INTRODUCTION

Due to the complexity of biopharmaceutical products, vast arrays of methods are utilized to fully characterize these complex molecules and their impurities - a significantly more difficult task than for typical small molecules. Some impurities are related to the drug product, while others are introduced during bioprocessing. Leachables are compounds that leach into the drug product formulation from disposables utilized in bioprocessing; whereas, residuals are introduced during bioprocessing. It is imperative that processes are validated to demonstrate clearance of these impurities and ensure product safety. Mass spectrometry plays a key role in providing data to understand, develop, and validate the process. This poster will cover experiences and capabilities supporting the safety testing of biopharmaceuticals.

BACKGROUND

Extractables are compounds that can be extracted from a component under exaggerated conditions such as in the presence of harsh solvents and/or at elevated temperatures. These compounds have the potential to contaminate the drug product and must be controlled to the extent that the components used are appropriate.

Leachables are compounds that leach into the drug product formulation from the component as a result of direct contact with the formulation under normal conditions or accelerated storage conditions. These compounds are typically a subset of extractables and must be controlled so that drug products are not adulterated.

Bioprocess Impurities are compounds that are inherent and/or added during the manufacturing of biopharmaceutical products. They fall into three broad areas -
- Host cell/source-derived: proteins and nucleic acids (DNA/RNA)
- Cell culture–related: inducers, antibiotics, media components
- Downstream-derived: resins, residual solvents, surfactants, leachables
Safety of Biopharmaceutical Products - Analysis of BioProcess Impurities: Residuals, Leachables & Extractables

DISCUSSION/RESULTS

Single-Use Products for BioProcessing: Potential Sources of Extractables/Leachables

Stabilizers and Related Compounds

Potential Sources of Extractables/Leachables

Plastic Films and Extractables

Extractables Database

Potential Impurities

Analytical Challenges

Potential Additives

Analytical Approach

Bioprocess Residual Impurities

Extractables & Leachables Concerns

Extractables & Leachables Studies Stages

Determination of Kanamycin in Bioprocess Stream

Kanamycin Linearity 1ppb to 100ppb

Kanamycin and Amikacin co-mixed at 10ppb
CONCLUSIONS

Characterization of bioprocess impurities, including residuals and leachables, is a critical aspect of process development and a regulatory requirement. Methods need to be developed and qualified to identify and quantify these impurities with a high degree of precision, specificity and accuracy.

Challenges include

- Wide variety of in-process sample matrices
- Range of potential impurities
- Lack of chromophores
- Need for extremely sensitive methods

Analytical tools such as mass spectrometry are required to overcome these challenges.

RELEVANT GUIDANCE DOCUMENTS

ICH: Q3A(R) Impurities in New Drug Substances
ICH: Q3B(R) Impurities in New Drug Products
ICH: Q3C(R) Impurities: Guideline for Residual Solvents