ICH Considerations on General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
and
Current Topics on Gene Therapy in USA

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ICH Gene Therapy Discussion Group

Topics

- **ICH Considerations on General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors**
- **FDA's Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events**
- **Other FDA GT-related initiatives**

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ICH Considerations on General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors

- published 10/2006
- available on ICH website http://www.ich.org

- short, two page document on *general principles* (1137 words)
- agreed upon by MHLW, FDA, EMEA, EFTA, Health Canada, and JPMA, PhRMA, EFPIA

ICH Considerations on General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors

- *Introduction:*
  - Integration events can result in insertional mutagenesis or genetic rearrangements that interrupt, induce or otherwise modify gene structure and/or expression.
- *Risk factors*
  - vector type, dose, route, and site of administration
  - vector type risk based on biodistribution profile, the replication capacity, tropism, and the integration potential
- *Non-clinical studies*
  - biodistribution studies
  - patient monitoring

ICH Gene Therapy Update

- *ICH Considerations*
  - Germline Integration of Gene Therapy Vectors , published 10/2006
  - Oncolytic Viruses, published 11/2008
  - Viral/Vector Shedding, target completion 6/2009
    - Stakeholder input Nov 2008 to April 2009
- *ICH Guidance*
  - Proposing to further develop Viral/Vector Shedding Considerations to formal guidance

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Key Events in Development of Guidance Document

- 1993, Letter to sponsors of retroviral vectors
  - **Life-long surveillance of subjects**
  - **Guidance document published 2000**
- March 6, 2000, “Gene Therapy Letter”
  - lack of good study conduct monitoring, including lack of long-term follow-up of subjects of retroviral vector-mediated gene therapy
- BRMAC Meetings*:
  - **November 17, 2000**
  - **April 5, 2001**
  - **October 24, 2001**

*Transcripts, www.fda.gov/cber/advisory/ctgt/ctgtmain.htm

Key Events in Development of Guidance Document (Cont'd)

- 2001, Implementation of recommendation to perform long-term follow-up of subjects in ALL clinical trials, regardless of vector
- June, 2004, Workshop on Long-term Follow-up of Participants in Human Gene Transfer Research*
  - Lack of scientific basis for 2001 recommendations
  - Lack of details for how to perform long-term surveillance
  - Legal consequences for long-term surveillance

*Nybert, K., et al, 2005, Molecular Therapy 10(6):976-980

Draft to Final

- Draft Guidance was published, August, 2005
- Docket was officially open for comments until November 21, 2006
- FDA reviewed comments
- Revisions were made based on comments received
- Final Guidance was published, November 28, 2006

General Themes of Docket Comments

- Misunderstanding of what's included in guidance. Technical comments about specifics of biodistribution/persistence preclincal study design
- All GT subjects should be followed for delayed AE
- Various suggested wording changes

Revisions to Guidance, 1

- Clarification of scope of guidance *(See Footnote to Introduction).*

  Following are NOT:

  – Inadvertent germ-line gene transfer risks
  – Post-marketing
  – Replication competent viruses
  – Vector shedding

Revisions to Guidance, 2

- Clarification of what is supplemented vs. superseded by this Guidance in

  Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors

  (this revised accordingly and released as Level II guidance on 11/28/06)

Revisions to Guidance, 3

- Updated methods recommended for biodistribution and persistence studies (*see Section IV.B.2, Tissue Collection and Analysis*):
  - Assay limit of quantitation with 95% confidence, <50 copies of vector/1 μg genomic DNA
  - Minimum of three samples/tissue. One sample should include spike with known amount vector DNA; used to assess assay sensitivity
  - Provide rationale regarding number of replicates for any individual tissue, taking into account size of tissue

What are the scientific bases for long-term risks?

