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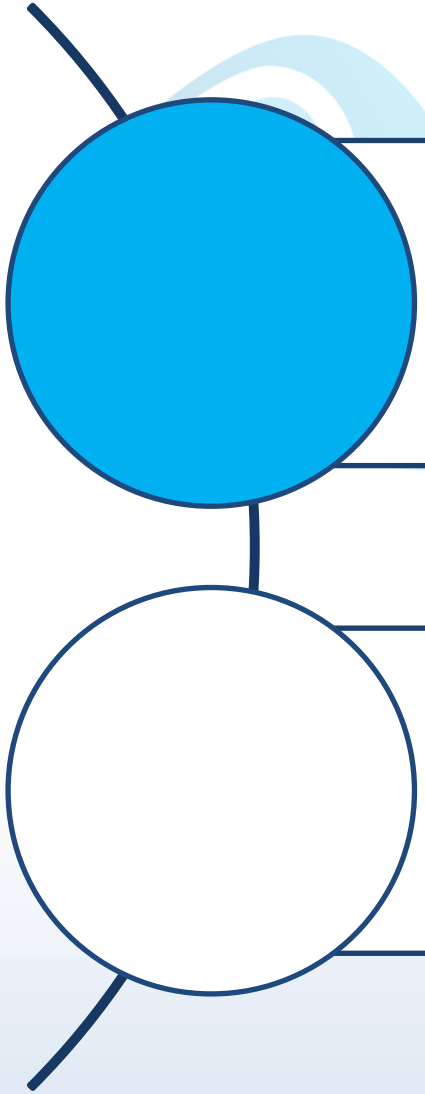
Lecture 8: Single Use Systems Validation

Topics



SUT Systems & Validation Considerations

Standards and Guidances

SUT in Biopharma

Why are companies embracing SUTs?

- Competition
- Orphan drugs
- Efficiency
- Flexibility
- Customisation
- Time to market
- Multiproduct
- Contamination
- Mature technology
- Lower costs*

How are Costs Reduced?

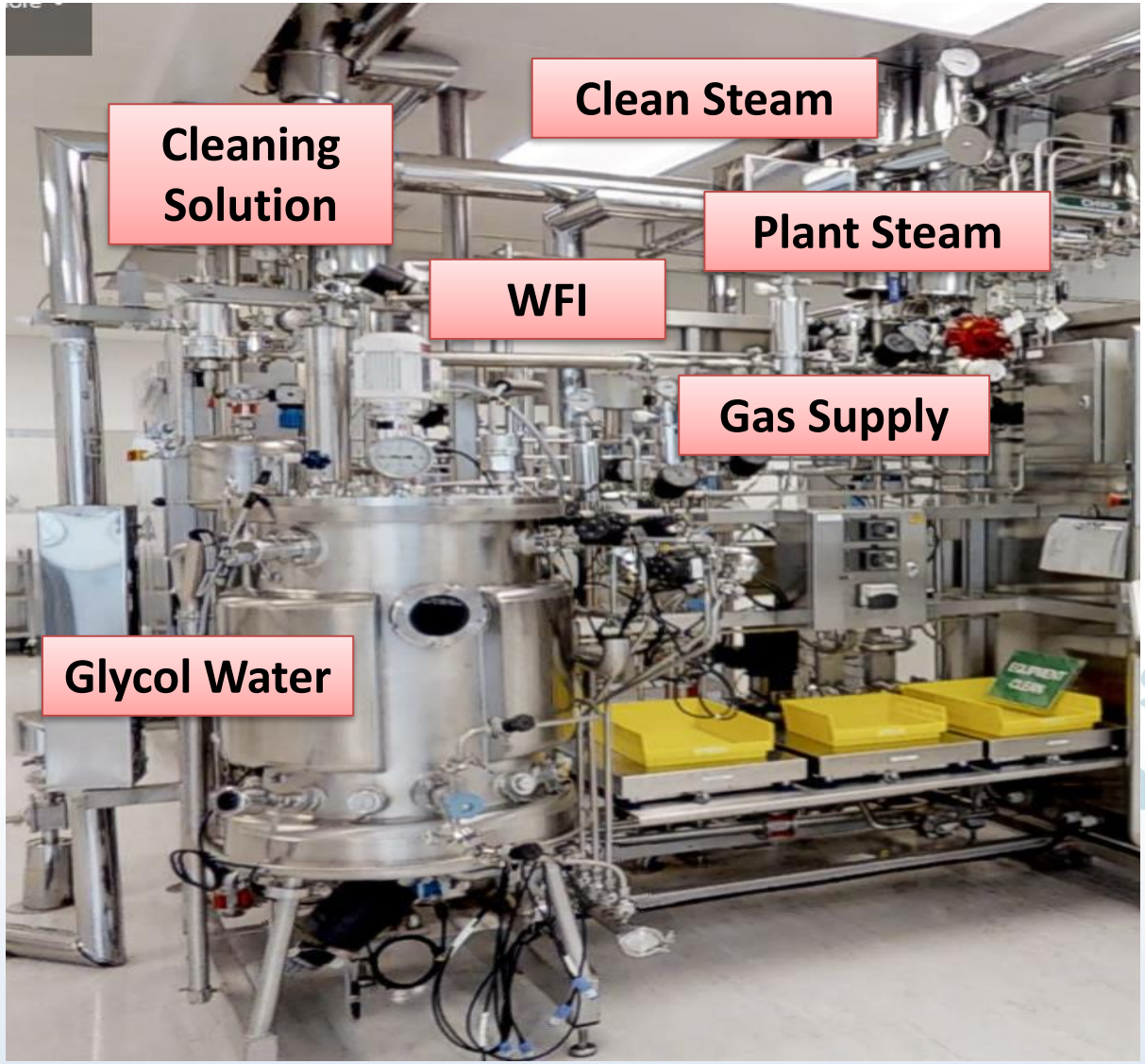
- Quicker turnaround
- No related validation
- Less maintenance
- Smaller clean utilities areas
- Quicker to market
- Lower capital investment

