Research Initiatives for Harmonization of Immunogenicity Risk Assessments for Generic Peptides

Andrew Graves
Director of Immunogenicity Assessment
Teva Pharmaceutical Industries, Ltd.

FY25 Generic Drug Science and Research Initiative Public Workshop

03 June 2025

Disclaimer

The opinions expressed in this presentation are those of the presenter and not necessarily those of Teva Pharmaceutical Industries Ltd. or its affiliates (collectively “Teva”). This presentation has been prepared for discussion purposes only. Neither Teva nor any of its employees or representatives make any representation or warranty, express or implied, as to the accuracy or completeness of any information contained herein. The information and examples presented originate from individual experience and may not represent the full scope and/or examples of Teva. Nothing contained within the presentation is, or should be relied upon as, a promise or representation as to the future and Teva expressly disclaims any obligation to update the information if it should change.

1

Background

2

Standardization & Harmonization

3

Expansion

4

Conclusions

1

Background

ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry

Guidance for Industry

MAY 2021

- The FDA finalized guidance for ANDAs for synthetic peptides in May 2021, and as part of that document established expectations for immunogenicity assessment of proposed generics.
- At time of publication, guidance was limited to synthetic peptides.
- Further research would aid both industry and the Agency by establishing and harmonizing best-practice approaches, leading to higher quality submissions as well as an easier and speedier review process.
- There are also opportunities for broadening the utility of these assays beyond the original scope.

Guidance for Industry- Synthetic Peptides (fda.gov)

1

Background

- Adaptive immunogenicity risk is typically summarized using a combination of *in silico* and *in vitro* approaches
  - While *in silico* provides a rapid and high-throughput option for computational risk assessment, current platforms are somewhat limited in accurate prediction due to the presence of non-natural amino acids in some products and many impurities.
  - *In vitro* adaptive immunogenicity risk can be assessed using multiple platforms, including:
    - HLA binding assays
    - MAPPs
    - PBMC cytokine release assays
    - DC:T co-culture assays
  - Predictive value of these assays in terms of clinical outcomes has not been thoroughly established
  - Subtle differences in the assays may lead to difficulty in interpretation and comparison between assays or studies

- Innate immunogenicity risk assessment is generally established using either reporter cell lines or cytokine release assays. The goal is to examine and compare products for the presence of potential innate immune response modulating impurities (IIRMIs) which, in turn, could trigger a loss of immune tolerance.
  - As with adaptive immunogenicity, the link to clinical outcome has not been fully established
  - Differences in the readouts, statistical approaches, and controls utilized can lead to difficulty in data interpretation and comparison

1

Background

2

Standardization & Harmonization

3

Expansion

4

Conclusions

2

Standardization & Harmonization

- Progress is being made to establish a set of standards for use with *in vitro* adaptive immunogenicity platforms as well as innate immunogenicity platforms.
    - Adaptive immunogenicity standards in development via partnership between EpiVax and CUBRC

EpiVax and CUBRC Awarded FDA Contract Worth $2M for Development of Control Peptides for Immunogenicity Risk Assessment Assays Supporting Regulatory Filings of Generic Peptide Drugs

Elena Iemma | October 24, 2024 | News

    - Innate immunogenicity standards developed with assistance from FDA, NIH, and NIST are undergoing testing prior to deployment

2

Standardization & Harmonization

- Establishing control standards is an excellent first step, evidence circulating in the field suggests a lot of research will be needed to understand these controls and how they work in a variety of assays prior to deployment.
    - A joint task force established by HESI/AAPS was set up to establish control standards for CD4 T cell assays for *in vitro* platforms
    - Scope confined to large molecule biologics
    - In first phase, approximately 11 labs participating
    - Initial set of data was presented at **2024 Immunogenicity & Bioassay Summit** (Laurent Malherbe)
        - Some controls known to be clinically immunogenic were immunogenic in all platforms tested
        - Some controls known to be clinically immunogenic were not immunogenic in all platforms
        - Does this mean that some platforms are limited in their predictive ability, or is it possible that different platforms are providing slightly different readouts?