Properties of Gene Transfer Systems with Potential to Cause Delayed Events

- Persistence of Vector Sequences
  - Integration
  - Reactivation/Latency
- Transgene-specific effects

Persistence of Vector Sequences

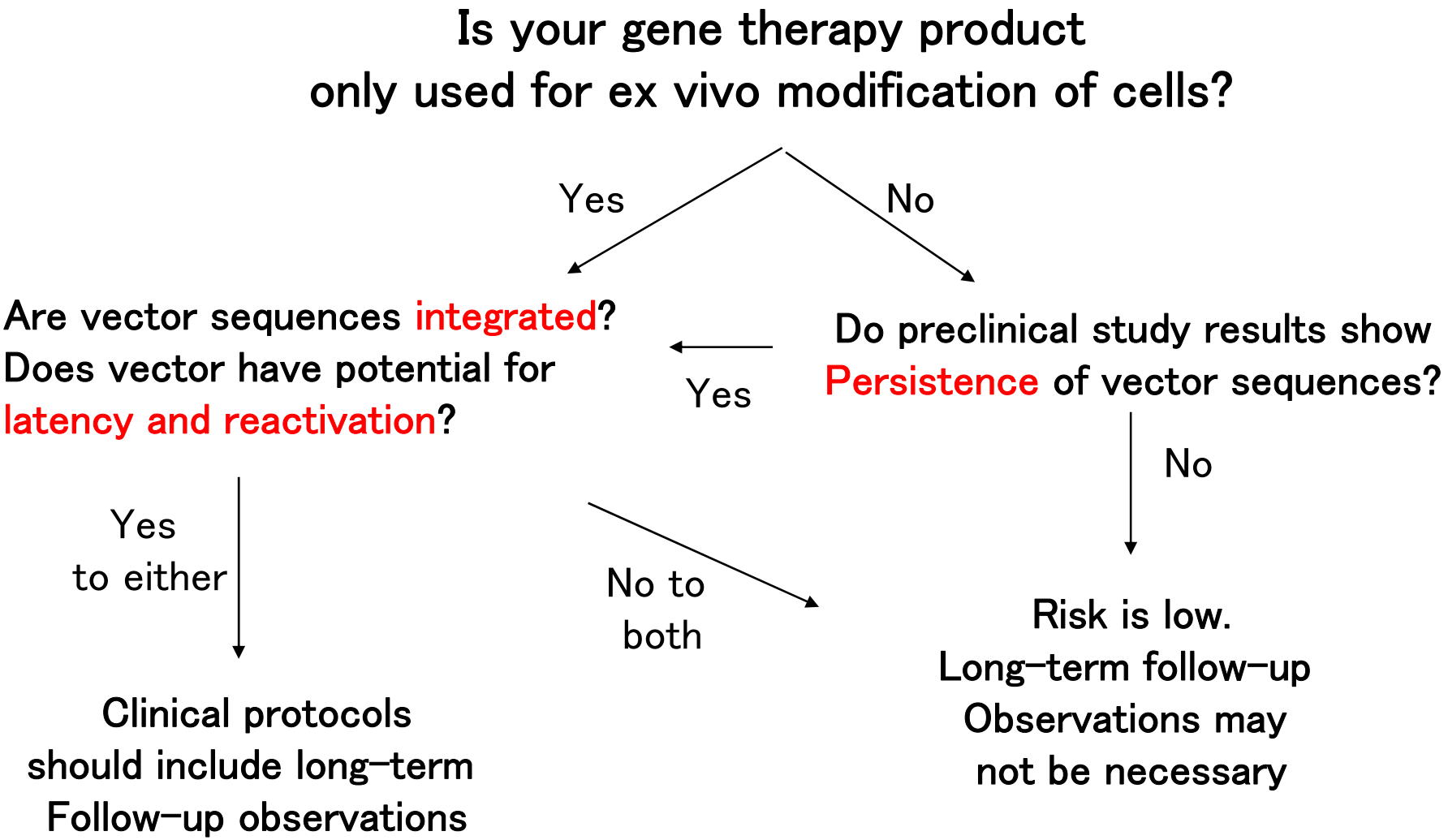
- Long-term risk of persistence will be influenced by
  - Mechanism of persistence
    - Ex, integration of vector (Potential for Insertional Mutagenesis)
  - Latency and potential for reactivation
    - Ex, Reactivation of herpesvirus carries risk of encephalitis
  - Immune status of subject
    - Ex, immune response or lack thereof may influence outcome relative to long-term risks

Transgene-Specific Effects

- Tumorigenic effects of transgene itself
- Transgene expression may induce autoimmune disease in genetic disorders
- Constitutive expression may induce unexpected effects when endogenous gene is tightly regulated (e.g., metabolic pathways)
- Ectopic gene expression

How does one determine whether long-term observations should be performed in a particular clinical trial?