Stainless Steel vs. Single Use - Footprint

150L Stainless Steel Bioreactor

200L Single Use Bioreactor

Stainless Steel Hard-piping



In stainless steel systems, each of these utilities must be hard piped directly to the bioreactor

This makes the plant very inflexible – one plant, one process!

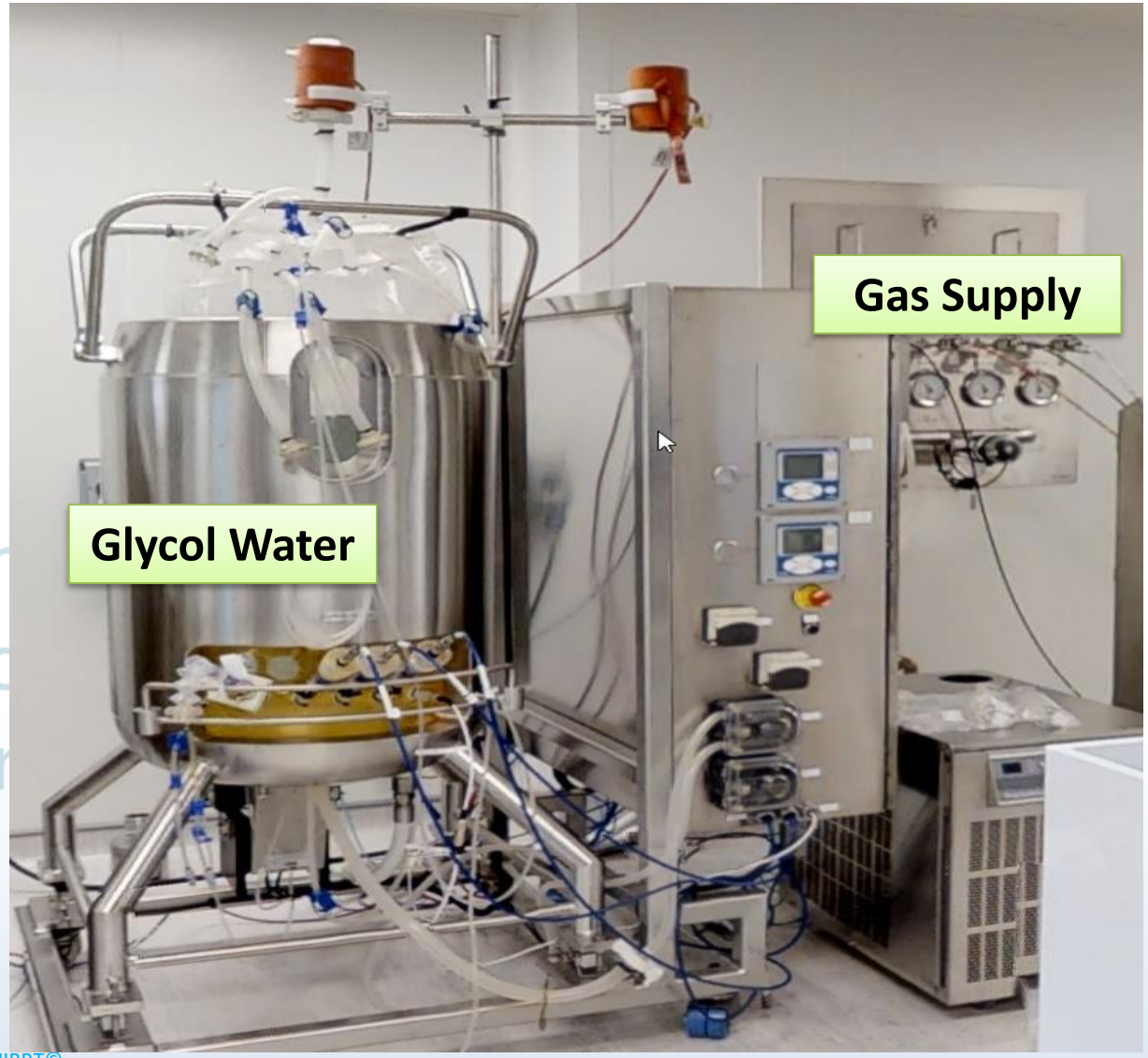
Single Use Hard-piping

In single use systems, clean steam, WFI and cleaning solution requirements have been eliminated

Gas supply line is still hard-piped to the room, but not to the bioreactor itself.

