
- Full sequence (therapeutic gene + genetic elements for selectivity/regulation/control - *no oncogenic/tumourigenic*
- genome or plasmid integrity, homogeneity and genetic stability of the vector and therapeutic gene.
- Expression of the therapeutic sequences and selectivity/regulatory elements delivered
- the tissue tropism, infectivity (in a variety of cell cultures), virulence, replication capacity, ratio of infectious to non-infectious particles, insertion sites
- Mean particle size and aggregates

Strimvelis EPAR on vector comparability :
potency, identity, genetic stability, aggregates and safety.



Comparability of GM-CELLS

Viral vector changes

- Critical process steps – CPP
- Consistency of the cell bank
- Infectious viral titre / total particules
- Infectivity
- Transgene sequence
- Transgene expression
- Stability
- Confirmation of transgene expression in permissive cell

+ Comparability of transduced cells (DS/DP)

Transduced cells

- Critical process steps - CPP
- Immunophenotypic profile
- Differentiation / scenescent
- Cell number, viability
- Transduction efficiency
- Vector copy number
- Transgene sequence
- Biological characterisation
- Potency
- Stability (accelerated)
- Confirmation with patient cells

Safety not part of comparability :
process related impurities, microbiological / viral safety
required to be kept to the minimum / absent as considered safe

Change management - Comparability

- *Change in raw materials*
- *Change in starting materials - viral vector - cells*
- *Process improvement*
- *Tech transfer*
- *Multiple sites*
- *…*

Consult authorities how to approach comparability requirements

Changes before clinical trials require data filiations – improvements welcome

Changes during clinical trials require prior approval (substantial amendment)

Improvement expected - Comparability to ensure safety

Changes after Market Authorization require prior approval (Variation)

Improvement acceptable based on Comparability to ensure safety and efficacy

Consult Variation Regulation →

COMMISSION REGULATION (EC) No 1234/2008

of 24 November 2008 Revised 2012

concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products


Thank You !
Questions?

Comparability in Cell and Gene Therapy

An ARM CMC Workshop Co-sponsored by USP

Michael Lehmicke

Director, Science and Industry Affairs

May 31st, 2019

Logistics

- **Break out sessions will be held in the adjacent rooms**
- **Reconvene in the auditorium for the end of day wrap up**
- **WebEx lines will remain muted for all sessions. Please use the chat function for questions.**
- **WebEx lines will remain active during the break out sessions**
- **For ARM members there is such a thing as a free lunch, but there are no free answers**
- **Notes from breakout sessions will be made available**

Alliance *for* Regenerative Medicine

About ARM

- **International Advocacy Organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
- **330+ Member Organizations**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Conducting key stakeholder outreach, **communication**, and education
  - Facilitating sustainable access to **capital**

Convening, Connecting, & Advocating for the RM Sector

Alliance *for* Regenerative Medicine

Clinical Trials

Alliance for Regenerative Medicine

1,028
Total Clinical Trials in Regenerative Medicine Worldwide

341
Phase I

595
Phase II

92
Phase III

Source data provided by: informa

ARM Efforts & Interests in CMC

- Regulatory approvals and successful clinical success of CGTx highlighted key challenges in CMC
- ARM convened CMC stakeholders in 2017 & 2018 to discuss challenges and opportunities
  - Project A-Gene, Project A-Cell
  - Need for CMC focused education sessions
- ARM S&T Committee made planning, coordination, and execution of CMC workshops a 2019 and 2020 priority

ARM Efforts & Interests in CMC

- Comparability - first in a series of ARM workshops
  - 60+ in person attendees from 30+ member organizations
  - Regulatory CMC, QA, Analytical Development, CTO …
- Comparability raised as a key issue by ARM members
  - Transitioning from lab scale (ph I/II) to production processes (ph. III/commercial release)
  - Scale up or scale out
  - Farm out or farm in
  - CMC Regulatory paradigms don’t fit CGTx

Agenda

8:15-9:00 **Registration and Breakfast** (*provided*)

9:00-9:10 **Introduction by ARM, review of efforts in CMC**

9:10-9:20 **Introduction by USP, review of USP efforts in CGRx**

9:20-9:40 **FDA Comparability Perspectives by Dr. Zenobia Taraporewala**

9:40-10:00 **CAT Comparability Perspectives by Dr. Margarida Menezes-Ferreira**

10:00-10:20 ***Coffee Break***

10:20-12:00 **Group Thought Exercises on Comparability**

12:00-13:00 **Lunch** (*provided*)