Criteria to Assess Potential Delayed Risks of Gene Therapy



How to Determine Persistence

- Biodistribution Study with multiple time points
- Vector is defined to persist if detectable levels of vector are present throughout all time points of the study without any downward trend over several time points.

Integration/Latency

- Can perform as part of the persistence study to identify whether vector integrates

Or

- Refer to Table 1

Propensity to Integrate

Or

- If integration occurs or cannot be defined, perform clinical long-term observations

Vector Type	*Propensity to Integrate*	*LTFU*
Plasmid	**No**	**No**
Poxvirus	**No**	**No**
Adenovirus	**No**	**No**
AAV	**No**	**No**
Herpesvirus	**No, but latency with reactivation potential**	**Yes**
Retrovirus	**Yes**	**Yes**

Exceptions

- Evidence for persistence of transgene expression without integration: preclinical studies show potential for long-term toxicity.

- Evidence for potential long-term toxicity due to specific transgene; potential for autoimmune response

- Alterations to non-integrating vectors that increase propensity to integrate

Use of Retroviral Vectors: Special Considerations May Apply

- *When*
  - Used to Transduce Target Cells with High Replicative Capacity and Long Survival
- *If*
  - Surrogate is accessible for assay
- Test for vector sequences every 6 months first 5 years; yearly next ten years; or until no vector is detected.
- Recommended Points to Include in Informed Consent: accurately reflect risk of cancer

Retroviral Vectors, Continued

- When at least 1% of surrogate cells have detectable vector (by PCR, or other sensitive method)
  - Assess the pattern of vector integration sites.
    - If oligoclonal or clonal, identify integration site
    - Compare to human genome; determine whether oncogene
    - Monitor for signs of malignancy

What is meant by “observing participants for delayed adverse events”?

Clinical Considerations

- Should be performed if
  - Criteria suggest that vector/gene therapy is associated with a high or uncertain risk
  - Information about product, taken as a whole, shows a need for long-term follow up
- Need not be performed if
  - Long-term observations may have limited scientific value

Long-term Clinical Observations May Have Limited Scientific Value

- Population characteristics:
  - Short life expectancy
  - Multiple morbidities
  - Exposure to other agents

Duration of Follow Up

- Duration of in vivo vector persistence
- Duration of in vivo transgene expression
- Exposures of study population
- Expected survival rates
- Other relevant factors

Elements of Observation: First 5 Years

- Record and maintain accurate case histories, including baseline information
- Detect gene therapy related events
- Record exposures to mutagens
- Visit health care provider annually
- Record new malignancy, neurologic disorder, rheumatologic or autoimmune disorder, hematologic disorder
- Elicit cooperation from study participants in reporting events

Observations: 6 – 15 years

- Contact annually, specific screening if indicated
- Continue appropriate follow up as indicated by results from previous years

Other considerations

- Perform all long-term follow-up observations in accordance with FDA regulations governing clinical trials
- Report to FDA, expedite if serious
- File annual reports with FDA
- Examine as indicated by emergence of adverse events
- Test for vector sequences at least annually, if technically feasible

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FDA Regulation of ex vivo gene modified cells

- FDA does regulate the final **gene modified cellular** drug product
  - Includes autologous gene modified cell products
  - Final cells subject to biological standards outline in 21CFR610 (e.g. purity, potency, identity, etc.)
    - flexibility in test methods
- USAN non-proprietary naming scheme for gene modified cells

Other FDA Initiatives

- Exemption of most Phase I investigational products from GMPs (July 2008)
- Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (October 2008)