Certain system designs may still require glycol water for cooling but again this needs only to be supplied to the room

All of this makes the facility more flexible – one plant, multiple processes!



Single Use Technology & Utilities

- **Stainless Steel shell with disposable bag** placed inside. The shell is also a **temperature control jacket** which must be hooked up to some form of TCU or heating/cooling solution supply.
- The only utility which needs to be hard-piped to the bioreactor from utilities area is **gas (air, O2, CO2, nitrogen)**
- Plastic/disposable tubing connects this air supply to the bioreactor bag. Connected/disconnected when bag is inserted/removed.
- The room will also require **a power supply**
- Areas where buffers/media are prepared will require hard-piped WFI

Single Use Systems Monitoring & Control

- **Input/Output (I/O) cabinet** receives signals from the control system and/or probes – **relays data** to control system or **reacts to parameter changes**.
- e.g heat/cool jacket, increase gas flow rates, turn on caustic pump
- **pH and dissolved oxygen probes** are standalone components. **Temp probe** is non-product contact.
- They are connected to cables which link to the I/O cabinet and inserted into the bioreactor bag during setup
- Control system (e.g. Delta V, Unicorn) used to monitor and control culture parameters
- Control system, I/O cabinet & Stainless steel support **can all be disconnected and moved**

Liquid Additions & Agitiation

- Peristaltic pumps on I/O cabinet (external pump can also be used)
- Liquid additions (buffer, media, antifoam) are prepared in a separate area and filled into single-use bags.
- These bags are wheeled to the bioreactor in totes and connected to the bioreactor bag using disposable tubing which is then placed into pumps.
- Agitator works by magnetic coupling. Magnet outside bag is part of the skid
- Bioreactor bag has an internal agitator with external magnet
- Magnets attach/couple. Magnets communicate based on signals from control system and cause the internal agitator to rotate

Costs Case Study

- AMGEN constructing their 2nd **"Next Generation"** plant in Rhode Island
  - **$200m**
  - Fully operational by 2022
- Stated advantages:
  - **75%** size reduction for the same active gram output
  - **25%** capital cost
  - ½ the construction time
  - ½ operating expense
  - **~45** miles of pipework not needed
  - **75%** reduction in CO2 emissions
  - **80%** less energy and water used

Ref. 13th Annual Report and Summary of Biopharmaceutical Manufacturing Capacity and Production; BioPlan Associates, April 2016

