



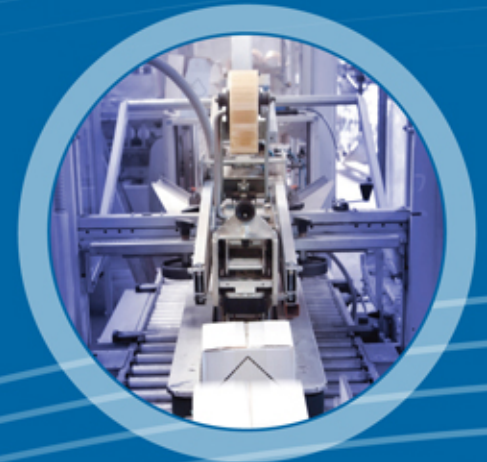
Connecting People, Science and Regulation®

Extractables and Leachables Aspects in Drug Product Manufacturing

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Purpose

- To introduce the issue of manufacturing system-related impurities in marketed drug products.
- To discuss a three tiered strategy for evaluating and managing manufacturing system related impurities which focuses not only on the system but also on the system's material of construction and components.
- To enumerate some of the tactical aspects associated with each of the three strategic tiers.



Introduction

- When a plastic material and a drug product come into close proximity, they may interact. One type of interaction is leaching, where a substance in the plastic material moves into the drug product and accumulates there.
- In certain situations, the accumulated leachable may adversely impact key quality attributes of the drug product, such as its safety, stability, efficacy, compliance, and functionality.
- Although historically the issue of the impact that plastic materials have on the key quality attributes of finished drug products has focused on packaging systems, the regulatory environment is evolving and plastic materials used in operations associated with the production of finished drug products are receiving increased attention.
- For example, documents such as ICH Q7 clearly establish that packaging systems used to store APIs and process intermediates must meet the same suitability for use expectations as do final product packaging.



The Case for Considering Extractables and Leachables – Regulatory Expectations :

Equipment shall be constructed so that 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.

Equipment Construction. *Code of Federal Regulations, Foods and Drugs* Title 12, Part 211.65. U.S. Government Printing Office, Washington, DC. Revised April, 2006.

Production equipment should not present any hazards to the product. The parts of the production that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

EUDRALEX Volume 4: Good Manufacturing Practices, Medical Products for Human and Veterinary Use. European Commission: Brussels, Belgium, 1998.



The Case for Considering Extractables and Leachables – Regulatory Expectations

These containers (used to store drug product intermediates and APIs) should not be reactive, additive or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

Q7; Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. *ICH Harmonized Tripartite Guideline*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 10 November 2000.



The Case for Considering Extractables and Leachables – Practical Experience

Numerous case studies have been published and presented which establish:

- 1. That substances can be extracted or leached from materials, components and/or systems used to manufacture drug products under actual manufacturing conditions.**
- 2. That such substances can adversely impact either the efficiency of the manufacturing process or the quality of the finished drug product.**

It is not just a myth, it is a reality!

