Pre- and post-market manufacturing changes: Categorization of major vs. minor changes and requirements for comparability assessment for gene therapy products

Mike Havert, PhD

bluebird bio

Advancing knowledge, awareness, and education of gene and cell therapy

AMERICAN SOCIETY of GENE & CELL THERAPY

Disclosures

- bluebird bio

Pre- and Post-market Manufacturing Changes

- Who we are:
  - ASGCT working group members involved in recent (and future) GT approvals,
  - Experience pre and post marketing manufacturing changes for GT products
  - Team members
    - Adora Ndu, Pharm.D, JD, Co-Chair – BioMarin
    - Fraser Wright, PhD – Stanford School of Medicine
    - Jennifer Mercer – BioMarin
    - Johannes C.M. van Der Loo, PhD - Children's Hospital of Philadelphia
    - Kenneth Miller, PhD – AveXis
    - Maritza C. McIntyre, PhD, Co-Chair - Advanced Therapies Partners LLC
    - Mike Havert, PhD – bluebird bio
    - Victor Lu, PhD – Innovative Cellular Therapeutics

Setting the stage…

- GT CMC challenges are characterization challenges
- Regulatory standard for risk and control in clinical studies
- Analytics enable manufacturing changes
- Early implementation of testing allows faster development

Outlook and Challenges for Cell and Gene Therapies

Optimistic Outlook for Gene Therapy

"… There is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable — or that the field still requires special oversight that falls outside our existing framework for ensuring safety"

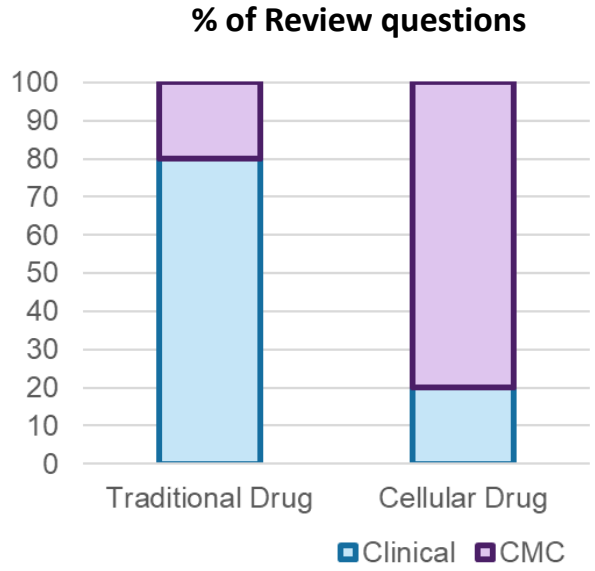
- ***Francis S. Collins, M.D., Ph.D., and Scott Gottlieb, M.D.***

August 15, 2018,
The NEW ENGLAND JOURNAL of MEDICINE

Challenges

"…In contrast to traditional drug review, some of the more **challenging questions when it comes to gene therapy relate to product manufacturing and quality**, or questions about the durability of response, which often can't be fully answered in any reasonably sized pre-market trial.."

- *Scott Gottlieb, M.D., Commissioner of FDA on Agency's efforts to advance development of gene therapies*
July11, 2018



Gene Therapy CMC Challenges are Characterization Challenges

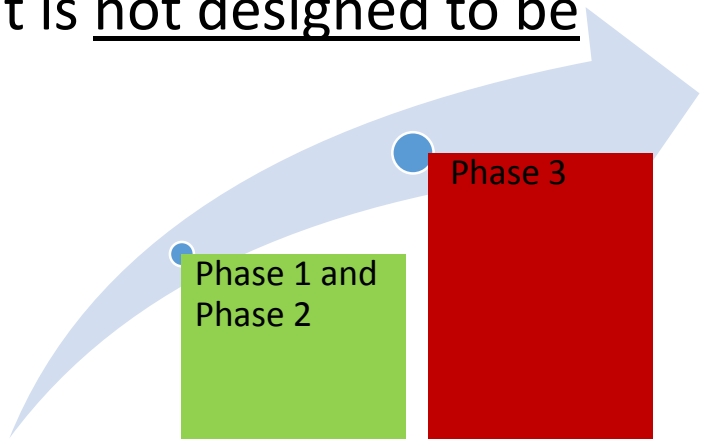
1. Complicated products
2. Variable cell inputs lead to variable cell outputs
3. MOA may not be fully understood
4. Incomplete or inadequate test methods