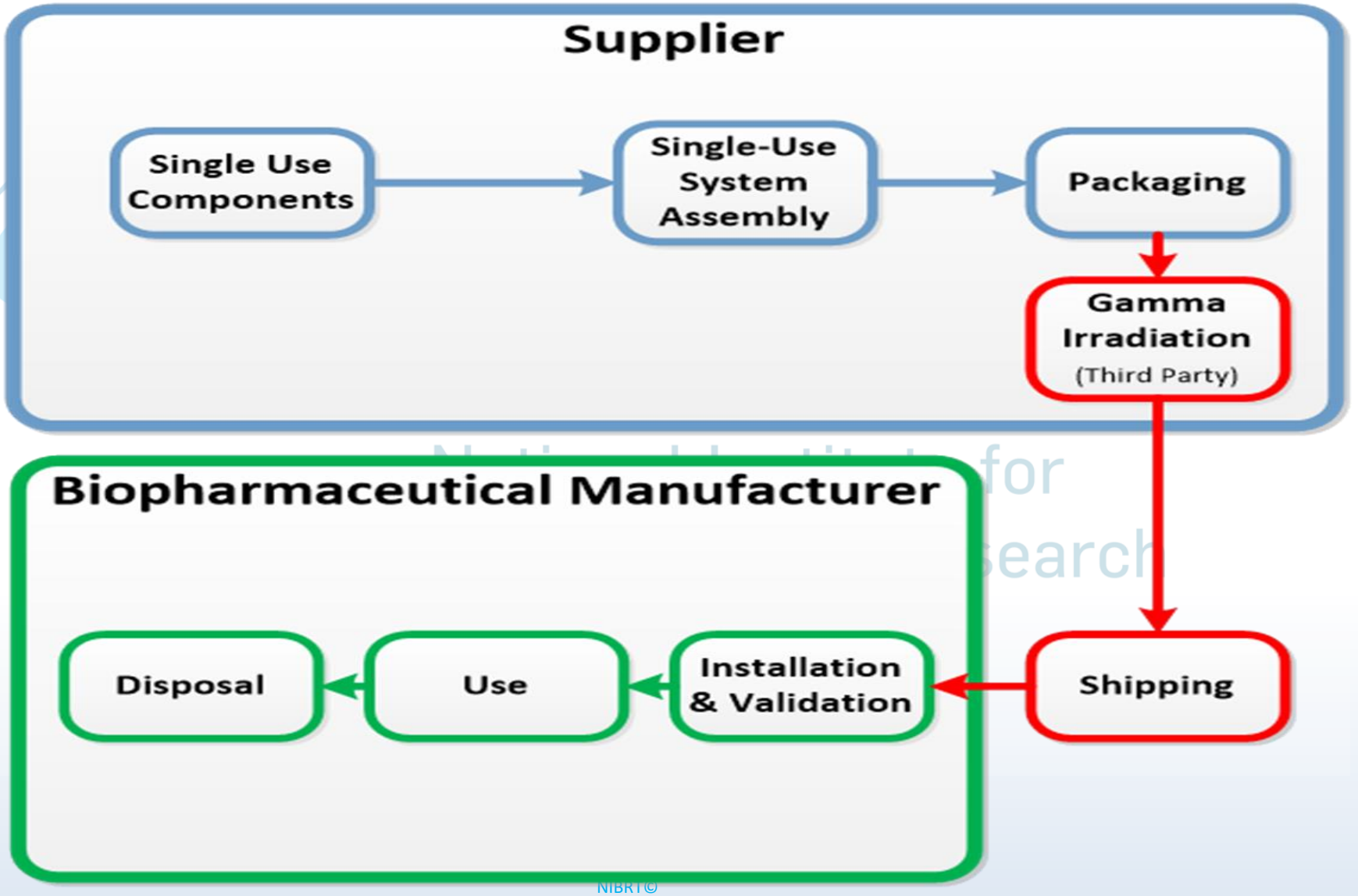
Validation Responsibility

- Some of the advantages offered by SUS can also result in a number variables and potential failure modes, which pose challenges in terms of validation of the SUS.

- While the ultimate responsibility for biopharmaceutical products falls with the manufacturers, the incorporation and validation of single-use technology can shift some activities to the SUS manufacturers in critical areas such as design and sterilization.

- Therefore, the approach to validation of SUS encompasses both the SUS manufacturer and the biopharmaceutical manufacturer.

SUS – Supplier Vs. End-User Responsibilities



Drawbacks

Manual

- Increased manual operations and complexity
- Lack of automation and sensors
- Staff retraining (higher skill)

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Materials

- More fragile material
- **Compatibility**
- Particulate generation

Biocompatiability

- Biocompatibility testing is a crucial facet of validating SUS.
- Polymers that are typically used for SUS include plastics and elastomers. Due to their composition, SUS therefore are susceptible to degradation and in some cases dissolution.
- Chemical entities contained within plastics used for SUS have the potential to elicit adverse effects on biological material which come into contact with them.
- Thus, it is necessary to validate the compatibility of all process-contact surface with the solution(s) that will contact them during routine operation.

Compatibility Studies

- A due diligence exercise should be exercised by the biopharmaceutical manufacturer to evaluate whether there are any gross incompatibilities to be considered.
- Compatibility studies should be validated using the intended process fluid under worst case conditions of contact time and temperature.
- These studies are typically performed by the SUS supplier in collaboration with the manufacturer and can be initiated prior to commissioning for each intended component of the SUS.
- After exposure of each component to the worst-case conditions, a functionality test should be performed to verify that the SUS is still fit for purpose.

Compatibility Failure Modes

- Examples of incompatibility failure modes would include:
  - Leakage (from an aseptic connector, tubing, biocontainer bag, or chromatography column)
  - Failed filtration process (failed integrity testing, filter blockage etc.)
  - Extractables and/or leachables in process fluid

Polymers and Known Incompatibilities

Polymers	Incompatible chemical compounds
Polycarbonate	High pH fluids, strong acids, chlorinated hydrocarbons, and hot water with constant exposure
Polysulfone	Dimethylsulfoxide, dimethylacetamide, chlorinated hydrocarbons, and acetone
Polyethersulfone	Dimethylsulfoxide, dimethylacetamide, chlorinated hydrocarbons, acetone, and polyethylene glycol at high temperature
Polyvinylidenefluroride	Dimethylformamide, diethylacetamide, and acetone
Polyamide	Low pH fluids
Polyethylene terephthalate	High pH fluids
Polyetherimide	Methylethylketone and chlorinated hydrocarbons
Low density polyethylene	Chlorinated hydrocarbons and some types of detergents/disinfectants that induce stress cracking
Ethylene vinyl acetate copolymer	Concentrated mineral acids, ketones, and chlorinated hydrocarbons
Polymethylmethacrylate	Strong acids and alkalis, ketones and chlorinated hydrocarbons
Silicone	Concentrated acids and alkalis, methylene chloride, and methylethylketone
Thermoplastic elastomers	Chlorinated hydrocarbons
Polyetheretherketone	Concentrated mineral acids and halogenated hydrocarbons

Materials: Extractables & Leachables

Extractables and leachables are most often **associated with polymeric and elastomeric materials** because of the **use of additives** to increase stability and aid in the formation of the material components.

Extractables – Compounds that can migrate from a material into a standard, model solvent **under exaggerated or worst case conditions**.

Leachables – Compounds that are shown to migrate into a drug product formulation under **normal process conditions**.