For Additional FDA Information and Guidance on Gene Therapy

http://www.fda.gov/cber/gene.htm

General information for OCTGT and related regulatory references

http://www.fda.gov/cber/genadmin/octgtprocess.htm

Comments and Questions

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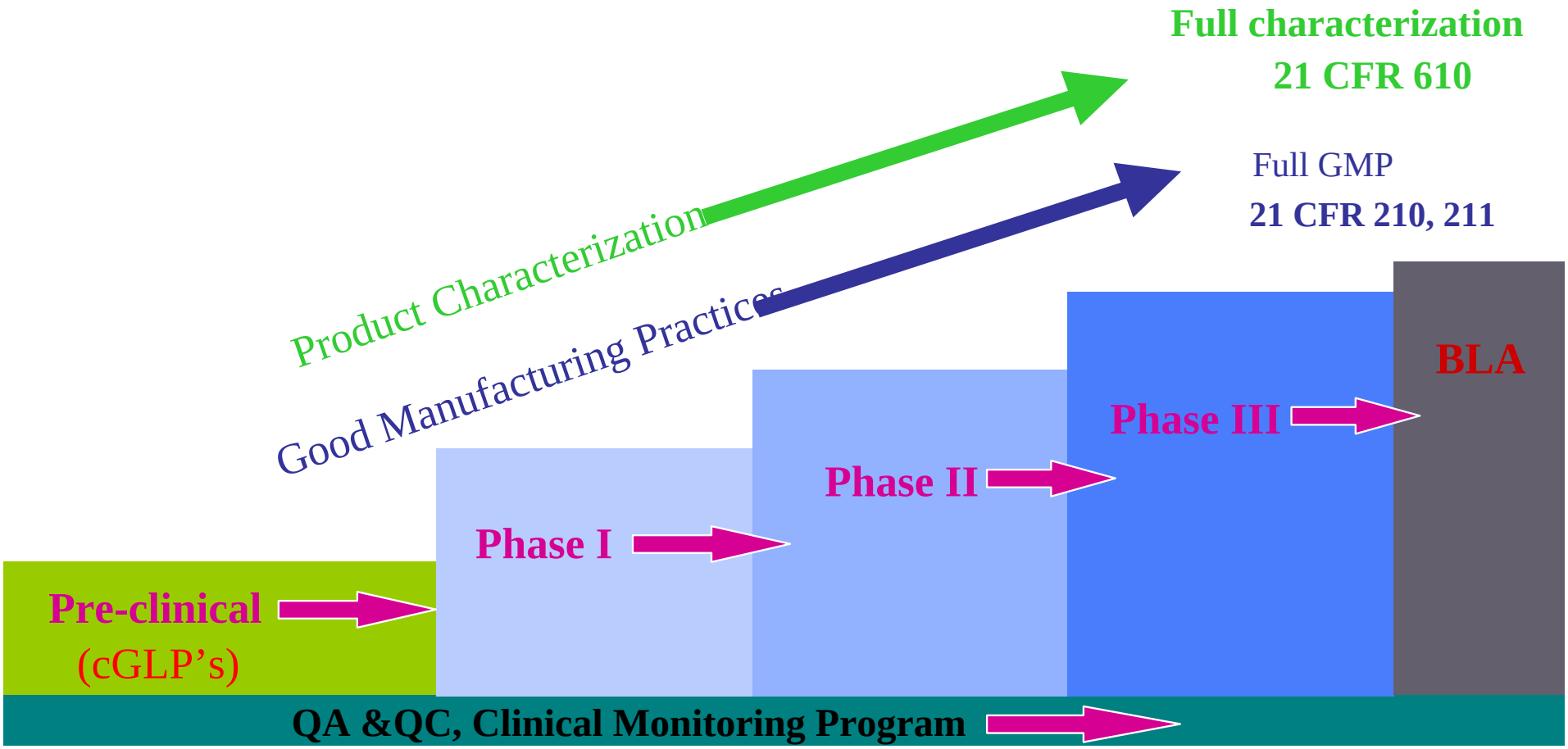
ICH & GTDG web site

http://www.ich.org

Back-up Slides

Step-wise Approach to Application of Regulatory Requirements



Investigational Studies & 21 CFR 211's

- Not always possible at phase 1 to fully comply with CGMP regulations (i.e., 21 CFR 211)
- Some CGMP regulations designed for repetitive, commercial manufacture of an approved product
  - Defined product quality attributes; uses an established manufacturing process

Final Rule

- In July 2008, FDA published a direct final rule in the Federal Register to amend CGMP regulations for human drugs, including biological products, to exempt most investigational “Phase 1” drugs from complying with the CGMP regulation (21 CFR 210/211)
  - http://www.fda.gov/cber/rules/gmpind.pdf

Companion Guidance

- In addition to the final rule, FDA published a guidance
  - **“CGMP for Phase 1 Investigational Drugs**”
  - to provide guidance for “recommendations on approaches to statutory compliance” for the manufacture of Phase 1 material
  - http://www.fda.gov/cber/gdlns/indcgmp.pdf