General Biological Product Standards

- Required prior to release of each lot of licensed product
- 21 CFR 610 Subpart B – General Provisions
  - 610.10 Potency
  - 610.12 Sterility
  - 610.13 Purity
    - Endotoxin
    - Impurity profile
  - 610.14 Identity
  - 610.30 Mycoplasma

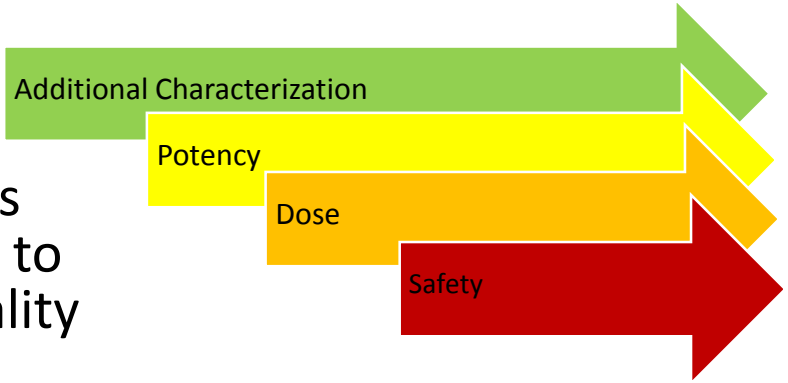
Regulatory Standards for Evaluating Risk

- CMC changes that impact Safety - 21 CFR 312.42(b)(1)(i)
  - FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that: (i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
- CMC changes that impact Efficacy - 21 CFR 312.42(b)(4)
  - FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled
  - Applies to all trials, but usually used for phase 3

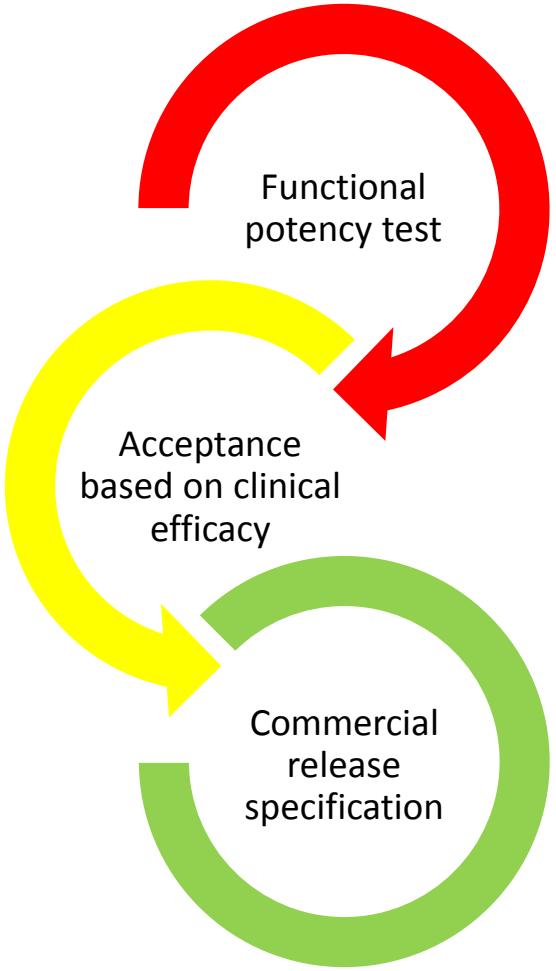


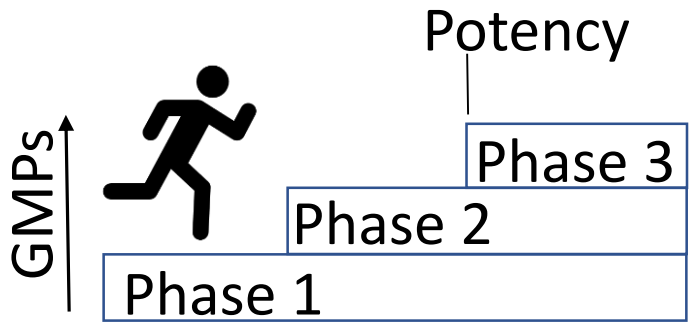
Better Analytics and Product Understanding Enable Manufacturing Changes