- Single-use technology must be evaluated with respect to their impact on final drug product in terms of safety and efficacy. The most notorious aspects of the validation of single-use technologies for use in biopharmaceutical is determining the impact of extractables and leachables to the manufacturing process with respect to use of each SUS.

Leachables

- Leachables occur during normal processing conditions and therefore have a direct threat to the patient. Leachables have potential to impact product safety in terms of toxicity, carcinogenicity, immunogenicity and also have potential to impact product quality by interacting with the active pharmaceutical ingredient and/or excipients. From a business risk perspective, there is also potential impact of leachables interacting with cells during culture, impacting cell viability and therefore overall product yields.

- As leachables typically occur at very low levels, and therefore potentially at levels beyond the limit of detection of defined analytical methods, it is therefore required to perform "extractables" testing to determine a "worst-case" level of potential impurities as these occur under aggressive/exaggerated conditions.

- However, it is also important to highlight that not all leachables may be found in extractables testing as manufacturing process fluids can interact differently with SUS

Validating SUS for Extractables and Leachables

- A typical approach to validating SUS for extractables and leachables is to first characterise the extractable levels (typically extractables testing is performed by SUS supplier).
- This is performed by first choosing a model extractable solvent that is representative of each process fluid that will be in contact with the SUS.
- The current industry standard for extractables evaluation was developed by the BioPhorum Operations Group

Materials: E & L Risks

Regulatory requirements must ensure systems do not adulterate the final drug product

- Risk assessment for every SU component (does not mean leachables study needed)
- Supplier data is extremely useful for risk assessment
- Companies own leachables studies are needed if deemed a risk based on high-risk extractables data.

BPOG (BioPhorum Operations Group)

- Working group set up to standardise testing of single use components
- Can be used to form a user requirement for a biopharma company
- Covers testing set ups (solvents, times and temperatures), analytic techniques to be used and report formats

BioPhorum Operations Group Protocol Examples

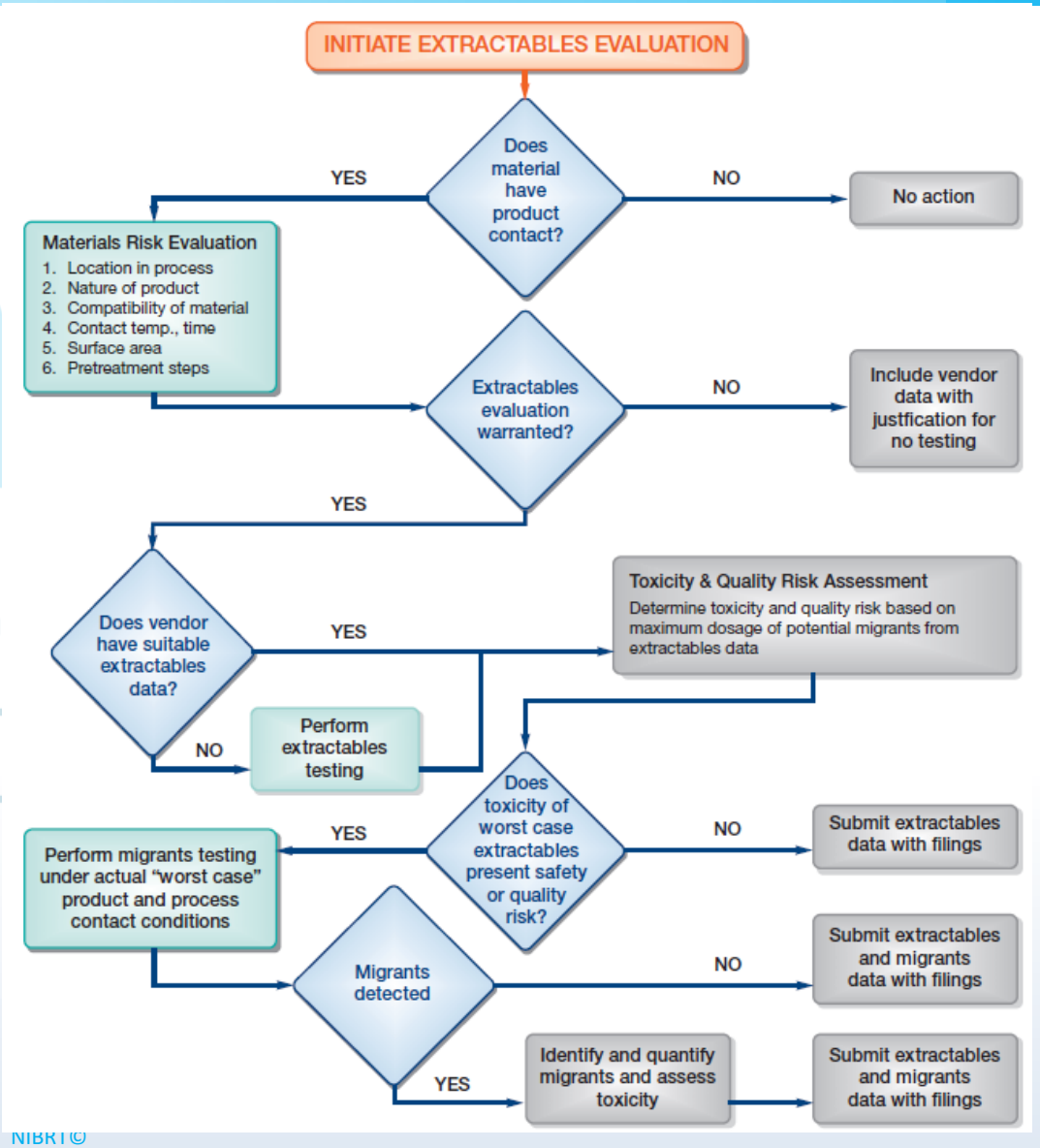
- Exposure of the SUS for a defined period to one of four model solvents, then evaluating the extraction profile of the solvent post-exposure:
  - 50% Ethanol
  - 0.5N NaOH
  - 0.1M Phosphoric acid
  - Water for Injection