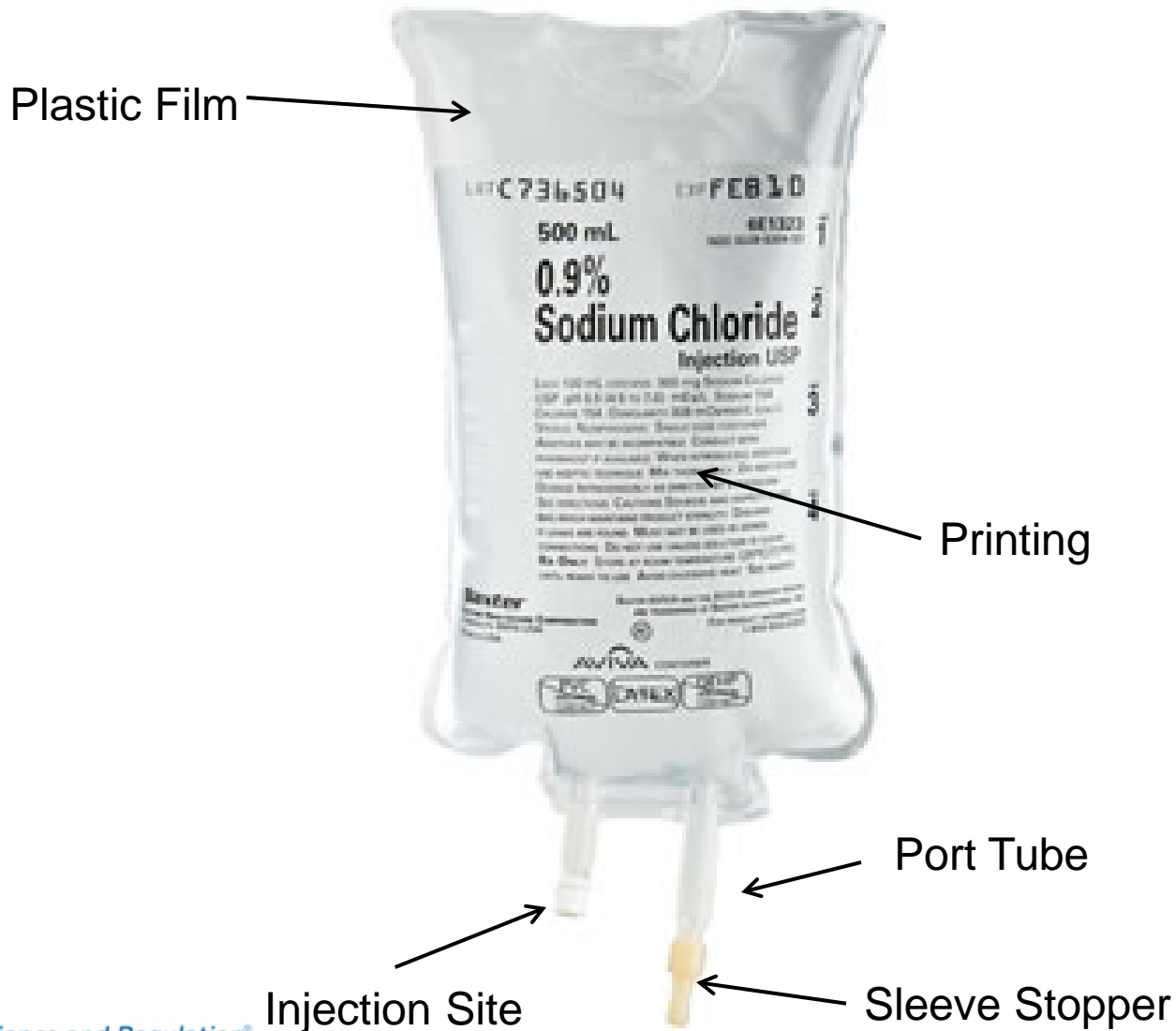


The Essential Questions

- 1. Do substances leach from manufacturing systems, their components and/or their materials of construction and accumulate in the finished product to such an extent that the quality attributes (e.g., safety efficacy, stability, etc) of the finished product are compromised?**
- 2. Do substances leach from manufacturing systems, their components and/or their materials of construction and accumulate in the manufacturing system and/or its associated process streams to such an extent that the manufacturing system's ability to produce product is compromised?**

