Centre for Biopharmaceutical Excellence

Cleaning Validation in a Biologics Facility – Case Study

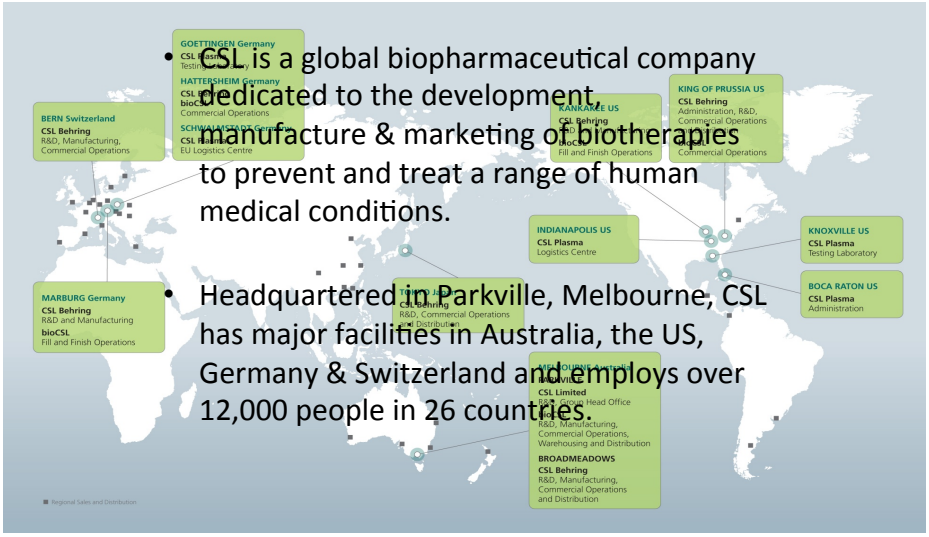
Industry Case Study

A Biologicals Company's Journey in Cleaning Validation
API vs. Biological Requirements
Continued Process Verification

This presentation will discuss

- Overview of CSL Behring
- Difference between API and Plasma industry
- Regulatory requirement / expectation
- Cleaning validation guidance
- CSL's Approach
- CPPs and CQAs – what to test
- Continued Process Verification (CPV)
- Conclusion

About CSL Behring



- CSL is a global biopharmaceutical company dedicated to the development, manufacture & marketing of biotherapies to prevent and treat a range of human medical conditions.
- Headquartered in Parkville, Melbourne, CSL has major facilities in Australia, the US, Germany & Switzerland and employs over 12,000 people in 26 countries.

Why clean?

- Why is there so much focus on cleaning from the regulatory agencies?
  - Cleaning is performed to remove product residues and non-product contaminating materials which could impact patient health &/or the quality of medicines
  - Effective cleaning is an essential component of QA and GMP and patient safety
  - Ineffective cleaning can lead to adulterated product, which can be contaminated by the previous product, by cleaning agents, and by other extraneous materials introduced into, or generated by, the process.

Potential contaminants

- Airborne particulate matter
- Dust
- Lubricants
- Product residues
- Decomposition residues
- Cleaning agents
- Micro organisms and endotoxins

Cleaning and Regulatory Requirement

- In the manufacture of medicinal products and APIs, the cleaning of facilities and equipment is an important measure to avoid contamination and cross contamination.
- In compliance with the GMP regulations, cleaning is performed and documented according to the described procedures.
- Regulatory expectation
  - Historically, cleaning effectiveness was often monitored only visually.
  - However, residues of APIs, excipients, protein degradation are increasingly an issue in inspections and audits.

Cleaning and Regulatory Requirement

- Cleaning procedures has to be validated to satisfy the following agency requirements:
  - FDA published Guide to Inspections of Validation of Cleaning Processes – 1993
  - PIC/S Guideline to Validation – PI -006-3 (2007)
  - Annex 15 address cleaning validation in a separate chapter. Moreover, the ICH Guideline Q7 “GMP for APIs” also requires cleaning validation

What do regulators expect from a manufacturer?