- The minimum level of testing for phase 1 INDs are not sufficient to understand complex biologic products
  - Safety tests
  - Dose escalation
- Critical Quality Attributes (CQAs)
  - Chemical, physical, biological and microbiological attributes that can be **defined**, measured, and continually monitored to ensure final product outputs remain within acceptable quality limits.
  - Potency and additional characterization
- Robust analytical assays enable an understanding of manufacturing changes



Early Implementation of Testing Enables Faster Development





Setting a commercial release specification with a functional potency assay takes time and planning

Guidance for Industry 2011 Potency Tests for Cellular and Gene Therapy Products https://www.fda.gov/media/79856/download

ASGCT Recommendations

- Robust analytical data packages along with robust quality systems will allow manufacturing changes at all phases of investigational studies
  - Comparability studies often require multiple rounds of engagement and discussion. These may be limited to formal meetings, which can create excessive delays and barriers to collaboration
  - Phase appropriate lot release criteria, CQA, and CPP should enable comparability
- Whether and how to implement post marketing manufacturing changes should be guided by the level of product understanding and the development of appropriate analytical methods.
- If needed, clinical bridging studies after clinical benefit has been established may be assessed with early time points, or surrogate endpoints, rather than the full pivotal clinical trial endpoints.

ASGCT/FDA Joint Platform Workshops

- Set up working groups for different product classes (platforms)
  - Retroviral vectors
  - AAV
  - CAR T/ TCR and/or Genetically modified stem cells
  - ASGCT and FDA representation
- Request a joint workshop
  - Educate and share information in a public workshop
  - Identify and fill knowledge gaps
  - CMC topics
    - Recommendations on development of phase appropriate CQAs and quality system
    - Identify common manufacturing changes and associated concerns with each
    - Provide framework to de-risk changes
  - Other potential areas covered
    - Establish approaches for IND enabling Pre-clinical toxicity studies
    - Recommendations for assessing platform durability and/or persistence of vector

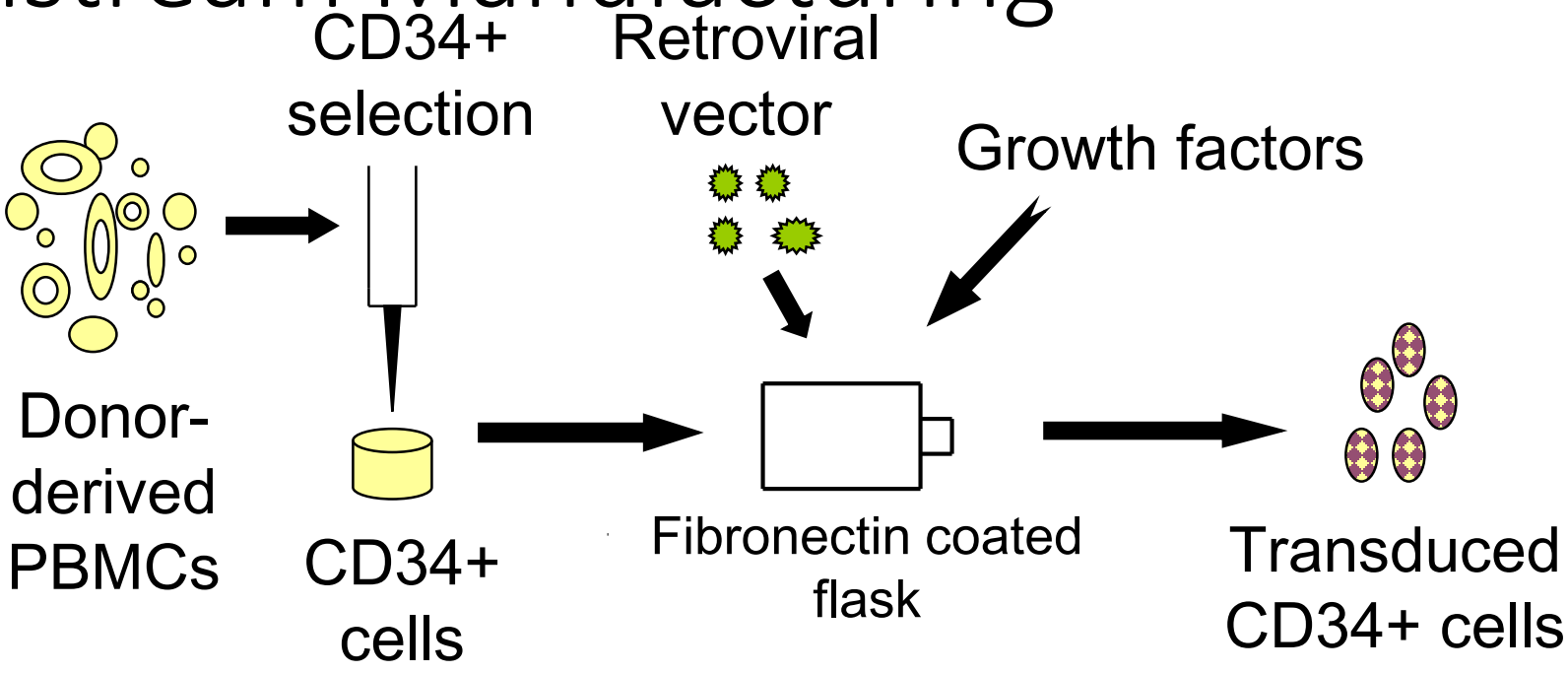
Thank you!