13:00-13:10 **Breakout Session Introduction**

13:10-14:10 **Concurrent Breakout Sessions**

14:10-14:40 **Coffee Break**

14:40-16:00 **Session Report Out and Workshop Summary**

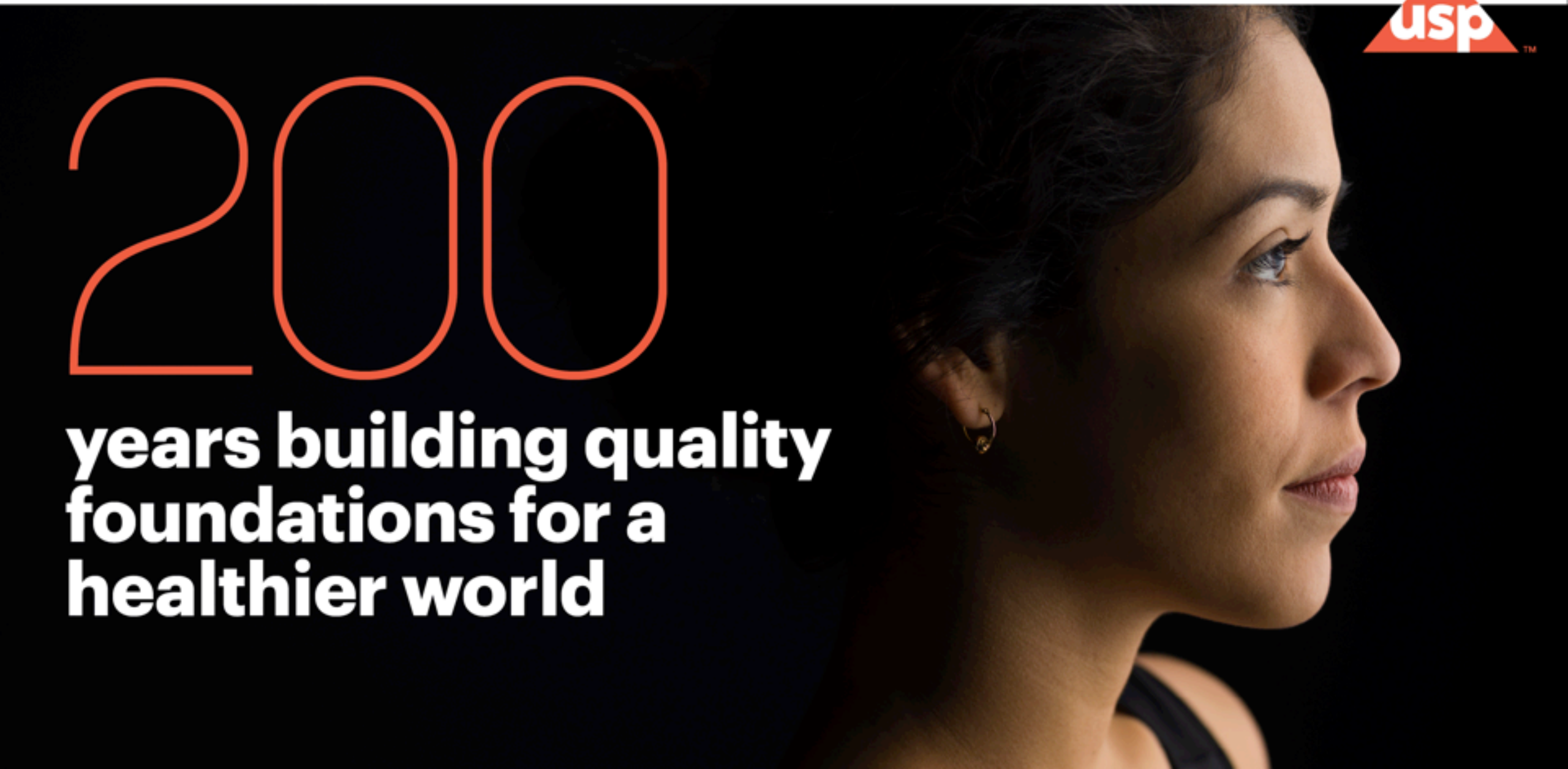
United States Pharmacopeia (USP)
Overview of Standards Setting for Cell & Gene Therapies