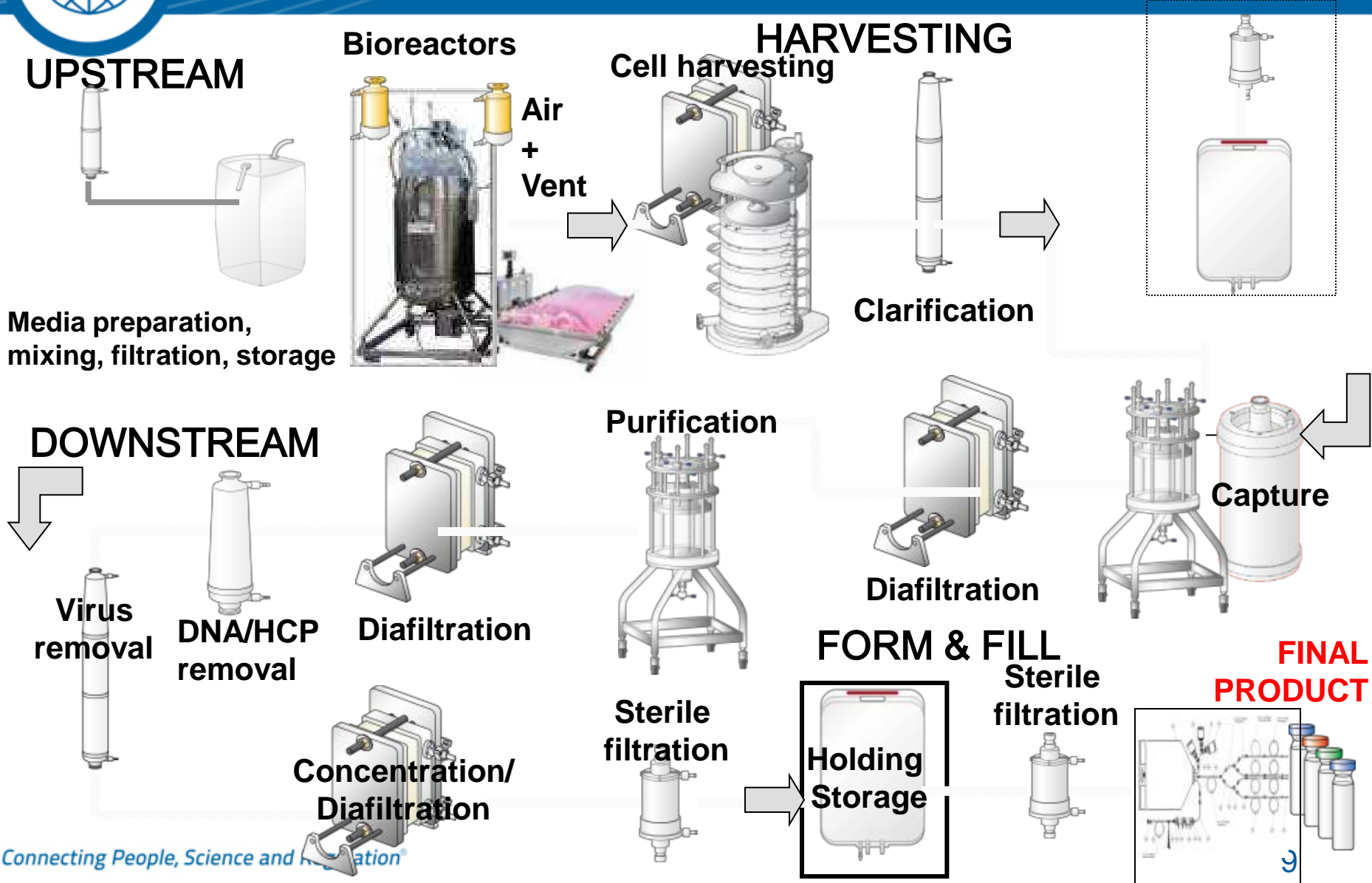


Why is assessing a Manufacturing System more complicated than assessing a Packaging System?





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Why is assessing a Manufacturing System more complicated than assessing a Packaging System?

Because a manufacturing system is more complicated than a packaging system!

1. Greater number and diversity of contact conditions.
2. Greater number of contacts.
3. Greater number of contact solutions.
4. “Dynamic” contact versus “static” contact.
5. Exit and Entrance gates.