Back up slides

Categorization of major and minor changes

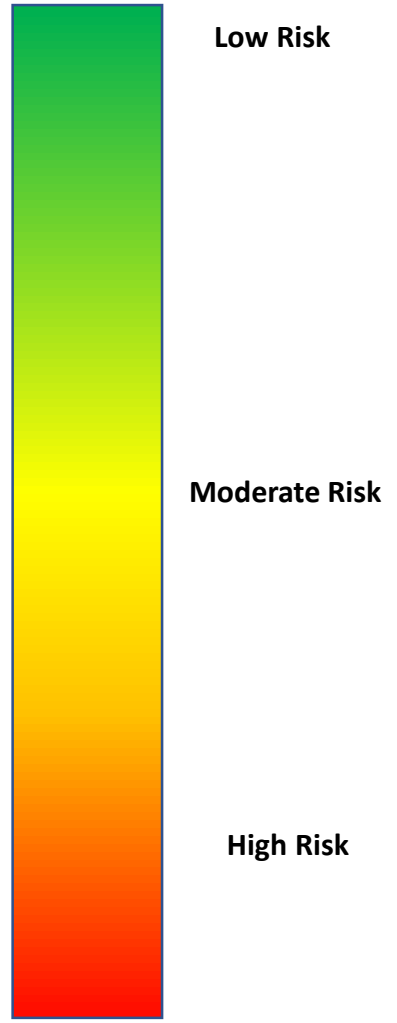
- Different products are different (e.g. changes in cell substrate expansion steps for AAV would be viewed differently than expansion steps for CAR T)
- Phases of investigation are different by design (changes that impact safety vs changes that impact efficacy)
- ASGCT categorization of changes (next slides)

Categorization based on Upstream and Downstream Manufacturing



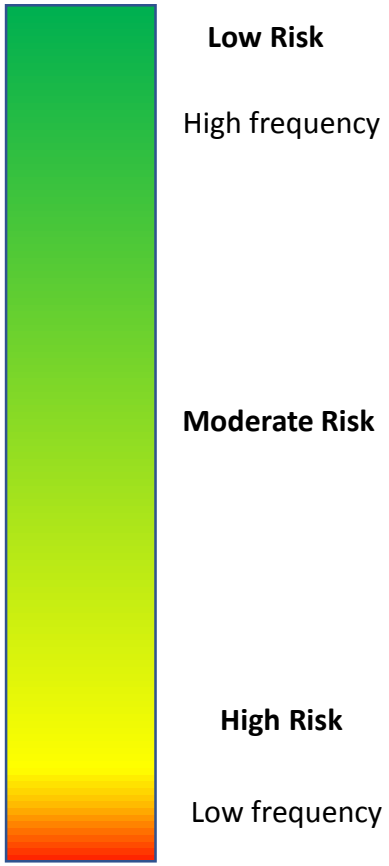
Risk Rainbow Continuum

- Changes to tubing, bags, plastic culture dishes
- Changes in collection and handling of cellular starting material (ex vivo modified GT)
- Changes in raw materials, reagents and ancillary materials
- Changes to production cell substrate (in vivo GT)
- Changes in chromatography parameters and purification strategy
- Changes to cell differentiation, selection, transfection/transduction steps, or allogeneic bank qualification
- Overall manufacturing changes



