Overview of Biologics Testing and Evaluation: Regulatory Requirements and Expectations

Audrey Chang, PhD, Senior Director
Development Services

BioReliance® by SAFC

Definition of Biologics: PHS Act, section 351

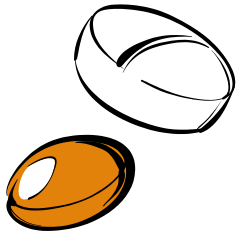
"Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product"

"Applicable to prevention, treatment, or cure of a disease or condition of human beings"

Biologics differ from Traditional drugs:

high MW, made with live cells (presenting an inherent and contamination risk), multiple critical process steps, less well characterized, complex heterogeneous mixtures, optimal rather than maximal dose, multiple or even unknown mechanisms of action, often immunogenic

Vaccine – flu, mumps
Monoclonal antibody
Gene therapy vectors



aspirin

Complex processes for manufacture, product testing and evaluation of safety and efficacy: all which are regulated by government authorities worldwide

BioReliance® by SAFC

Historical Safety Incidents – Highlights from the Biologics Chapter

- 1901: Diphtheria antitoxin contaminated with tetanus from an infected milk horse (led to the Biologics Control Act of 1902)
- 1945: Yellow Fever Vaccine contaminated with Human Hepatitis B from HSA isolated from human blood
- 1955: Poliovirus vaccine made in monkey primary cell lines contaminated with SV40
- 1970+: Human blood and plasma derived products responsible for numerous cases of HIV, Hep A, B, C, vCJK transmission to patients

The advent of producing biologics using Continuous cell culture technology is the single most important reason why there are no cases today

BioReliance® by SAFC

Regulatory Agencies

World Health Organization

- US Food and Drug Administration (FDA)
  - Center for Drugs Evaluation and Research (CDER)
    - Recombinant proteins, monoclonal antibodies, protein hormones
  - Center for Biologics Evaluation and Research (CBER)
    - Specialized biologics - vaccines, gene therapy, cell therapy
- Japan
  - Pharmaceuticals and Medical Device Agency (PMDA)
- EU European Medicines Evaluation Agency (EMEA)
  - Product marketing applications

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

European Medicines Agency
New URL: ema.europa.eu

pmda
Pharmaceuticals and Medical Devices Agency, Japan

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

USP
U. S. Pharmacopeia
The Standard of Quality℠

ICH
harmonisation for better health

Biological Safety Testing is Mandated by Regulatory Agencies Worldwide

BioReliance® by SAFC

US Regulatory Framework:
Three-Tiered System

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Statutes (Laws):

Passed by Congress and signed by the President

- ❑ Food, Drug & Cosmetic Act (FD&C Act)
- ❑ Public Health Service Act (PHS Act)

Regulations (details of the law):

Written by FDA and approved by the Executive Branch

- ❑ 21 CFR (Code of Federal Regulations)

Guidance (FDA's interpretation of the Regulations):

Written and approved within FDA

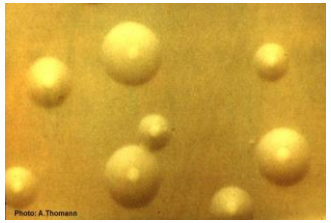
- ❑ Advice non-binding on FDA or sponsor

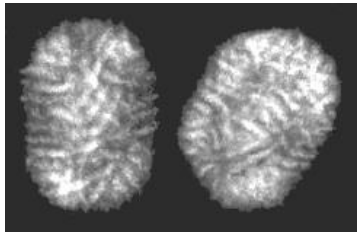
BioReliance® by SAFC

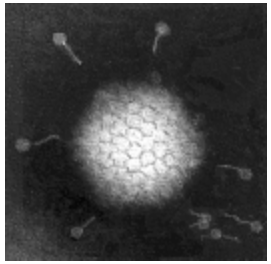
BioSafety Testing Categories

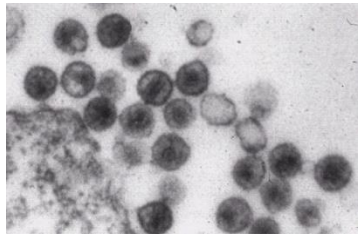
Biological Product

- Identity/Product Characterization
- Purity
  - Bacteria, fungi – sterility
  - Mycoplasma
  - Viruses