The Assessment Triad as a Strategy (1)

Material Characterization; Screening and Selection

Minimize risk moving forward by recognizing and eliminating potential “bad actors”

Component Qualification

(Simulated Extraction Study)
Worst-Case Safety Assessment
Extractables as **probable** leachables

System Qualification

Actual Case Safety Assessment
Measurement of
confirmed and targeted
leachables



The Assessment Triad as a Strategy (2)

Material Characterization, Selection and Screening:

Every material used in a manufacturing process should be sufficiently well characterized that

- it is purposely selected for use, and**
- its selection can be justified.**



The Assessment Triad as a Strategy (3)

Component Qualification:

Every component used in a manufacturing process should be tested for extractables

- **with a rigor that is consistent with the risk that the extractables could end up as leachables in the manufacturing system's output, and**
- **under conditions that are consistent with the conditions the component experiences during the manufacturing of the output.**



The Assessment Triad as a Strategy (4)

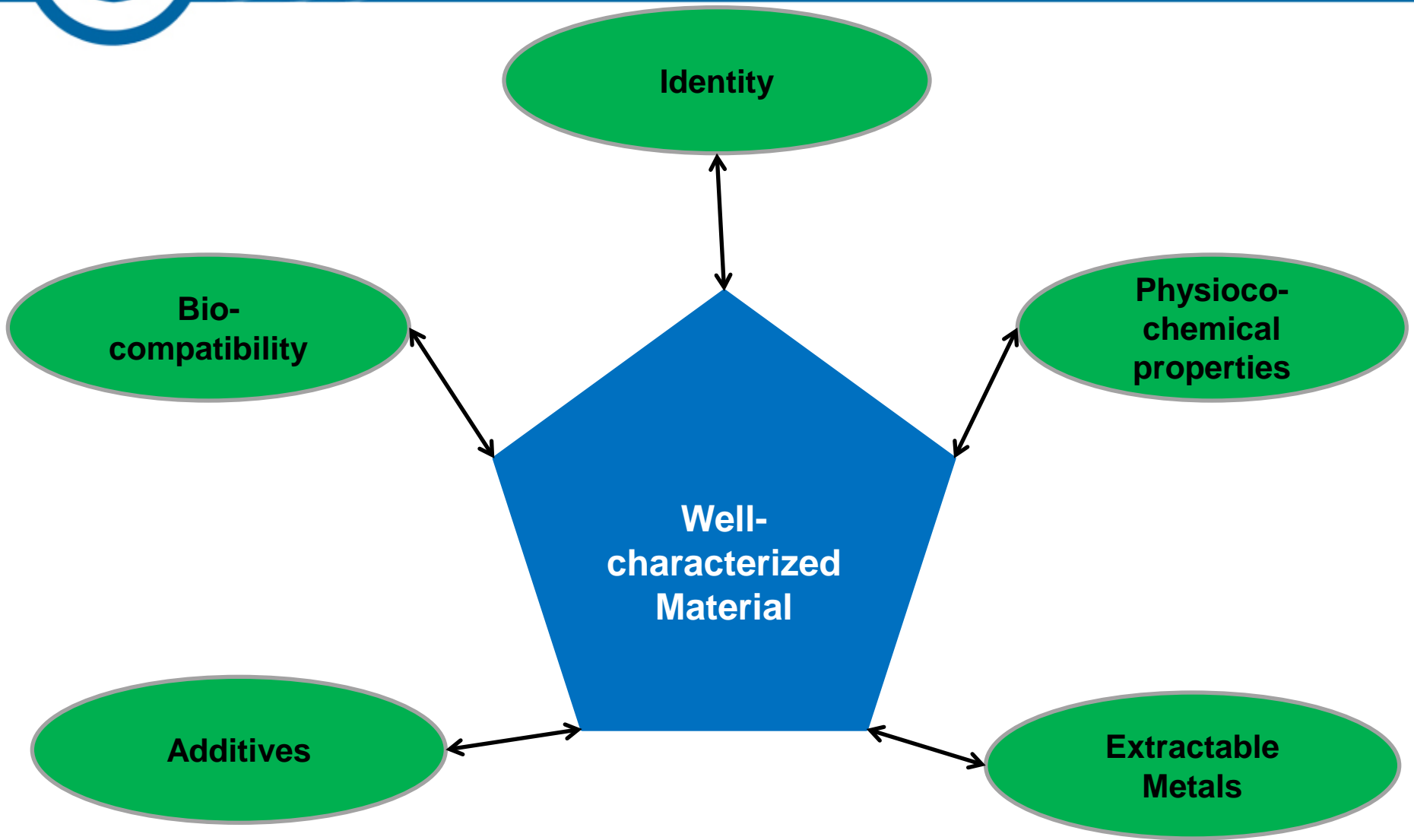
System Qualification:

The entire manufacturing system should be tested for finished product impact by testing the finished product for leachables. The specific testing process used should be

- driven by the knowledge gained during material characterization and component qualification, and
- consistent with the clinical use of the finished product.



Assessment Tactics; **Material Characterization per <USP <661.1>**





Value Proposition; **Material Characterization** per <USP <661.1>

If I have characterized a material of construction as indicated on the previous slide, I can

- **select materials for use based on relevant and meaningful data, and**
- **explain and justify my decision.**



Assessment Tactics; **Component Qualification**

Every component used in a manufacturing process should be tested for extractables with a rigor that is consistent with the risk that the extractables could end up as leachables.

- **Low risk components may not need extractables testing at all**
- **High risk components may need extensive extractables testing.**

But how do we establish the risk so that we can properly set the rigor?



Component Assessment Risk Factor Analysis (1):

Use of risk management principles and concepts to manage the product safety risk associated with leachables from packaging and/or manufacturing systems is a cornerstone of global regulatory and industry thinking related to safety assessment. Industrial scientists and regulators agree that risk management has a definite strategic role in terms of designing, implementing and interpreting effective and efficient impact assessments with respect to extractables and leachables. In fact, regulatory guidance for container/closure systems makes very clear reference to, and makes very extensive use of, risk assessment processes and procedures (for example, Table 1 in the FDA Container Closure Guidance).



Component Assessment Risk Factor Analysis (2):

Hypothetical Risk Evaluation Matrix.			
Risk Variable	Risk Level	Risk Value	Product Risk Index
Material Type	Reactive	10	1
	Interactive	5	
	Inert	1	
Extraction Strength of Solution	Organic	10	1
	Water/organic	5	
	Water	1	
Contact Duration	> 30 days	10	5
	24 hr to 30 days	5	
	< 24 hr	1	
Contact Surface Area	> 5000 cm ²	10	5
	2000 – 5000 cm ²	5	
	< 2000 cm ²	1	
Contact Temperature	> 70°C	10	5
	25° - 70°C	5	
	< 25°C	1	
Proximity to Finished Product	Final Product	10	10
	Purified to Final Product	5	
	Remote from Final Product	1	
Total Risk Index (< 20 = low, 20 – 50 = moderate, 50 – 60 = high, > 60 = reject)			27



Component Assessment Risk Factor Analysis (3):

Virtue of the Risk Evaluation Matrix:

- It reflects a systematic, rational, and standardized approach that in the **best** case reproducibly and consistently provides an actionable outcome.

Curse of the Risk Evaluation Matrix:

- The quantitative aspects of the Matrix are subjective and cannot be justified by scientific principles or accumulated scientific knowledge.
- Risk Matrices are not consistent between users.
- Risk matrices conclude “low risk” and support “no testing” too frequently.