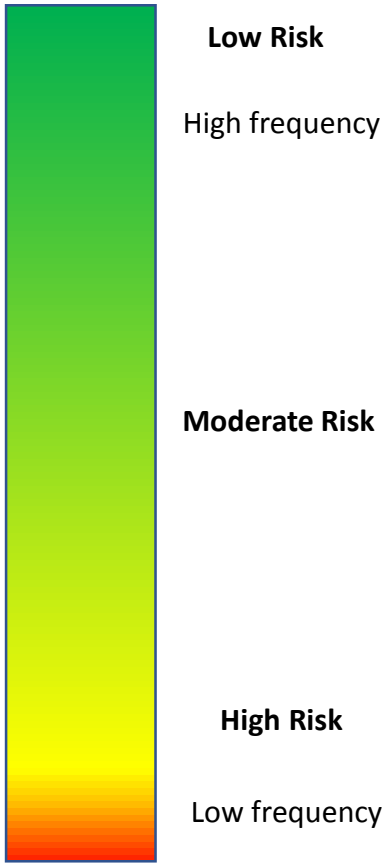
Changes to Tubing, bags, plastic culture dishes

- Change in supplier – single use, disposable components
- Change in material grade
  - Clinical grade, cleared as device 510(k)
  - Non-Clinical Research grade
  - Common or commercial grade
  - In-house or company specification
- Changes to product contact surfaces
  - Leachables/extractables
  - Binding, loss or inactivate product
- Change in delivery device components (not part of product manufacturing)



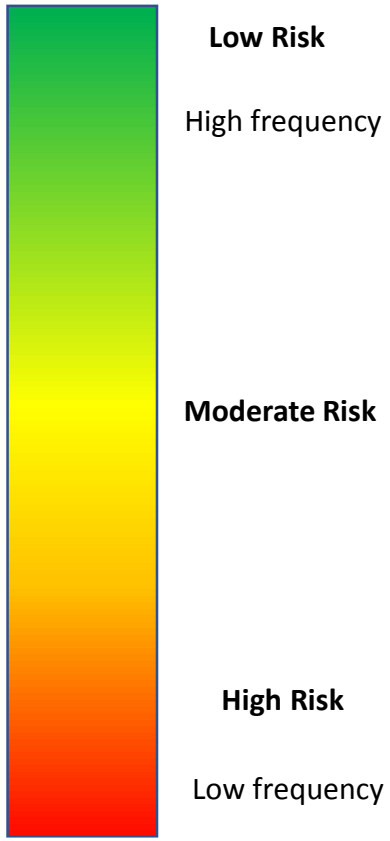
Change in collection and handling of cellular starting material

- Change from open to closed transfer and centrifugation during manufacture
- Change in cell starting material collection process
  - Scalpel/forceps to suction
  - Fenwal Amicus to Cobe Spectra
- Change from shipping Fresh to Frozen apheresis



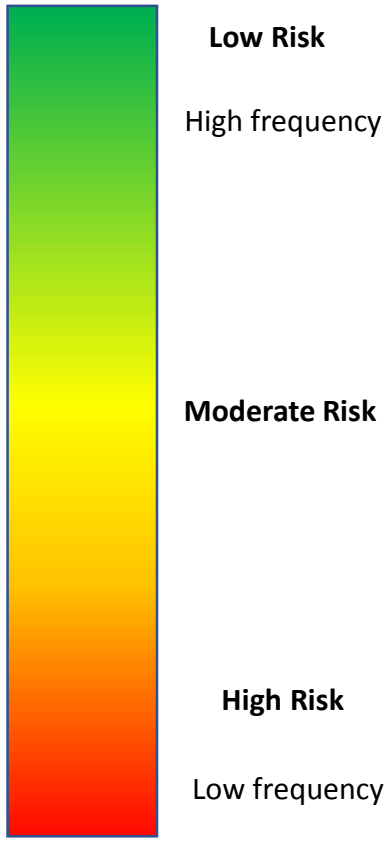
Changes to Raw materials, Reagents, Ancillary Materials

- Change in supplier
- Change involving a chemical or pharmacopeia grade material
- Addition of new raw material, reagent, or ancillary material
- Removal of existing raw material, reagent, or ancillary material
- Change involving a complex or incompletely defined biological material (FBS, cell scaffold)
- Changes known to impact CQA