BioReliance® by SAFC

Biologics Safety Testing: Multiple Laboratory Disciplines

Microbiology

Sterility
Bioburden
Mycoplasma
Microbial Identity

Molecular Biology

MP-Seq™
DNA/RNA Sequencing
Pinnacle Q-PCR™
Standard PCR
Biodistribution

Immunology

ELISA
Cell Based Assays
Electrochemiluminescence
Western Blots

Virology

In Vitro Virus Screening
In Vivo Virus Screening

Cell Biology

Electron Microscopy
FISH for genetic stability
Karyology
Histology

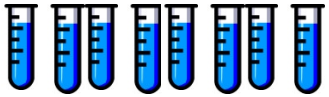
Analytical

Stability
Degradation
Identity
Purity
Potency
Efficacy

BioReliance® by SAFC

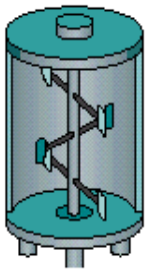
Generic Biologics Production and Testing Points

Master Cell Bank (CLC)

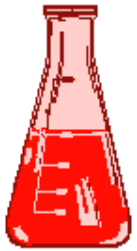


Working Cell Bank (CLC)

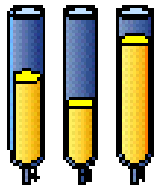
End of Production Cells (CLC)



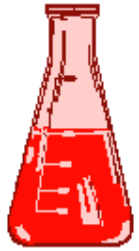
Production



Unprocessed Bulk (LRT)



Purification (Clearance Studies)



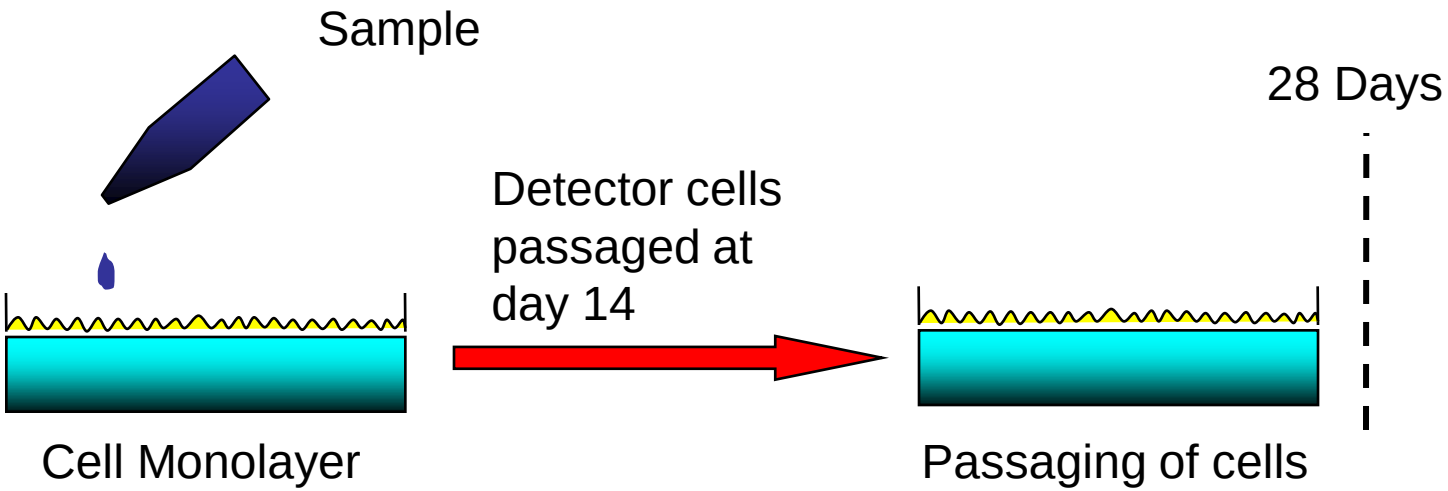
Purified Bulk (LRT)

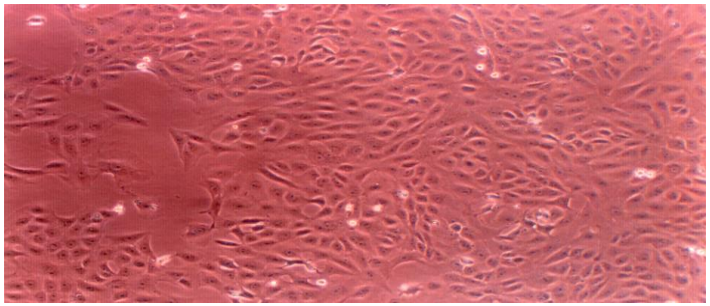
Final Product (LRT)