Fouad Atouf, Ph.D.
Vice President, Global Biologics

ARM Comparability Workshop-- May 31, 2019

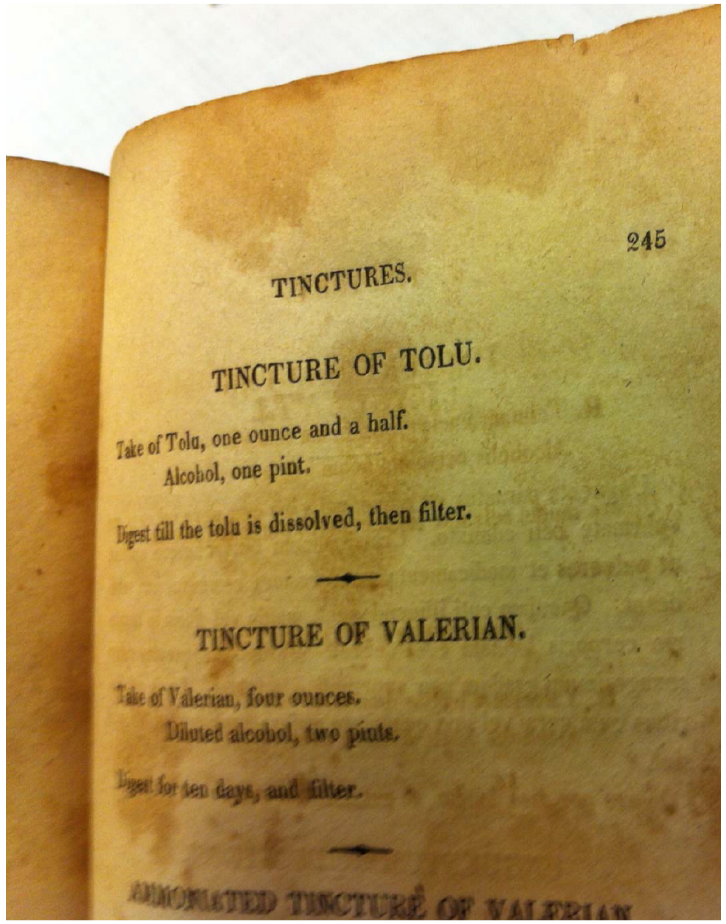
200

years building quality foundations for a healthier world



From recipes for pharmaceutical preparations to standards with test and specifications

1820



245

TINCTURES.

TINCTURE OF TOLU.

Take of Tolu, one ounce and a half.
Alcohol, one pint.

Digest till the tolu is dissolved, then filter.

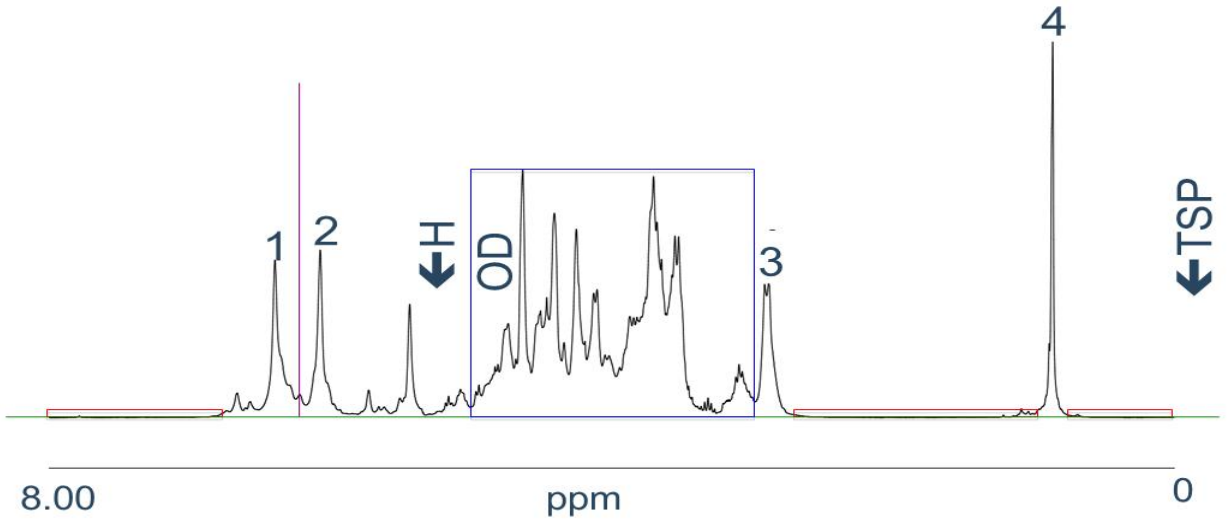
TINCTURE OF VALERIAN.