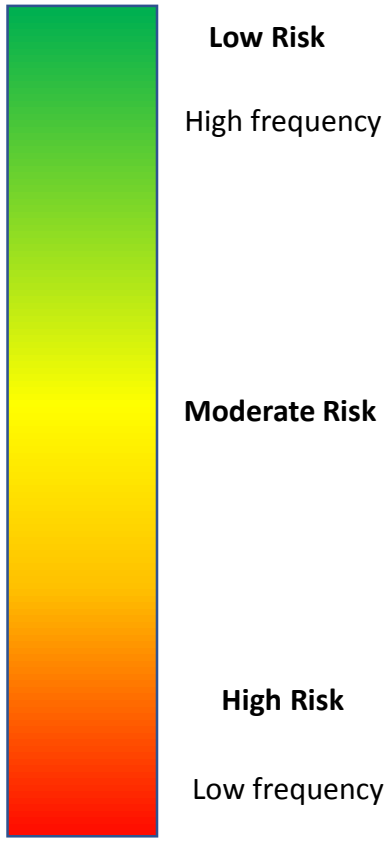
Changes to production cell substrate

- Qualification of WCB or MCB per protocol
- Change in the number of expansion steps
- Change from transient transfection to use of a stable production cell line
- Change to a different production cell substrate (i.e. HEK293 to SF9)



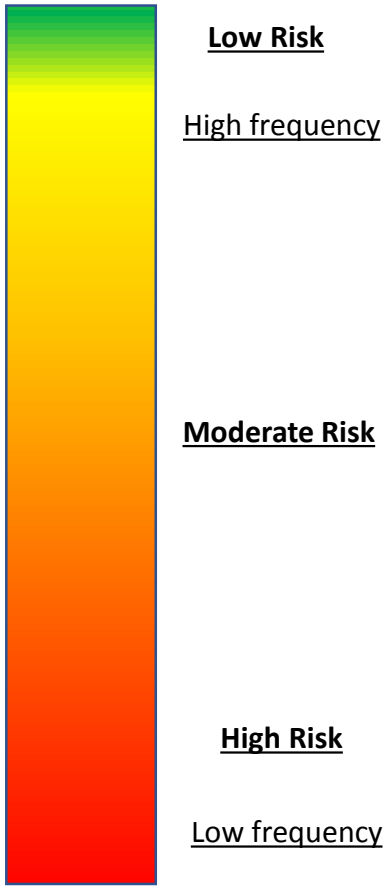
Changes in chromatography parameters and purification strategy

- Change in chromatography resin
- Addition or removal of a chromatography step
- Change from gradient density ultracentrifugation to column chromatography-based purification



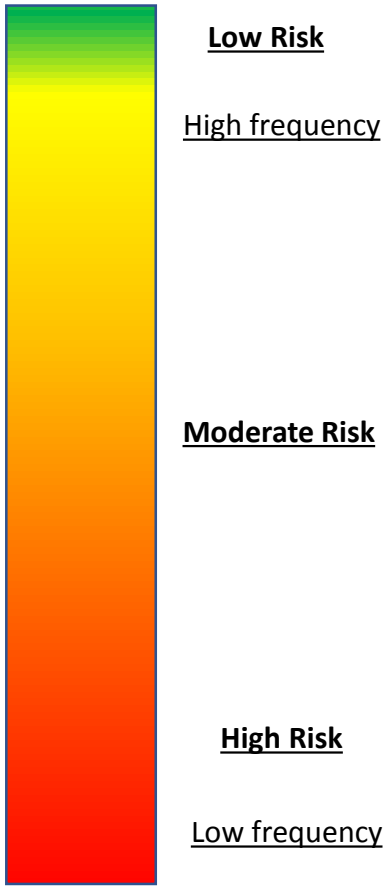
Changes to cell differentiation, selection or transfection / transduction steps, or allogeneic bank qualification

- Change in transfection step (CaPO to PEI)
- Extend hold time or culture expansion
- Change of transduction parameters (MOI, addition of enhancers)
- Change in cell selection methodology
  - Ficoll PBMC, CD3 or multiple marker selection
- Change in differentiation to alter cell phenotype



Overall manufacturing changes

- Change to fully automated production
- Change in manufacturing platform from transient plasmid transfection to viral infection
- Change vector sequence including in the gene of interest, regulatory sequences