- Bench scale or coupon studies to prove that the chosen cleaning process works and can be reproduced at full scale
- The following consideration should be given when designing a cleaning process:
  - *the solubility of the materials to be removed;*
  - *the design and construction of the equipment and surface materials to be cleaned;*
  - *the safety of the cleaning agent;*
  - *the ease of removal and detection;*
  - *the product attributes;*
  - *the minimum temperature and volume of cleaning agent and rinse solution; and*
  - *the manufacturer's recommendations*

Challenges

- Migration of bench scale studies to full scale within the facility is effective and can be reproduced
- Cleaning system and facility should be designed to avoid it being source of contamination and built up of dust & dirt
- Process equipment should be designed so that it can be easily cleaned throughout and can be reproduced

Challenges

- Cleaned equipment should only be stored in a clean and dry condition
- For biologicals a focus on viral inactivation steps and scale down/scale up to support clearance claims
- Evaluation of cleaning process related Critical Process Parameters (CPP's)
- Evaluation of cleaning related Critical Quality Attributes (CQA's)

Challenges

- Potential chemical interaction with non stainless steel surfaces (e.g. gaskets, seals etc.)
- Carry-over of product, non product and cleaning agent residue
- Consideration for Dirty Equipment Hold Time and Clean Equipment Hold Times
- For manual cleaning process a well documented procedure must be in place
- Verification strategy (continued vs. continuous)

API vs. Plasma Derived Products

	API (Small Molecule)	Biological (Large Molecules)
Facility	Multi product facility	Can be combination of both single product or multi product facility
Source	Chemical based	Derived from Blood
R&D study	Toxicity data required	Viral reduction study required
Pre validation	Coupon Studies for residue recovery expected Concurrent thereafter	Coupon and Scale down studies prior to full scale validation
Detection method	API Specific assay	Generally non specific assay (TOC)
Viral safety	Not applicable	Two dedicated viral reduction steps within the process
MACO limit (Safety Factor)	Generally 1/1000 (higher risk due to its chemical nature – foreign to human body)	1/1000 or 1/100 (low risk – protein exist in human body)

Setting MACO limits

The *standard* approach for setting limits for actives in pharmaceutical manufacturing is to utilize a carryover calculation allowing 0.001 of a minimum therapeutic dose in the maximum dose of any subsequently produced product. For a rinse or swab sampling procedure for drug product manufacturing, this is expressed as:

$$MACO = \frac{(0.001) * (\text{min.dose Act.A}) * (\text{B.S.}) * (\text{S.A.})}{(\text{max.dose Prod. B}) * (\text{S.S.A.}) * (\text{S.E.A.})}$$

Where:

min.dose Act.A = minimum therapeutic daily dose of the cleaned active
max.dose Prod.B = maximum therapeutic daily dose of next manufactured drug product
B.S. = minimum batch size Prod.B
S.A. = sampled area
S.S.A. = shared surface area between the two products
S.E.A. = solvent extraction amount (for rinse sampling, this is “final rinse volume”)

API Vs Plasma Derived Products

Safety Factors

- Conventional drug actives are usually substances which are *foreign* to the human body
- Plasma based products the plasma components are inherent in humans (Albumin, Hemostasis factors, Immunoglobulins)
- Fractionation process purifies and concentrates the active ingredients from plasma starting material
- The **0.001** safety factor was designed for products which are given daily over a patient's lifetime