Take of Valerian, four ounces.
Diluted alcohol, two pints.

Digest for ten days, and filter.

2019

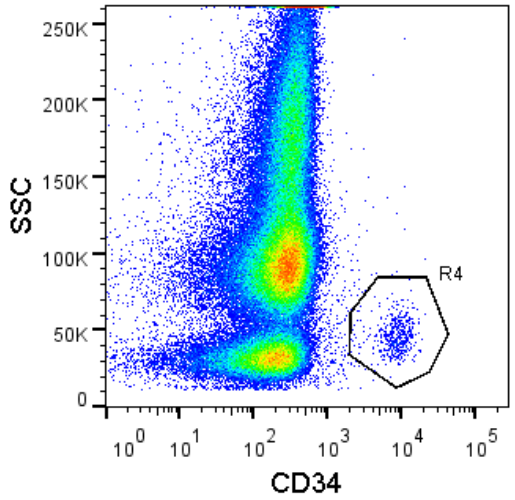
Sophisticated procedures and acceptance Criteria to describe medicinal articles in the market place



Acceptance Criteria

- No unidentified signals greater than 4% of the mean of signal height of 1 and 2 are present in the following ranges: 0.10-2.00, 2.10-3.20, and 5.70-8.00 ppm.
- No signals greater than 200% signal height of the mean of the signal height of 1 and 2 are present in the 3.35-4.55 ppm for porcine heparin.

Standards for method performance—USP chapter <127>
Enumeration of CD34+ stem cells—Flow Cytometry



USP CD34+ Cell Enumeration System Suitability Reference Standard is used to calibrate instruments, assess reagents and ensure correct gating for data acquisition and analysis

For use with specified USP compendial tests. Not for use as a drug. See SDS prior to use at www.usp.org/sds.

Lot: F045V0

USP REFERENCE STANDARD

CD34+ CELL ENUMERATION SYSTEM SUITABILITY

1.24 x 10^4 CD34+ Cells

Danger! Causes skin irritation. May cause an allergic skin reaction. Causes serious eye irritation. May cause allergy or asthma symptoms or breathing difficulties if inhaled. Suspected of damaging fertility or the unborn child.

Store in a freezer. See USP Certificate for reconstitution instructions and additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1084292 Material mfd. in United Kingdom

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Avoid breathing dust. Wash thoroughly after handling. Contaminated work clothing must not be allowed out of the workplace. Wear protective gloves/protective clothing/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of water. If skin irritation or rash occurs: Get medical advice/attention. Take off contaminated clothing and wash before reuse. If inhaled: If breathing is difficult, remove person to fresh air and keep comfortable for breathing. If experiencing respiratory symptoms: Call a poison center/doctor. If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists: Get medical advice/attention. If exposed or concerned: Get medical advice/attention.

CD34+ CELL ENUMERATION SYSTEM SUITABILITY

USP Catalog No.:	1084292
USP Lot No.:	F045V0

Additional Information:

USP CD34+ Cell Enumeration System Suitability Reference Standard is made from mobilized peripheral blood collected by apheresis of a G-CSF mobilized donor. The reference standard contains human leukocytes, erythrocytes and CD34+ cells that have been fixed and lyophilized.

Store USP CD34+ Cell Enumeration System Suitability Reference Standard in a freezer. Allow the vial to warm up to room temperature. Reconstitute the entire contents of the vial with 500 µL of water, use immediately as a system suitability standard as described in <127> Flow Cytometric Enumeration of CD34+ Cells. After reconstitution in 500 µL of water, the concentration range is 16-34 CD34+ cells/µL.