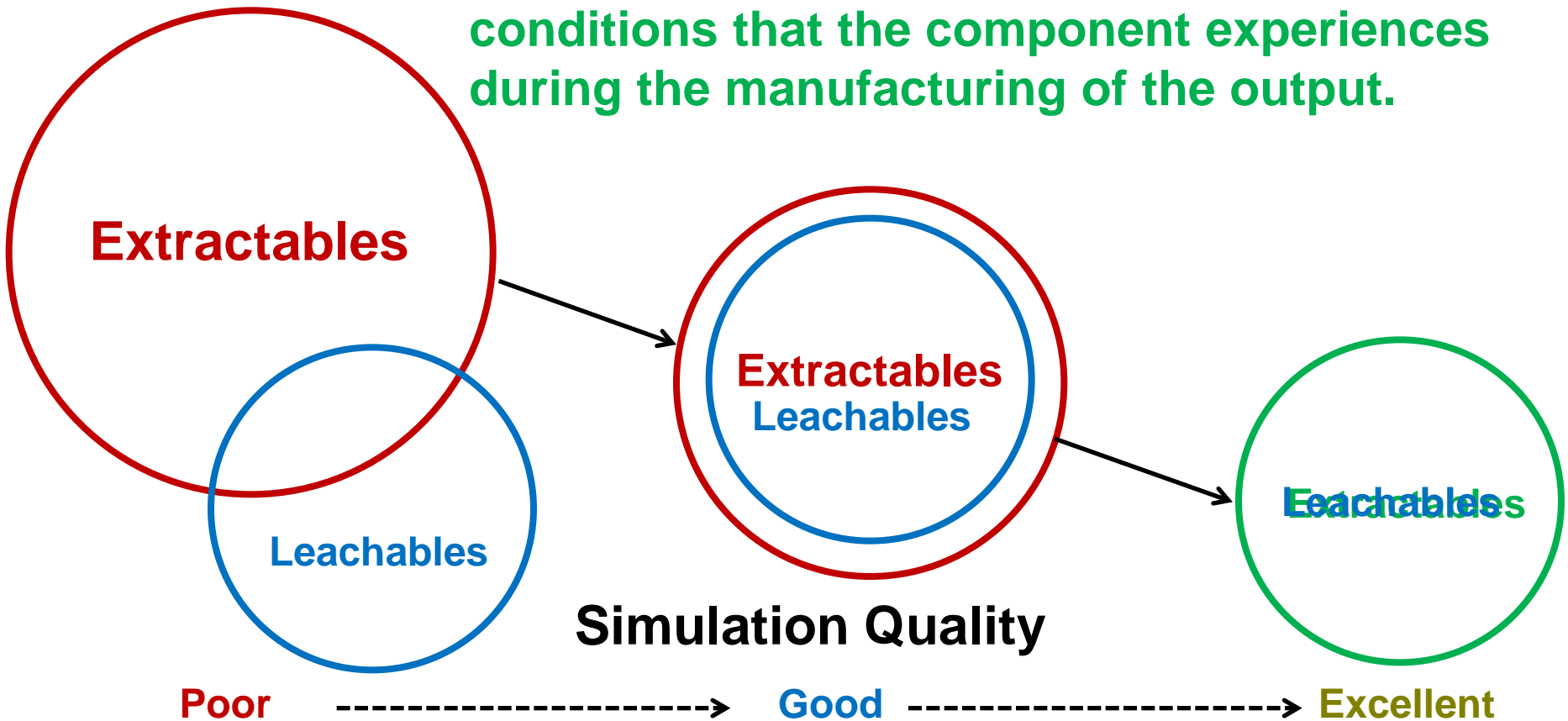
Component Assessment Risk Factor Analysis (4):

1. Are all the relevant dimensions captured in the matrix?
2. Are the risk values used in each dimension science-based? In most situations, the published risk factors appear to be intuitive, experience-based or arbitrary.
3. Are all the dimensions properly weighted? In most situations the various dimensions are equally weighted in terms of their impact on safety.
4. Is the aggregate effect of the dimensions additive (which is the process used in most applications) or are the inter-relationships between dimensions more appropriately expressed by a more complicated function?
5. Are risk scores properly calibrated? For example, how has one determined that a risk score of 15 is “safe” and a risk score of 60 is “unsafe”?
6. What are the criteria or tests necessary to establish the qualitative “levels’ within each Risk Variable? For example, how does one establish whether a material is “reactive” “interactive” or “inert”?
7. Given the great diversity of manufacturing operations, is it possible that a single matrix can be adopted that will “cover all the bases”?



