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Importance of GMP in controlling cell substrates and production processes for biologicals — two case studies

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Importance of GMP in controlling cell substrates and production processes for biologicals: 2 case studies

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Da Nang 2018

Outline

- Briefly remind ourselves of the critical manufacturing points in production of biologicals - viral vaccines and rDNA products
- Discuss the issue of viral safety of products made using mammalian cells
- Look at two case studies that illustrate importance of following cGMP
- Outcomes and lessons learned

Critical manufacturing points

- Cell substrate - mammalian cells / bacteria / yeast / insect / plant cells or avian eggs
- **Cell banks / cell culture / fermentation - batch or continuous production systems**
- For rDNA products, DNA sequence of cloned gene / genetic stability
- Separation and purification of vaccine virus or protein product
- Characterization of resulting protein + glycosylation or other post-translational modifications or vaccine virus
- Product / host cell related impurities (including residual DNA; **Viral safety issues for mammalian cells**)
- Emphasis on consistency of production

Biologics - slight changes in process can have a major impact on clinical performance / safety of the product. Consistency of production critical.

Viral safety of biological products – critical issue

- Many biologicals produced in mammalian cells – enable glycosylation of rDNA products
- Measures put in place to ensure absence of adventitious infectious agents in product – **a SAFETY issue**
- A contaminating virus MIGHT be devastating to a recipient (patient)
- A contaminating virus MIGHT spread from recipient to contacts / community - threat to health of a country
- **Contamination of cell lines, production process intermediates and products also has considerable economic consequences for manufacturer**
- **Might lead to supply issues with significant public health impact**

Examples of biologicals produced in mammalian cell lines

- **Live virus vaccines**

Polio (primary monkey kidney cells, diploid cells, Vero cells), MMR (diploid cells, MRC5), Rotavirus (continuous cells, Vero cells)

- **rDNA protein products**

Growth hormone, Factor VIII, t-PA, monoclonal antibodies, cytokines, etc. etc. (continuous cells CHO, PER.C6, MDCK)

Viral safety of biological products – source of contamination?

- Cell substrate itself
- Biological materials used in production (other than the cell substrate)
- During production processes

VIRAL CONTAMINATION

- **All relevant guidelines** consider possible viral contamination **of live viral vaccines** and **rDNA products** produced in **any mammalian cell** as a **major issue** to be addressed. These cells have the capacity to propagate viral agents.
- Here see the benefits of early experience of viral vaccine production – a cell substrate issue
- Early guidance provided a framework for moving forward with production of rDNA products in mammalian cells and guidance has been updated periodically to take account of new scientific information and technologies.

Detailed Guidelines available
A belts and braces approach

- *WHO Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological products and for the characterization of cell banks (2010)*: ICH, national guidance
- Production based on cryopreserved cell bank. Master cell bank, working cell bank exhaustively screened for virus contamination, with documented history.
- **Control of raw material used in production – e.g. growth media, enzymes**
- Closed systems for growth of cell culture
- **Testing of each cell culture lot for viruses**
- **Validation of viral removal / inactivation by downstream processing** (this only possible for rDNA protein products - unlike live viral vaccines)

Does the system work?

- Generally yes: Testing evolved and updated with time - now includes range of traditional and molecular methods (PCR, PERT assay for reverse transcriptase depending on circumstances)
- However, viral contamination has occasionally occurred but contained and usually prevented from getting into product on the market
- **Seems that not all contaminations are reported publically**; manufacturers concerned about bad publicity in media (see Nature 472, (2011) 389-390)
- Some manufacturers have reported contaminations - MVM, Genentech 1993, 1994: Vesivirus 2117 , Boehringer-Ingelheim 2003: Vesivirus 2117, Genzyme (Belgium and USA), 2008: PCV 1 & 2, GSK and Merck, 2010.

2 case studies illustrating two very different outcomes

- Genentech experience
- Genzyme experience

Genentech experience with contamination in cell culture 1993

- Contamination of large scale cell culture by Minute Virus of Mouse (MVM) detected during routine production control process
- Testing takes time and product already well on way through downstream purification processes by time detected
- Lot production promptly stopped, reported to US FDA and clean up started
- Investigation of source instigated

Genentech experience with contamination in cell culture 1993

- No definitive source of contamination identified; consistent with media used in production as source. Feral mice from land surrounding plant examined but no MVM found
- Clean up process expensive
- **At no time was a contaminated product let through the system and the regulator was aware of all developments**
- New PCR and infectivity assay developed to speed up early testing and introduced routinely

Genentech experience with contamination in cell culture 1994

- New PCR and infectivity assays used and nothing found for 12 months
- Then another MVM positive signal but this time contamination detected before any downstream processing started. **Downstream protected**
- Source again highly likely to be contaminated cell culture media but not shown directly
- New heat treatment of medium developed, approved by FDA and installed
- **No viral contamination detected since 1994**

The Genzyme Experience

- Several bioreactor runs (Belgium and USA, 2008–2009) terminated early due to poor growth of cells – **suspected contamination**. Seem not to have dealt with problem promptly. Eventually informed FDA.
- US FDA warning letter and re-inspection
- Virus identified as Vesivirus 2117 using PCR in 2009: not known to be a human health risk but interferes with growth of CHO cells.
- Likely introduced by contaminated media
- USA plant shut down for major clean up and re-organization. Virus had spread into manufacturing facility – bioreactors and expensive chromatography columns. Clean up very costly.

The Genzyme Experience

- Global supply of two rDNA derived orphan drugs, Cerezyme (Gaucher's disease) and Fabrazyme (Fabry's disease), were seriously compromised and the products rationed. No alternative to Fabryzyme
- Cause of concern to regulators (e.g. Health Canada) as to how to handle the situation.
- Overall Genzyme needed lot of GMP actions, stock prices dived and together with sales shortfall left the company vulnerable to takeover - acquired by Sanofi in 2011

Outcomes and lesson learned

- **Virus contamination is a serious business.**
- Manufacturers need to deal **promptly** with contamination or suspected contamination (compare Genentech and Genzyme)
- As new inexperienced manufacturers come into operation it is essential that they understand the need for great care and attention regarding development and production of biological products.
- Role of NRA in overseeing these developments is critical
- **Continued vigilance essential. Don’t be complacent.**

References - viral contamination

- Zhan D, et al (2002) Detection of minute virus of mice using real time quantitative PCR in assessment of virus clearance during the purification of mammalian cell substrate derived biotherapeutics, Biologicals 4, 259-270
- Garnick RL, (1996) Experience with viral contamination in cell cultures Dev Biol Stand 88 49-56
- June 2009 Press Release from Genzyme
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THANK YOU FOR YOUR ATTENTION