- Analytical methods such as Fourier transform infra-red spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (NMR), high performance liquid chromatography (HPLC/UV) and liquid chromatography nuclear magnetic resonance spectroscopy (LC/NMR) are then used to characterise the levels of extractables and in essence a comprehensive list of compounds that have potential to form leachables.

E&L Risk Assessment

Key risk assessment areas

1. Distance from final product
   - Upstream components are less of a risk
2. Exposure temperature
   - Higher temperatures are higher risk
3. Exposure duration
   - Higher risk the longer the contact time
4. Process fluid interaction
   - Stronger solvents will cause more leaching
5. Dilution ratio
   - Less process fluid means concentrated leachables



Ref: Bestwick and Colton. Extractables and leachables from single use disposables. Bioprocess Validation

Microbiological Tests

- Microbiological hold studies are usually carried out on product final containers, sample bags and storage bags.
- This involves injecting a sample of a micro-organism into product container and leaving for a period that would be typical for that product container.
- The challenged product is then sampled and tested, and the expectation would be to retrieve a suitable volume of microorganism; validating that the polymeric product contact materials do not inhibit microbial growth.
- This test is repeated with different microbes which are typical of the clean room product environment. If the polymeric PCMs of the SUS inhibit microbial growth this could result in patient safety issues.

Drawbacks

Manual

- Increased manual operations and complexity
- Lack of automation and sensors
- Staff retraining (higher skill)

Materials

- More fragile material
- Compatibility
- Particulate generation

Manufactured

- Increased consumable storage/cost/disposal
- **Supplier dependence**
- Scale & standardisation

Supplier Dependence

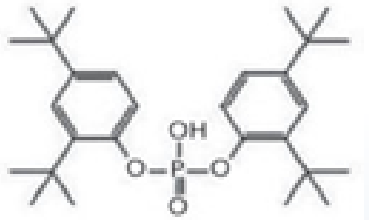
- When using SUSs, the biopharmaceutical facility loses some control over its production process. The manufacturing facility becomes dependent on the supplier to ensure SUSs are made of high-quality materials, are readily available, and are fit for purpose.
- Require consistent supplies of disposables from vendor. Will supplier be able to meet demands?
- Vendors like to continuously update products, while we need the item to remain static so that validation holds
- Systems have been validated, so changing the vendor may not be straightforward

Supplier's Manufacturing Process

- The supplier should assemble the SUS in an ISO grade 5 environment and the SUSs should then be treated with gamma irradiation to ensure sterility (Sandle and Saghee, 2011).
- The correct gamma radiation dose should be applied, and the SUS should be checked for degradation for its associated shelf life. The biopharmaceutical company will have to audit this SUS manufacturing and sterility process and will have to validate that it is acceptable.
- There should be rigorous tests for rupturing of SUSs built into the quality control process.
- The supplier's change control process should be robust enough to ensure that the biopharmaceutical company is notified of any potential change to the process or any change to the raw materials.

The Case of the Two-armed Bandit

- Antioxidant **(TBPP)** added to polyethylene
  - inactivates hydroperoxides that form during irradiation
- TBPP is oxidised to bis(2,4-di-tert-butylphenyl)phosphate **(bDtBPP)**
  - two-armed chemical structure: 'two-armed bandit'
- Inhibits cell growth – cell line dependent
- Once it was discovered, levels of **bDtBPP** in the plastic were reduced