USP standards and examples of applications cell and gene and tissue therapies

Documentary standards – General chapters

<1046> Cell and Tissue Based Products
<1047> Gene Therapy Products
<1043> Ancillary Materials
<1027> Flow Cytometry
<1024> Bovine Serum
<90> FBS Quality Attributes and Functionality Tests
<89> Enzymes used as ancillary materials
<92> Growth Factors & Cytokines
<127> Enumeration of CD34+ Cells

Monographs for cell and tissue-based products

Reference Standards

Physical RS associated with ancillary material monographs (FBS, Trypsin, Collagenase)
Freeze dried cells as Reference Standards (e.g. CD34+ Cells)

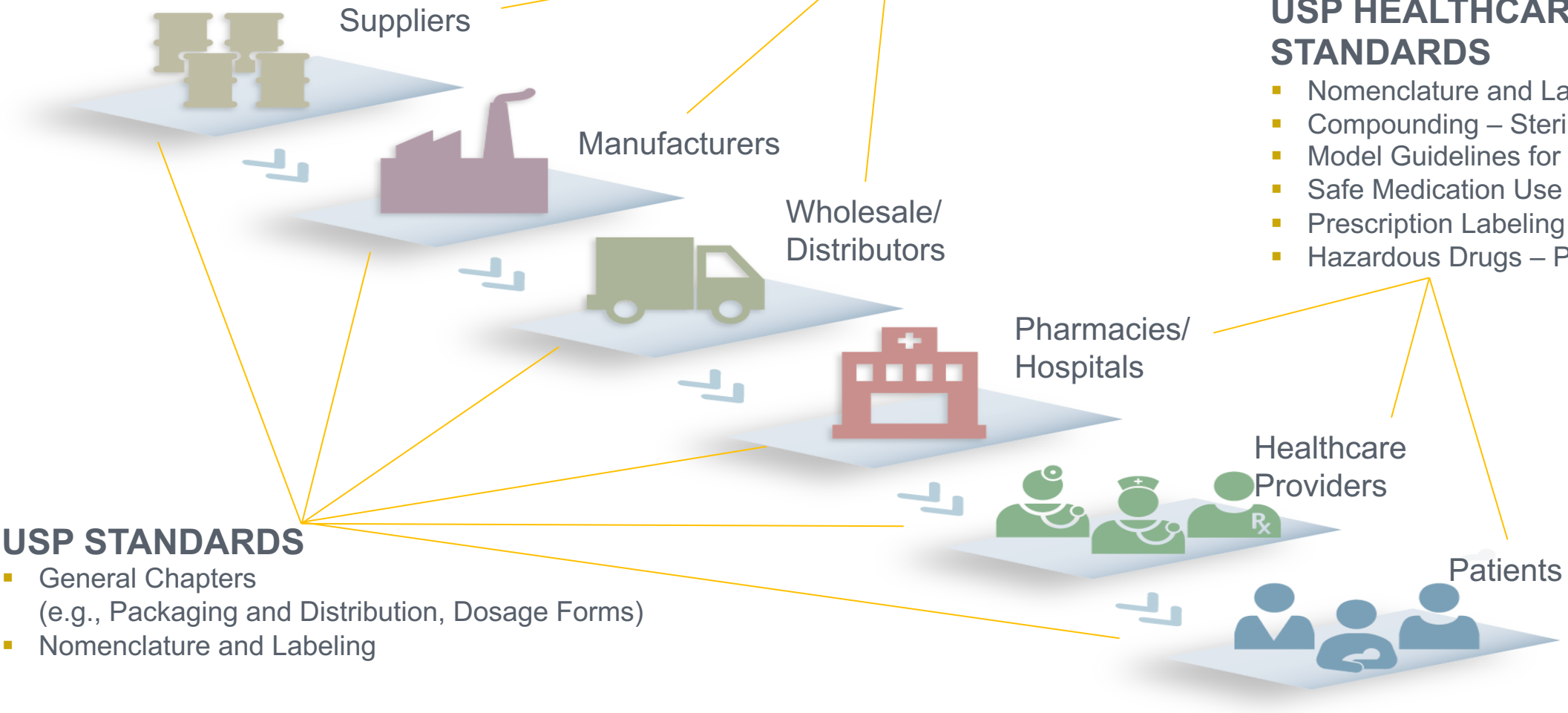
Integrity of the global supply chain

USP STANDARDS

- General Notices
- General Chapters
- Monographs and Reference Standards

USP HEALTHCARE QUALITY STANDARDS

- Nomenclature and Labeling
- Compounding – Sterile and Nonsterile
- Model Guidelines for Formularies
- Safe Medication Use
- Prescription Labeling
- Hazardous Drugs – Practitioner Handling