Phase I CGMP Guidance

- Guidance for Phase 1 INDs:
  - recognizes that some controls and the extent of controls differ between investigational and commercial manufacturing, as well as phases of clinical studies
  - articulates the expectation that there will be greater control over the process through the various IND phases

Phase I CGMP Guidance : Scope

Applies to:

- investigational new drug and biological drug products used during phase 1 development

- investigational recombinant and non-recombinant therapeutic products, vaccine, **gene therapy**, allergenic, plasma derived, and somatic cellular therapy products as well as in vivo diagnostics

Phase I CGMP Guidance : Scope

Does not apply to:

- **human cell or tissue products regulated solely under Section 361 of the PHS Act**
- blood and blood components
- products regulated as devices
- already approved products/and or in phase 2/3 used in other phase 1 studies
- PET products

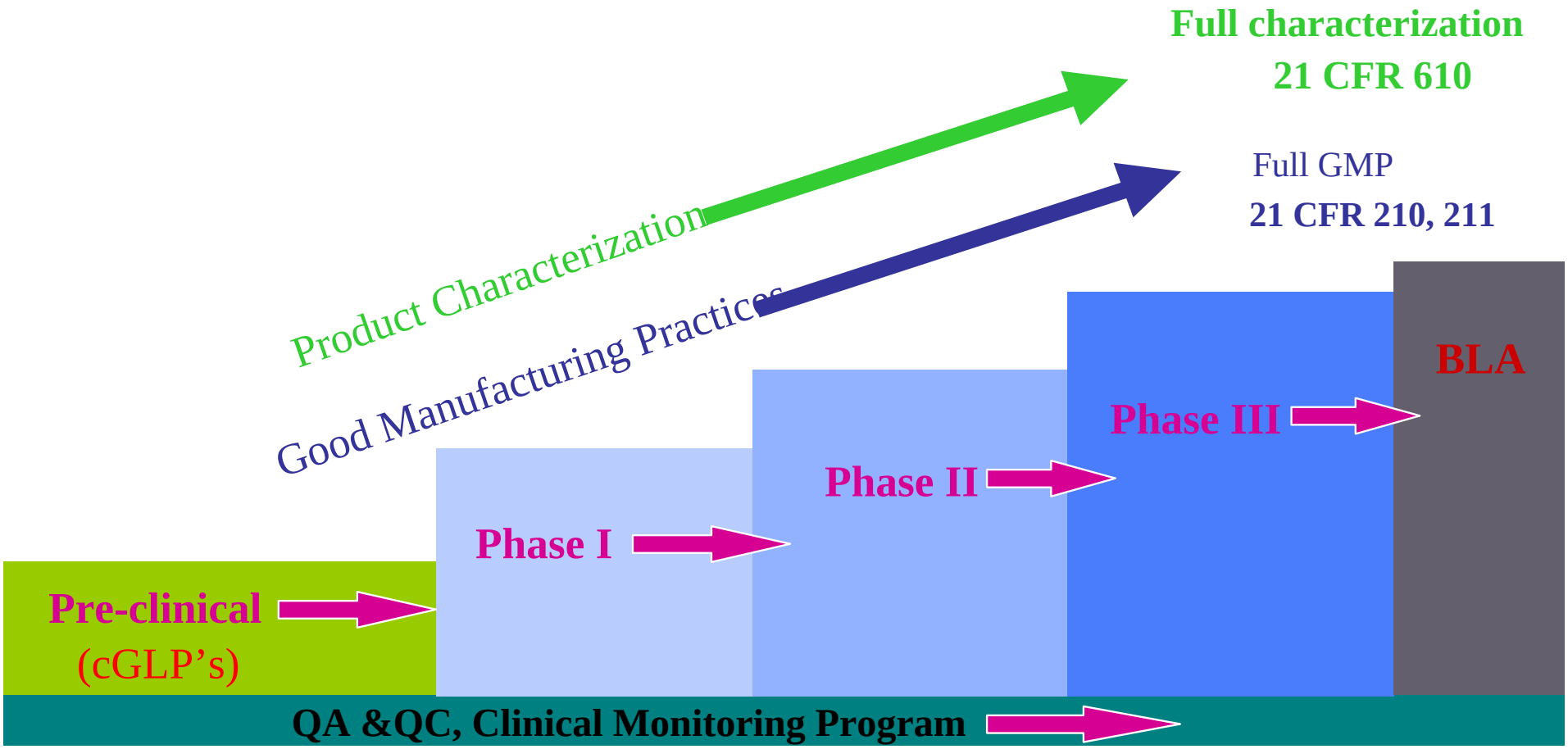
Phase I CGMP Guidance: Key points

- Effective quality control standards for Phase 1
  - Well defined written procedures
  - Adequately controlled equipment
  - Accurate and consistent recording of all data (manufacturing and testing)
- Implement CGMP consistent with good scientific methodology, product development and quality principles
- Avoid cross contamination
- Prevent microbial contamination

Phase I CGMP Guidance

- Phase 2 and 3 manufacturing will continue to be subject to parts 210 and 211
- “We are considering issuing additional guidance and/or regulations to clarify FDA expectations with regard to fulfilling the cGMP requirements when producing investigational drugs for phase 2 and 3 clinical trials”

Step-wise Approach to Application of Regulatory Requirements



Potency Guidance

- Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (October 2008)
  - Provides manufacturers of cellular and gene therapy (CGT) products, with recommendations for developing tests to measure potency
  - For IND and BLA stages
  - Does not make recommendations regarding specific types of potency assays, nor does it propose criteria for product release.
  - http://www.fda.gov/cber/gdlns/testcellgene.htm

Potency Guidance

- Internal potency assay working group (CBER product offices and CDER/OBP)
- Cellular, Tissue, and Gene Therapies AC meeting, 2/2006
  - Transcripts available at http://www.fda.gov/ohrms/dockets/ac/cber06.html#CellularTissueGeneTherapies
- Experience and practical examples from the regulation cellular and gene therapies

Biologics Products Standards

21 CFR	Test	Test Method
610.9	Alternative Methods	
610.10	Potency	Product specific
610.11	General Safety	*Exempt
610.12	Sterility	Specified
610.13	Purity	Specified
610.14	Identity	Product specific