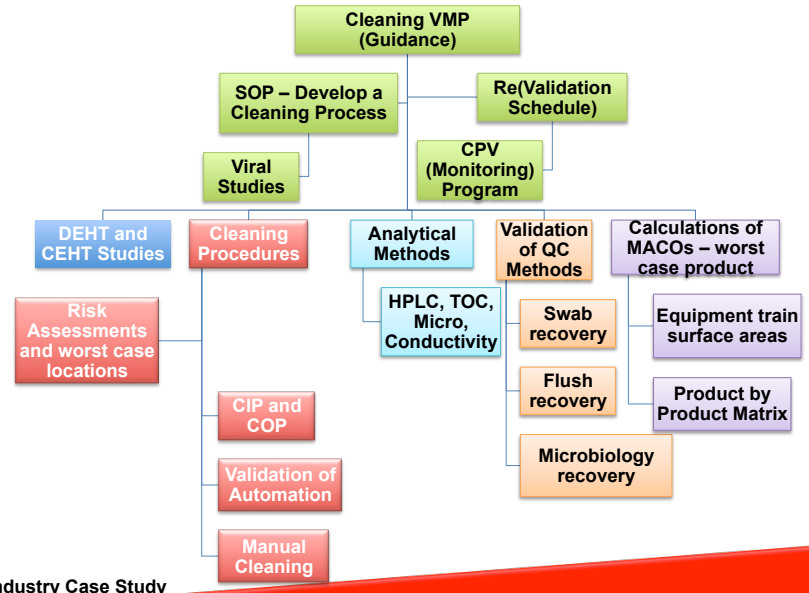
Uniqueness of plasma based products

- Plasma based products are generally given based on a significant or life threatening situation, and are generally given for a limited time at a frequency that may not be on a daily basis.
- Using NaOH in the cleaning process will destroy the biological activity and degrade plasma proteins to fragments or denatured entities.
- Fragments (which are smaller in molecular weight) often removed by downstream processing such as ultra-filtration or chromatography purification process.

Uniqueness of plasma based products

- Immunotoxicity of protein is reduced with smaller molecular weights (FDA CDER, Guidance for Industry: Immunotoxicology Evaluation of Investigational New Drugs, October 2002).
- For these reasons mentioned above, one can make a case for using safety factor of 0.01 for determining MACOs for plasma fractionated products.
- This case needs the be supported by a medical opinion.
- This approach, if viable, can reduce the burden on cleaning active residues.

Scope of Cleaning Validation Program



Validation Plan

- Validation Plan should include the following:
  - How clean is a clean piece of equipment?
    - *Setting limits should have a sound scientific basis*
  - An in-depth risk assessment on the cleaning process
  - Prospective, Concurrent, Retrospective Validations as well as Re-validations
  - List of equipment (common vs. dedicated, Pre-VI vs. Post-VI)
  - List product manufactured using the same equipment
  - Product matrix

Validation Planning

- Clearly define product and non product contact surfaces
- Worst case sampling location based on the equipment design
- If grouping strategy is applied, clear rational for this approach
- "Test until clean" not alternative to validation
- Usually minimum three consecutive successful PQ runs is acceptable, but its up to the organisation to decide (the end goal is to have a stable, reproducible process based on risk assessment)

Validation Plan continued

- Define CPP's and CQA's by risk FMEA based assessment
- Sampling / monitoring strategies
  - Surface Swab (for small or worst location) vs. rinse water (large area)
  - TOC Vs. Micro BCA
  - Testing for residual cleaning agent (conductivity or pH)
  - Endotoxin
  - Microbial
  - Visual Inspection
- Stability and recovery studies for TOC and Micro BCA test

Validation Plan continued

- Inclusion of **Dirty Equipment Hold Time (DEHT)** and **Clean Equipment Hold Time (CEHT)**
- Storage location and condition (must be dry and have minimal influence from the storage area) – preferably closed storage

Continued and Continuous Process Verification

- Clean Group was formed in August 2012
  - The main objectives were:
    - Draw together site knowledge of cleaning technologies
    - Review the sites current control strategy in relation to potential contamination
    - Introduce changes to improve control over potential contamination
    - Strengthen the oversight of these controls
- Members who represent the Clean Group comprise Subject Matter Experts from cross functional areas within the business.

Why Continuous Process Verification

- Re-validation is disruptive and is generally concurrent – occurs semi – annually… raises risk if OOS occurs
- EMA and FDA Process Validation Guidance expects a CPV program for all production processes
- CPV programs provide significantly more information:
  - able to review trends
  - able to quickly make adjustments
- Use a quick turnaround method if possible eg.
  - Final flush sample (not swab)
  - TOC and conductivity, possibly bioburden
- CPV monitors selected CPPs and some CQAs