Polyethylene Resin

Supplier's Packaging & Transport Process

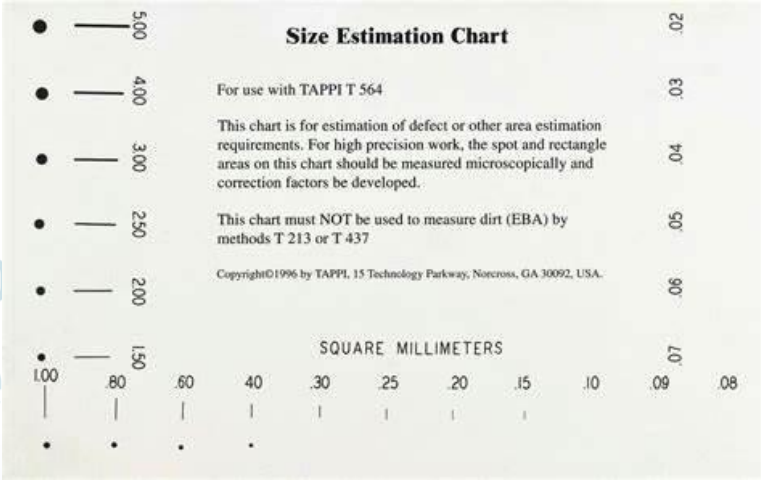
- The supplier's packaging process will have to be validated for consistency and robustness to ensure SUSs are not damaged in transit.
- For example, all bag connectors are wrapped adequately to negate penetration into the bag when folded, as this could lead to potential failures when the bag is filled.
- The shipping process also must consider the temperature extremes during air/sea/road transport and the potential risk of polymeric degradation this may pose during transport.

Manufactured: Risk Assess/Audit Supplier

Below are some examples of checks and information that may be requested:

- Identify methods established for product qualification (i.e. helium leak testing, liquid ingress, vacuum decay test, pressure retention test, tensile test, compression test, microbial challenge test, residual seal force)
  - Details of test methods and hold studies
  - Summary of qualification plan, execution, and results

- Identification of each equipment used to seal film and to seal ports to film
  - Equipment maintenance requirements/schedule
  - Equipment calibration requirements/schedule
  - In-process seal testing
  - Frequency of the testing (e.g., every 4 hours, every shift, each unit)



- Quality Control
  - Use of the TAPPI Test Method T 564 chart and statement of minimum defect size (e.g., 0.2 mm^2) that leads to film rejection.
  - Pinch-clamp qualification - demonstrate full flow stoppage on clamp engagement

Manufactured: Standardisation

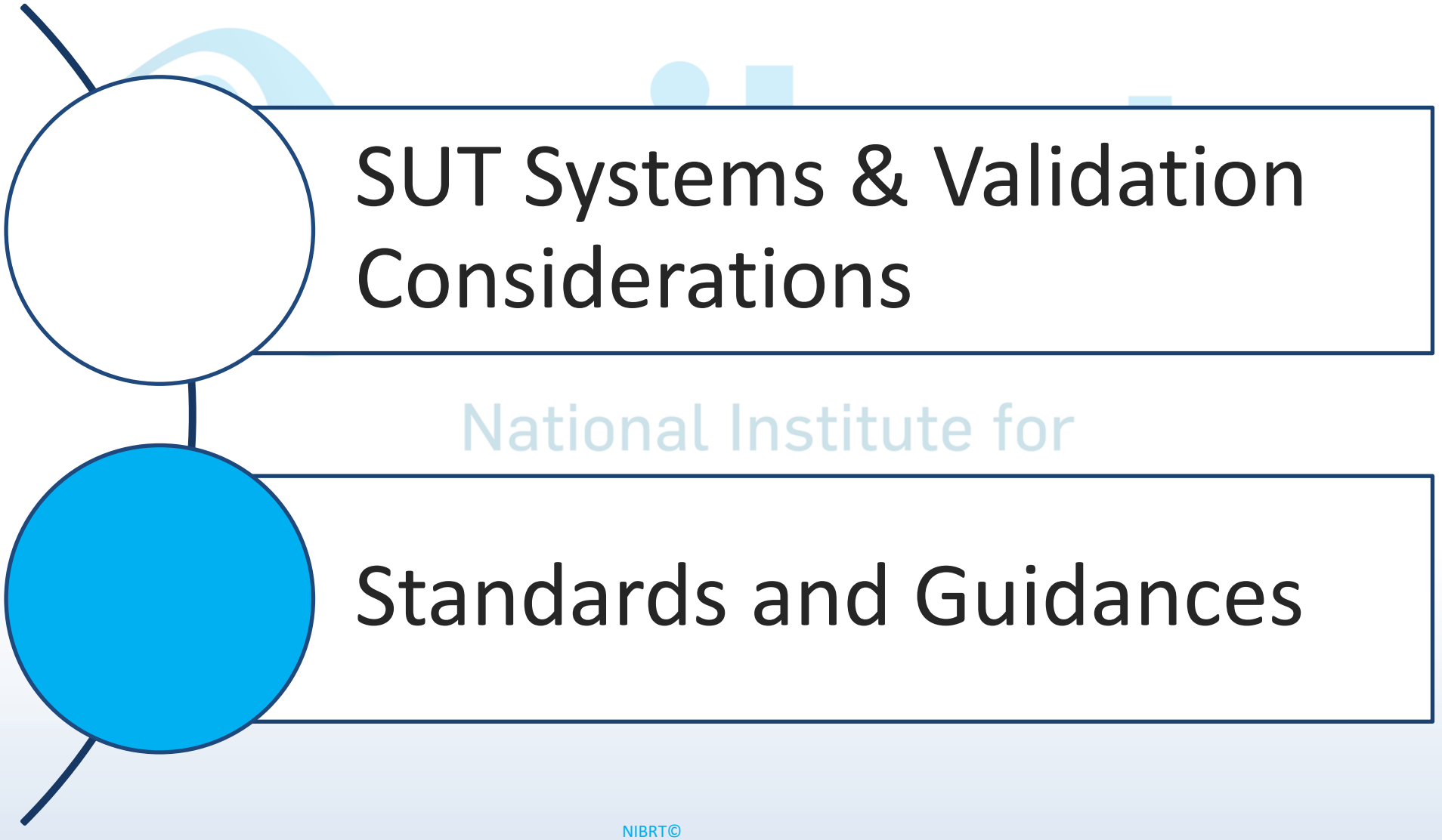
Need for standardisation of single use technologies