CLC = cell line characterization and LRT = lot release testing

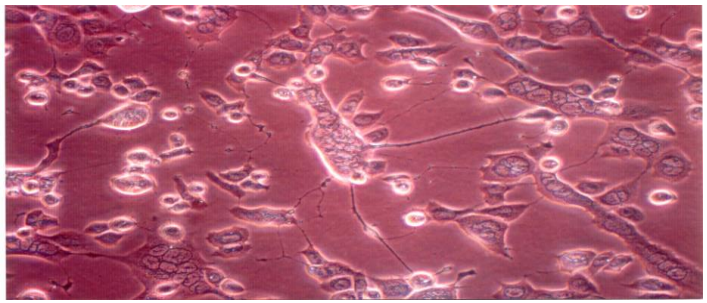
BioReliance® by SAFC

In Vitro Cell Culture Virus Assay





Uninfected Vero cells



HSV-infected Vero cells

BioReliance® by SAFC

Detection of Adventitious Viruses Using the In Vitro Adventitious Virus Assay

20 Years of BioReliance (US) Testing – Summary

- **Cell Lines (MCB, WCB, EPC)** - **No viruses detected**
- **For non- CHO cell production** - **No viruses detected**

- **For CHO cell production - The following viruses were detected in unprocessed bulk:**
  - **Reovirus – Two positive studies; attributed to serum***
  - **Cache Valley virus – Four positive studies; attributed to serum***
  - **Calicivirus – Two positive studies**

- ***Over a twenty year period, BioReliance testing (over 15,000 in vitro viral assays), there were only eight positive studies for adventitious viruses, which represent 0.05% of assays performed***

- ***That means 14,992 negative results reported***

BioReliance® by SAFC

Confidence in evaluating result is based on Assay Validation

"Validation of an assay method is the process of establishing by laboratory studies, that the performance characteristics of the method meets the requirements for the intended applications"

A regulatory requirement

- Guidance for Industry: Bioanalytical Method Validation, FDA. Effective date: 22-May-2001.
- Text on Validation of Analytical Procedures. Test and Methodology. ICH Harmonized Tripartite Guideline, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Q2(R1). Effective date: 06-Nov-2005.
- Validation of Compendial Methods <1225>, United States Pharmacopoeia, Volume 35. Effective date: 01-Dec-2012.

BioReliance® by SAFC

Question: Why Validate?

- *Regulatory requirement*
- *Assay validation is part of overall quality assurance program*
  - *Quality Control of critical reagents/standards*
  - *Quality Assurance of conduct and evaluation of test*
- *Validation provides confidence that a result is reliable*
- *Good science requires well-planned, well executed, well documented assays with meaningful interpretation of data*
- *Sound Study Design – meaningful system suitability controls*
- *Ongoing process: risk assessment and maintaining validation*

How much testing is enough? Are we doing the right tests?

Recent Instances of Viral Contamination of Continuous Cell Culture in Biological Products

Virus	Possible Source	Material Tested/Product
Minute Virus of Mice	Medium/unknown	CHO cells/bulk
Human Rhinovirus	Unknown	BHK bulk
Bovine Viral Diarrhea Virus	Bovine serum	Various Cells
Bovine Polyomavirus	Fetal Bovine serum	Raw Material (FBS)
Epizootic Hemorrhagic Disease Virus	Bovine Serum	CHO bulk
Reovirus	Bovine Serum	CHO and BHK cells/bulk
Nodavirus	Latent infection	Insect cells
2117 Calicivirus	Unknown	Bulk
Porcine Circovirus	Trypsin	Final product -vaccine

BioReliance® by SAFC

Challenges Facing Industry and Regulators

- Continuing contamination incidences
- Discovery of new viruses
- Use of new cell substrates
  - New transformed cells for vaccine production, insect cell lines
- New product types
  - Advanced therapies: gene therapy, cell therapy including stem cells, tissue engineering
  - Biosimilar products
- New production processes
- New endpoints for clinical trials
  - Biomarkers, pharmacogenomic analysis

- Development of new, rapid methods to detect contaminants
  - How and when to use, interpreting results
    - PCRs, rapid microbiology methods, immunological assays, Massively Parallel Sequencing

Thank You!

Audrey Chang, Ph.D.
Senior Director, Development Services
Audrey.chang@bioreliance.com

BioReliance, by SAFC
14920 Broschart Road
Rockville, MD 20850

www.bioreliance.com

BioReliance® by SAFC