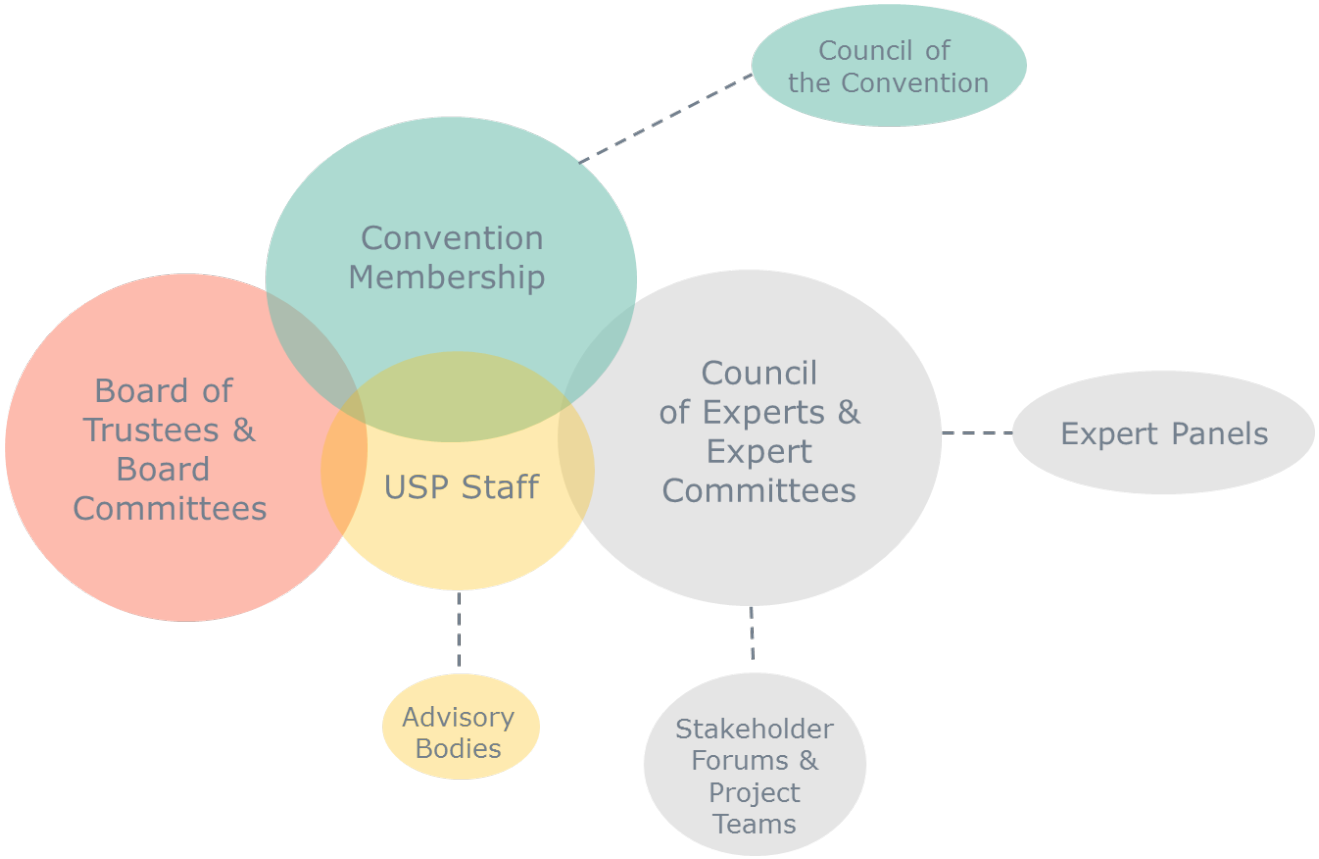
USP STANDARDS

- General Chapters
  (e.g., Packaging and Distribution, Dosage Forms)
- Nomenclature and Labeling

Mission

To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods

USP standards-setting bodies



Council of Experts oversees USP's scientific and standards-setting decisions. Members of the Council are elected by the USP Convention Membership at its every-five-year meeting.