- Ensuring connectivity between components and uniform vessel dimensions
- Minimum requirements and/or general guidance based on best practices
- BPOG guide

Standardisation could lead to the unwanted “race to the bottom” scenario and quality is lost

Interconnectivity of information sharing between skids

Topics



US

Title 21 of the Code of Federal Regulations 211.65 (1):

- *"Equipment shall be constructed so that the surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements"*

US Pharmacopoeia

- All polymeric product contact materials (PCMs) require USP Class VI certification in accordance with USP <88>, in vivo biological tests in animals. Class VI testing extensively investigates the reaction in the body, skin, and living tissue to ensure safety.

- There are 6 classes of certification established by the USP, Class VI is the most rigorous and it ensures that there are no unfavourable or long-term bodily effects due to chemicals which can leach out of plastic materials into product streams during manufacturing.

US Pharmacopoeia

- Additional testing can be carried out as per USP <87>, in vitro testing with mammalian cells, to establish if any potential sensitivity exists between cell growth and the polymeric materials which could cause reduction in yields.

- However, testing in accordance with USP <87> is additional and many Biopharmaceuticals require only a Certificate of Compliance (COC) from equipment manufacturers that states the plastics, elastomers (or any other material) potentially in contact with the biopharmaceutical process meet US Pharmacopeia Class VI Testing.

- USP 665 – Guideline for Plastics used in single use and multi use assemblies for pharmaceutical manufacturing

Europe

ICH Q7 – GMP Practice Guide:

- *"Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications."*

EU Good Manufacturing Practice:

- *"Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive … that it will affect the quality of the product"*

EU GMP Annex 1

- Specific risks associated with SU systems
  - Interaction between product and product contact surface
  - Fragility
  - Increased complexity and number of manual operations
  - Design of assembly
  - Performance of pre-use FIT
  - Integrity testing (of assembly)
  - Pin-hole and leakage
  - Compromising system during removal from package
  - Assessment of suppliers
  - Particulate contamination

Quality Requirements

BPOG have made a Single-Use User Requirement (SUUR) Toolkit. They state that it can help:

"equip the industry with common tools to enable clear and consistent communication of user requirements and supplier capabilities in accordance with ASTM E3051"

Example quality requirements:

- Extractable profile of wetted components
- Biological and chemical compatibility with product/process fluid
- Structure/mechanical and closure integrity
- Compatibility to conditions such as pH, temp, pressure
- Qualification of critical components
- Limits for bioburden/endotoxin and particulates
- Manufacturing environment for components
- Inspection on receipt of components
- Inventory control
- Not-wetted components must be considering regarding their possible effect on contacted wetted-components

BioPhorum Operations Group
Connect · Collaborate · Accelerate

Standards & Guidance

ICH Q1A:
Stability testing of new drug products and substances: container closure system

ICH Q3A, Q3B:
Impurities in new drug substances and products

ICH Q3C:
Guidelines for residual solvents

ICH Q7A:
Good manufacturing practice guidelines for active pharmaceutical ingredients

ISO 10993 part 13:
Identification and quantification of degradation products from polymeric medical devices

ISO 15747:
Plastic containers for intravenous injection

ISO 11737-1:
Microbial control Conformance

ISO 11137-1, 11137-2, 11737 and 13004:
sterilization process validation

Particulates:
Non visible Conformance to compendial standards USP <788>, USP <789>, EP 2.9.19, EP, JP 6.07, WHO IP (5.7)
Visible Conformance to compendial standards USP <790> / <1790>, EP 2.9.20

Extractables:
BioPhorum protocol, USP <661>, Ph. Eur 3.1.1-3.1.7 and USP<665>

Oxygen Transmission standards:
ASTM D3985-05 (2010), ASTM F1927-14

Water Vapor Transmission standards:
ASTM F1249-13

Biocompatability Conformance to standards:
USP <88> Class VI, ISO 10993 (Part 6, 10, and 11)

Physiochemical Conformance to standards:
USP <381>, <661>, EP 2.1.9

Process contact material other than plastic:
Metallic materials inspection certificate according to EN 10204:2004
Ceramic glass parts Certification USP <660>, Fed Spec DD-G-541a, ASTM E-438, ISO 5385, DIN 7079/7080, EP 3.2.1

Endotoxin:
USP <85>, EP 2.6.14

Thank You