Assessment Tactics; **Component Qualification (1)**

Every component should be tested for extractables under conditions that are consistent with and which simulate those conditions that the component experiences during the manufacturing of the output.





Assessment Tactics; **Component Qualification (2)**

Why Simulation as opposed to something more “aggressive” or “harsh”?

- 1. It is frequently not possible to perform the necessary functions of discovery, identification and quantitation in the actual process stream solution or drug product.**
 - a. Drug products and process streams are too chemically complex to perform the processes of discovery and identification.
 - b. Extractables are present in process streams and leachables are present in drug products at such low concentrations that the processes of discovery and identification are difficult, if not impossible, to perform.
- 2. As noted in the previous slide, a simulation study provides that extractables profile that is the closest to the product’s leachables profile.**
- 3. The simulation study may apply modest exaggeration factors which make the study more “efficient” than other options.**



Assessment Tactics; **Component Qualification (3)**

A Word on Standardized Extraction Procedures

- 1. Does it make any sense that the conditions that components experience during manufacturing are the same for each component?**
- 2. Does it make any sense that the extraction conditions for components should be the same?**
- 3. Does it make any sense that a single set of uncomplicated extraction conditions could be relevant for all components?**
- 4. Does it make sense that components can be grouped or classified based on where they are used in the manufacturing process and their conditions of use?**
- 5. Does it make sense that a set of customized and relatively uncomplicated extraction conditions could be relevant for individual component groups?**