Expert Committees are responsible for developing and revising USP documentary standards and for approving Reference Standards. Expert Committees publish proposed standards for public comment, then review public comments related to the draft standards. The standards are adjusted based on Expert Committee consideration of the public comments, and then are adopted by those USP expert volunteers by a majority vote.

Expert Panels are formed to provide additional expertise on a particular compendial topic, thereby supplementing Expert Committee expertise. Expert Panels are advisory to one or more Expert Committees; they are not decision-making bodies.

Areas our standards address

2015–2020 Council of Experts

Healthcare Quality & Safety Collaborative Group

- Nomenclature & Labeling
- Compounding
- Healthcare Quality & Safety

Chemical Medicines Monographs Collaborative Group

- Chemical Medicines Monographs 1
- Chemical Medicines Monographs 2
- Chemical Medicines Monographs 3
- Chemical Medicines Monographs 4
- Chemical Medicines Monographs 5
- Chemical Medicines Monographs 6

Biologics Collaborative Group

- B101 Peptides
- B102 Proteins
- B103 Complex Biologicals
- BIO4 Antibiotics
- GC Biological Analysis

Excipient Monographs Collaborative Group

- Excipient Monographs 1
- Excipient Monographs 2

Dietary Supplements/ Herbal Medicines/Foods Collaborative Group

- Non-Botanical Dietary Supplements
- Botanical Dietary Supplements & Herbal Medicines
- Food Ingredients

General Chapters Collaborative Group

- Chemical Analysis
- Physical Analysis
- Statistics
- Microbiology
- Dosage Forms
- Packaging & Distribution

2020-2025 standards development

2020-2025 Council of Experts – Expert Committees

Chemical Medicines

1. Antibiotic, antiviral, & antimicrobial
2. Cardiovascular, cough, cold & analgesics
3. Gastrointestinal, renal, endocrine,ophthalmic, oncology, dermatology & animal health
4. Nonradioactive imaging agents, aerosols, radiopharmaceuticals, psychiatric, & psychoactive
5. Pulmonary & steroids
6. Over-the-counter (OTC) methods & approaches

Biologics

1. Peptides & insulins
2. Therapeutic proteins
3. Advanced therapies (cell, gene, tissues, & genome-editing)*
4. Antibiotics using microbial assays
5. Complex products & vaccines

Excipients

1. Simple: Carbohydrates, minerals & salts
2. Complex: Polymers,oils, fats, waxes, plants & clays
3. Excipient test methods*

Dietary Supplements & Herbal Medicines, Food Ingredients

1. Food ingredients
2. Non-botanical dietary supplements
3. Botanical dietary supplements & herbal medicines
4. Admission, evaluation & labeling*