610.15	Constituent Materials	
610.30	Mycoplasma	**Specified
---	Viability, Phenotype, etc	

*Cellular Therapies are exempt from general safety testing
**Only required for cells that are cultured

Potency

21 CFR 600.3 (s):

The word potency is interpreted to mean the specific ability or capacity of the product…to effect a given result.

21 CFR 610.10:

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency…

Challenges to Potency Assay Development for CGT product

- Complex mechanism of action
- Multiple active components
  - Potential for interference or synergy
- Product variability
  - Starting cells or tissue
  - Replicating error prone virus
- Limited lot size and limited material to test
  - Autologous cellular product
- Limited stability
  - Cellular product
- Lack of appropriate reference standards

Potency vs. Clinical Effectiveness

- Can’t easily develop a single test that can measure product attributes that predict clinical efficacy
- Clinical effectiveness demonstrated by adequate and well-controlled clinical investigations
- Clinical study results may be used to establish correlation(s) between the product’s clinical efficacy and a potency measurement(s)

What to measure for potency?

- Need understanding of the biological properties of your product
- Need to collect data throughout preclinical and clinical development
- Recommended to measure a wide range of product properties in additional to lot release tests
  - Assess which product attributes best correlate with potency
- If multiple known active ingredients, should assess biological activity of all active ingredients

Potency Assay Attributes

- Results obtained for product release decision
- Able to fully validate the assay
- Demonstrates relevant product activity
- Quantitative readout
- Stability indicating
- Demonstrates product consistency

Potency Measurements

- Direct: Biological assay
  - E.g. in vivo animal studies, in vitro cell or tissue culture system
- Indirect: analytical assay(s) directly correlated to biological activity
  - E.g. Flow cytometry, ELISA, PCR/molecular, biochemical assay
- Matrix of multiple assays where the combined results, constitute an acceptable potency measurement
  - One assay not sufficient
  - Use of complementary assays

What is Necessary to Correlate

Influenced by

- Type and relevance of the correlation(s) being made
- The quality of product information you have accumulated
- How well the biological activity is understood
- How well the surrogate measurements(s) reflects biological activity

Potency assay development

- Start collecting product and assay characterization data during early investigational phases
- Communicate with your CMC reviewer
  - Amendments to IND
    - Informal discussions
  - Formal meetings