Assessment Tactics; **Component Qualification (4)**

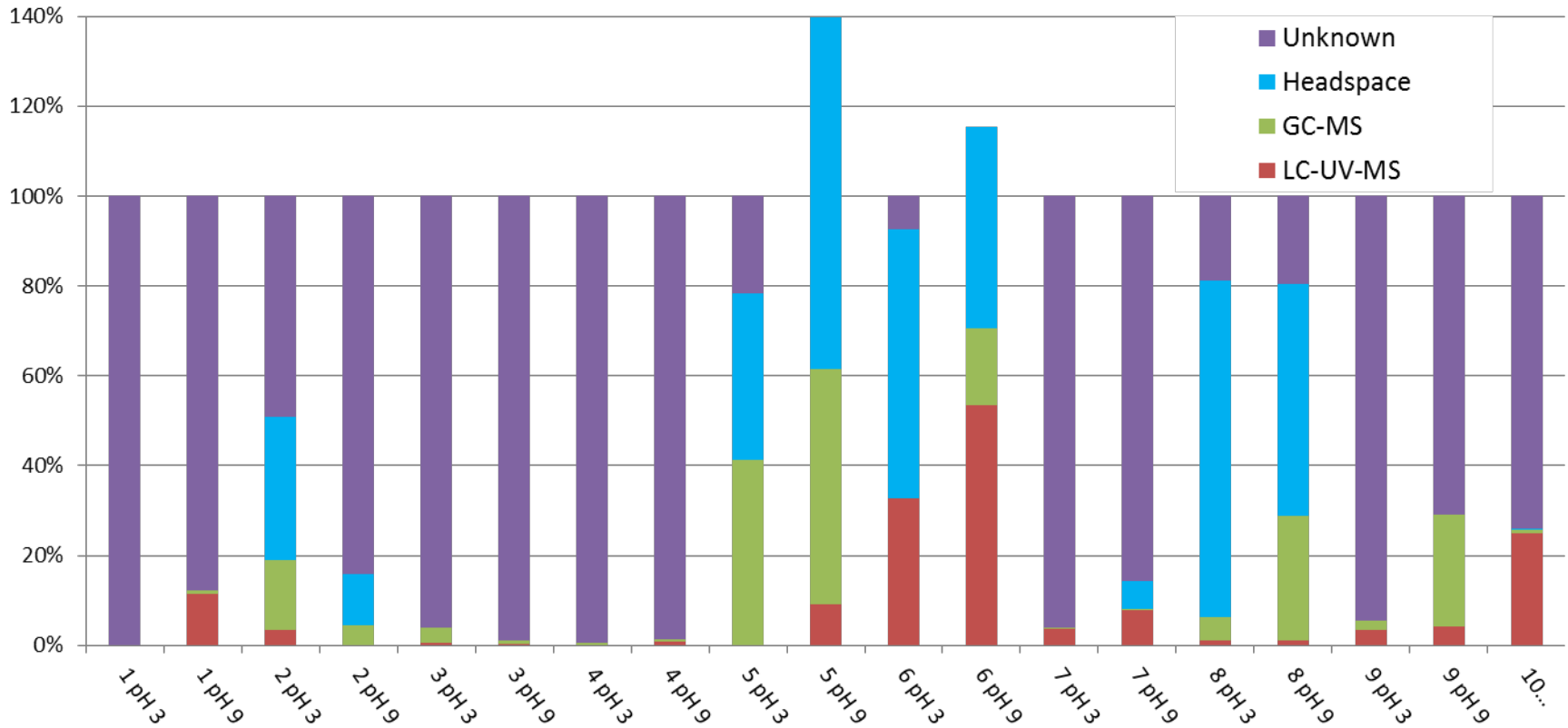
A Word on Standardized Extract Analysis Procedures

- 1. Does it make any sense that the extracts of components that are very different compositionally and physically contain the same extracted substances at the same extracted levels?**
- 2. Does it make any sense then that that the analytical methods used to discover, identify and quantify extractables from one component would be equally applicable to another, dissimilar component?**
- 3. Does it make sense that components can be grouped or classified based on their composition and conditions of use?**
- 4. Does it make sense that the suite of analytical methods used, and/or their operating conditions, can be customized for components that have been grouped based on their similar compositions and conditions of use?**



Assessment Tactics; Component Qualification (5)

TOC Reconciliation Results for 10 Test Articles. The shaded areas indicate that portion of the TOC that was reconciled by the organic extractables captured by the individual test methods. The area shaded in purple is thus that portion of the TOC that is due to organic extractables that were not captured by the chromatographic screening methods. While the screening methods were well suited for the extracts of the bag materials (samples 4, 5, and 6), the methods were less comprehensive for characterizing filter extracts.





Assessment Tactics; **Component Qualification (6)**

Use of Vendor Data – It is all about relevance, applicability and completeness

- **Generation of the Extracts**
 - Was the process by which the extracts were generated a reasonable simulation of the user's conditions of contact?
- **Testing of the Extracts**
 - Were the test methods sufficiently comprehensive and sensitive to produce a valid extractables profile?. (It is always proper to ask not only “what extractables did you find?” but also “What extractables could your test process have missed?” and “How do know you didn't miss anything or that your concentration estimates and identifications are good?”)



Assessment Tactics; **System Qualification**

The entire manufacturing system should be tested for finished product impact by testing the finished product for leachables by a testing process that is

- **driven by the knowledge gained during material characterization and component qualification, and**
- **consistent with the clinical use of the finished product.**

These points mean that:

- **Manufacturing system related leachables monitored in finished drug products should be intentionally chosen and targeted,**
- **Leachables specifications should be based on the known toxicity of the leachable, and**
- **Leachables specifications should be driven by the clinical use of the drug product.**