Healthcare Quality & Safety

1. Nomenclature & labeling
2. Healthcare quality
3. Compounding
4. Healthcare information & technology*

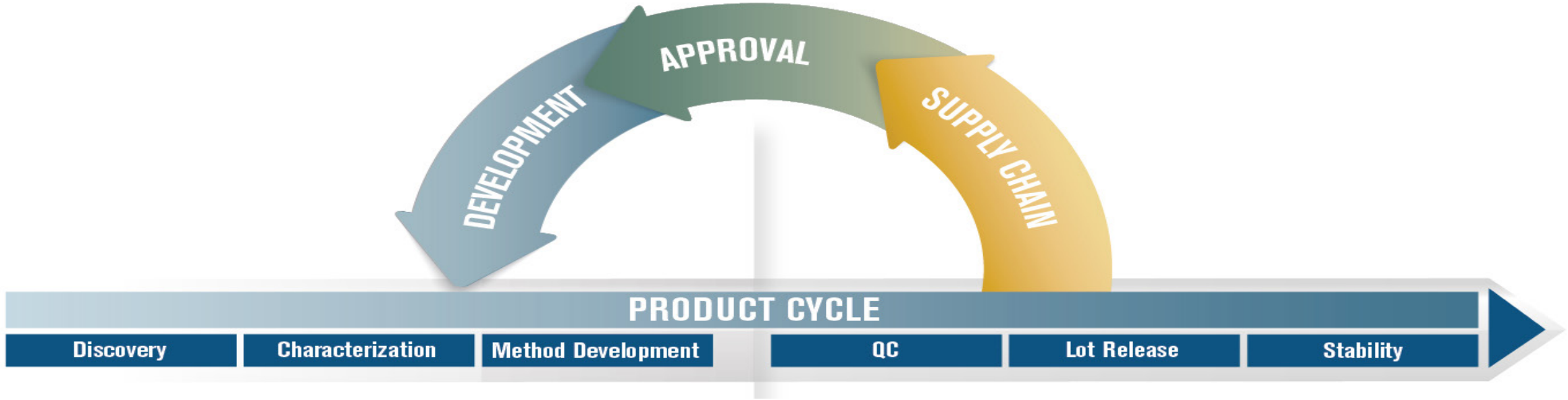
General Chapters

1. Packaging & distribution
2. Microbiology
3. Dosage forms
4. Chemical analysis
5. Physical analysis
6. Statistics
7. Measurement and Data Quality*

* Represents a new Expert Committee

Performance standards

- Support biologics analytical testing throughout the product lifecycle
- Used to ensure and demonstrate methods and process performance
- Broadly targeted at product families or classes



Assays and technologies

- Expanding focus beyond specific product classes
- Evaluating standards for technologies and assays with broad application

Examples:

Technology
LC, HPLC
Electrophoresis
MS
NMR
Flow cytometry
Immunoassays
PCR
Genomics

Assays
Protein characterization
Potency (Bioassays)
Residual HCP, HC DNA
Contaminants viral, microbial
Particulates, metals
Sequencing: deletion/ insertion
Algorithms, software

Vector copy number standard and potential uses

- Standard for Determination of Vector Copy Number
  - Jurkat T cells were transduced with a lentiviral vector, followed by clonal selection to identify clones containing 1, 2, 3 and 4 integrated provirus per cell using both qPCR and sequencing
  - Parental cells used for 0 copies/cell
- Potential Uses
  - Validation of internal standards
  - Vector copy number data is also used for titration of vector preparations
  - VCN is tracked in transduced cells as a very high copy number per cell could indicate a higher potential for insertional mutagenesis
    - The FDA recommends that the integration copy number shall be <5 copies per genome (presentation by Dr. Vatsan at ISBioTech 2017 conference)
    - Used to track cells after infusion to assess the stability of the product in vivo
  - Validation of Linear amplification mediated (LAM)-PCR for integration site analysis

Other standards under consideration

STANDARDS FOR AAV

- Roundtable in March 2019 cosponsored with NIH-NINDS and NCATS
- Potential standards and next steps
  - New collaborative study with existing AAV2/8 RSMs for qPCR/ddPCR and infectious titer standardization
  - AAV9 vector as a new standard
  - AAV empty capsids
  - AAV plasmid standards with multiple AAV specific targets as a broad PCR standard
  - Raw materials standards, possibly both best practices and reference standards (e.g. plasmid DNA)

STANDARDS FOR mRNA

- Roundtable held in November 2018
- Potential standards and next steps
  - Standard for T7 RNA polymerase activity
    - Consensus needed on template choice (length, composition)
    - Non-radioactive assay preferred
    - mRNA at a defined concentration to standardize dose determining assays
  - mRNA size standards across a range, e.g. 500, 1000, 2000, 3000, 5000, 7500, 10000, 12500, and 15000 nucleotides

2020–2025

call for candidates

Join us on the Journey

Collaborate with highly dedicated leaders from science, medicine, healthcare practitioners, industry and academia to help us establish standards that make it possible for 2 billion people around the world to have access to quality medicines, dietary supplements and foods.

Important dates:

Jul 2018: USP launched the 2020-2025 Call for Candidates

Jan 2020: Deadline for Expert Committee chair applications

May 2020: Deadline for Expert Committee member applications

Jul 2020: 2020–2025 Council of Experts and Expert Committees begin their work

For additional information visit **callforcandidates.usp.org** or contact **USPVolunteers@usp.org.**

Thank You

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