Example of a CPV Program

Critical Process Parameters CPP	Acceptance Limit
Dirty Equipment Hold Time **(C)**	Site Standard for portable tanks < 24 hours** Mandatory clean required at 48 hours**
Cleaning Agent Contact Time **(C)**	≥ 10 minutes per CIP path
Final Flush Temperature **(C)**	WFI ≥ 70 °C
Critical Quality Attribute CQA	**Acceptance Limit**
Microbial of Rinse Water **(S)**	**Alert:** > 1cfu / 100mL. **Action**: ≥ 10 cfu / 100 mL
Conductivity - in-line monitor **(C)**	**Alert:** > 2.0 uS/cm^2 **Action:** >2.75 uS/cm^2
Conductivity flush (Lab Sample) **(S)**	**Alert:** > 2.0 uS/cm^2 **Action:** >2.75 uS/cm^2
TOC of Rinse Water Flush **(S)**	**Alert:** > 275 ppb. **Warning:** > 500ppb. **Action Limit:** based on 1/100 MACO
Visual inspection equipment **(C)**	Visually Clean

Current Continuous Process Verification

- For automated cleaning process the Siemens software monitors and controls all the Critical Process Parameters (CPP's)
- For automated cleaning process the Siemens software monitors and Dirty Equipment and Clean Equipment Hold Time
- For automated cleaning process TOC is monitored after every clean for fixed and portable vessels
- For all automated and manual cleaning process the final rinse water conductivity is monitored
- All clean equipment is visually cleaned prior to use and dried prior to storage

Continuous Process Verification - Responsibilities

Weekly Trends

- Weekly trend summaries should include the following
  - Alert, warning and action excursions from a CPP or CQA for each cleaning sequence
  - Deviation raised
  - Any out of trend results (2 consecutive alerts)
- Under the control of manufacturing management

Continuous Process Verification – Responsibilities continued

- **Monthly Trends**

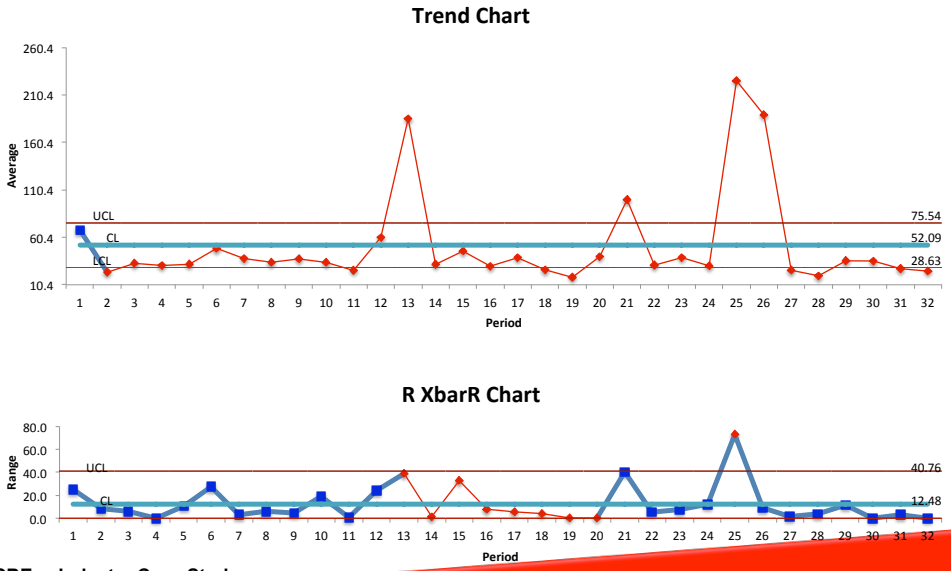
  Monthly consolidated trend reports forwarded to the Clean Group and QA Compliance for review.

- **Annual Trends will be part of the PQR program.**

  Annually QA, Validation, Production Management and members of the clean group should review the trend data to ascertain applicability of established limits frequency of monitoring and sampling intensity and targeting of any re-validation program**

** Re-validation in the first year will not be reduced however in subsequent years the re-validation program will depend on CPV trends.

Recent CPV Trend Data – April 14



Conclusion

- There is a substantial difference between how API and Plasma based products are manufactured and administered
- Based on process/product mix, and a medical evaluation, a MACO limit of < 1/1000 may be justified for plasma products however may be difficult for regulators to approve.
- Continued process verification and trending provides a better understanding of cleaning processes than periodic re-validation

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Centre for Biopharmaceutical Excellence

Steve Williams,
Director, CBE Pty Ltd
www.cbe-ap.com.au
☎ +61(0)417116476
✉ steve.williams@cbe-ap.com.au