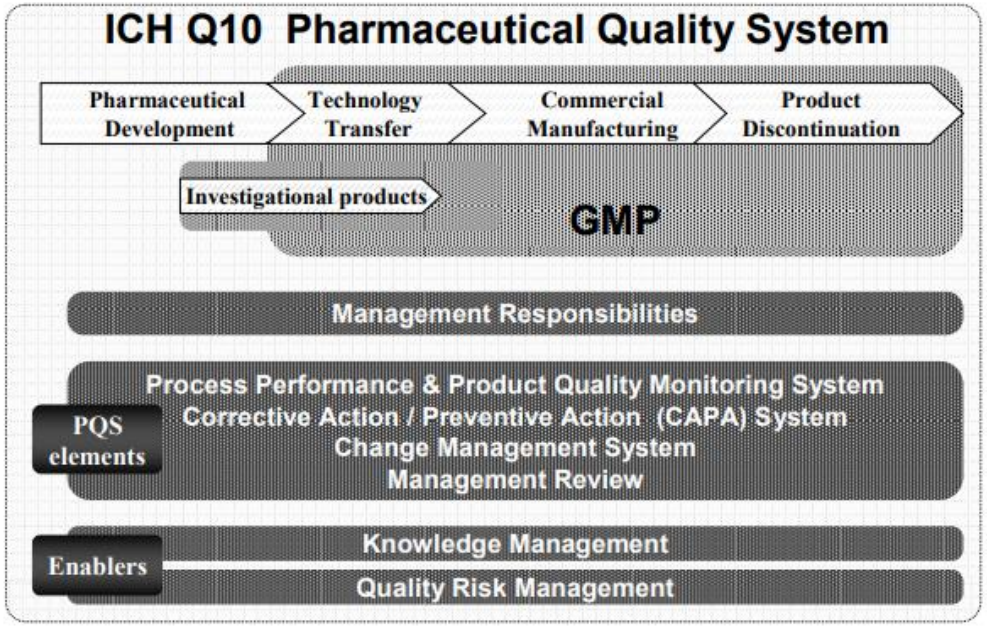


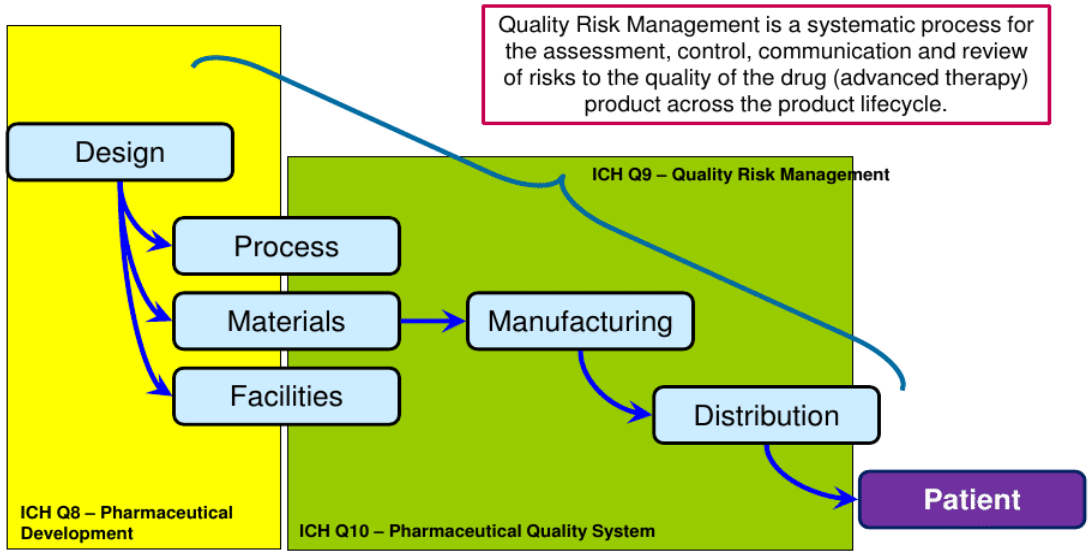
Quality System and Change Management

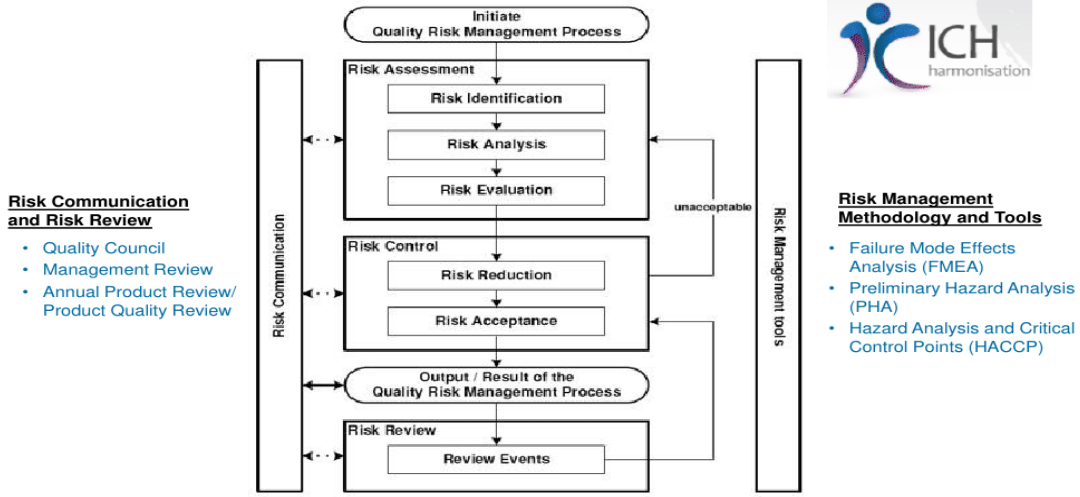
- Quality System Guidance
  - Sponsor specific
  - Appropriate and proportional to stage of development
  - Change Management

Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP regulations 2006

Quality System from ICH







IND Guidance

- INDs have varying level of CMC detail
- Commitment to perform manufacturing and testing as stated
- Changes that could affect product safety, identity, quality, purity, potency or stability should be submitted prior to implementation
- Quality Unit should be described

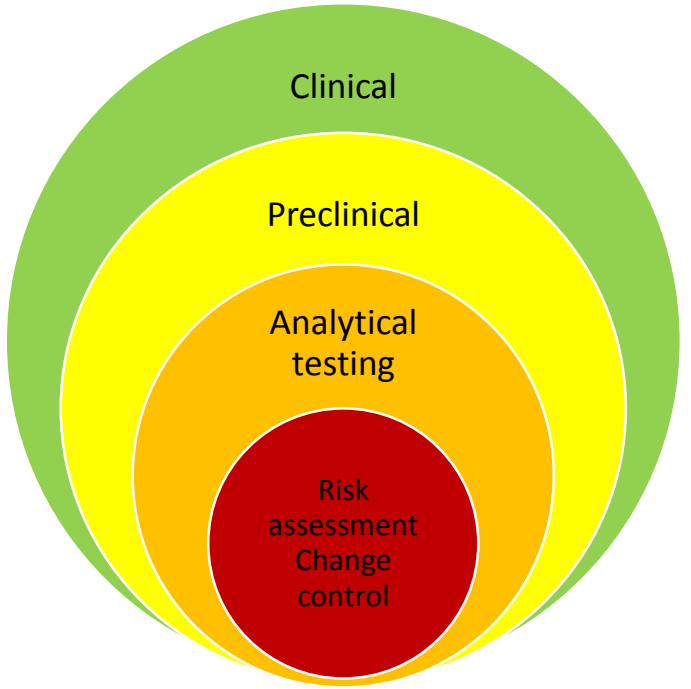
Draft Guidance for Industry 2018 Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
https://www.fda.gov/media/113760/download

ASGCT Quality System feedback

- All changes should be monitored and tracked by an IND Sponsor through a quality system
- FDA may not be aware of all changes occurring under IND
- Gaps in reporting may occur when
  - Sponsor's quality system didn't trigger a regulatory filing
  - Sponsor's quality system didn't the identify change
  - CMOs report changes to an IND Sponsor based on a quality agreement (IND sponsor may not "know" of the change)

Changes after demonstration of clinical benefit (bridging studies)

- If needed, clinical bridging studies after clinical benefit has been established may be assessed with early time points, or surrogate endpoints, rather than the full pivotal clinical trial endpoint.
- ASGCT WG recommends that sponsors are highly proactive in communication with the FDA and that FDA actively engage as early as possible regarding the need for clinical bridging studies in order to adequately plan manufacturing changes that enable supply of the product once approved for use.



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