2

Standardization & Harmonization

- **RESEARCH OPPORTUNITY:**
  - HESI/AAPS consortium limited its scope to large molecule biologics, but there is a research need to understand the differences in platforms used by generics sponsors while also ensuring broad utility of control standards in development by EpiVax/CUBRC and FDA/NIH/NIST
  - FDA should consider partnering with industry sponsors and CROs through CRCG, USP, AAM, and/or AAPS to establish a consortium as part of the rollout for controls for immunogenicity to ensure utility across multiple formats
  - Consortium could also research other aspects of immunogenicity risk assessments (for example, expectations for fit-for-purpose assay validations or applying different statistical approaches to a standardized data set to understand impact on data interpretation)
  - **Ideal outcome is one or more white papers outlining best practices and expectations for immunogenicity risk assessments supporting ANDA applications for generic peptides**

1

Background

2

Standardization & Harmonization

3

Expansion

4

Conclusions

3

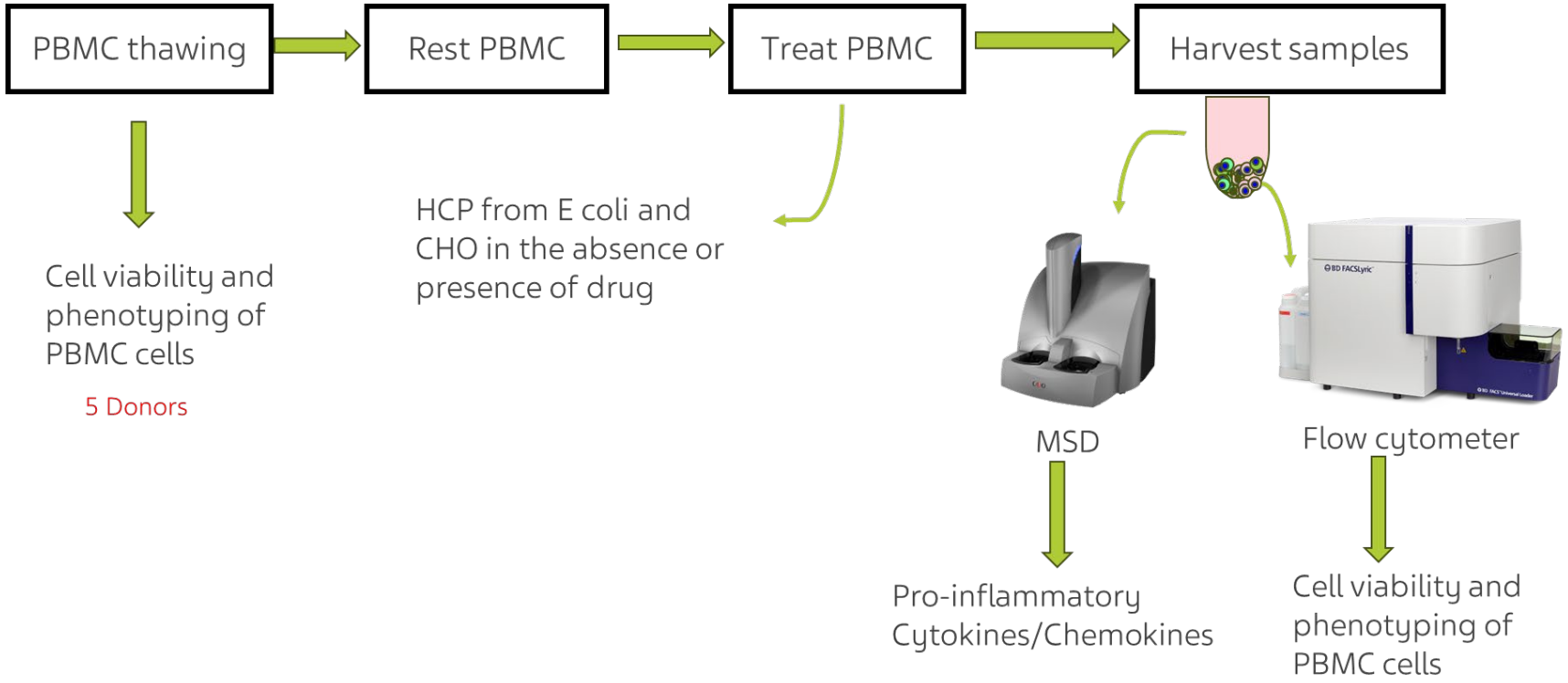
Expansion

- Guidance for generic peptides, originally published in May 2021, was limited in scope to only generics of synthetic origins
- There may be a number of regulatory concerns preventing recombinant generic peptides from being considered via 505(j) pathway
    - Must the generic product be manufactured from the same host?
    - What are the specification limits of host cell proteins (HCPs) in the final product?
    - How do you assess the immunogenicity of the HCPs present in the final product?
- Despite these questions, expanding the 505(j) pathway to accommodate recombinant generic peptides should be a benefit that expands the availability of generic products to the American public
- The maturation of *in vitro* and *in silico* immunogenicity tools may allow for consideration of recombinant generic peptides in the near future with some additional research

3

Expansion

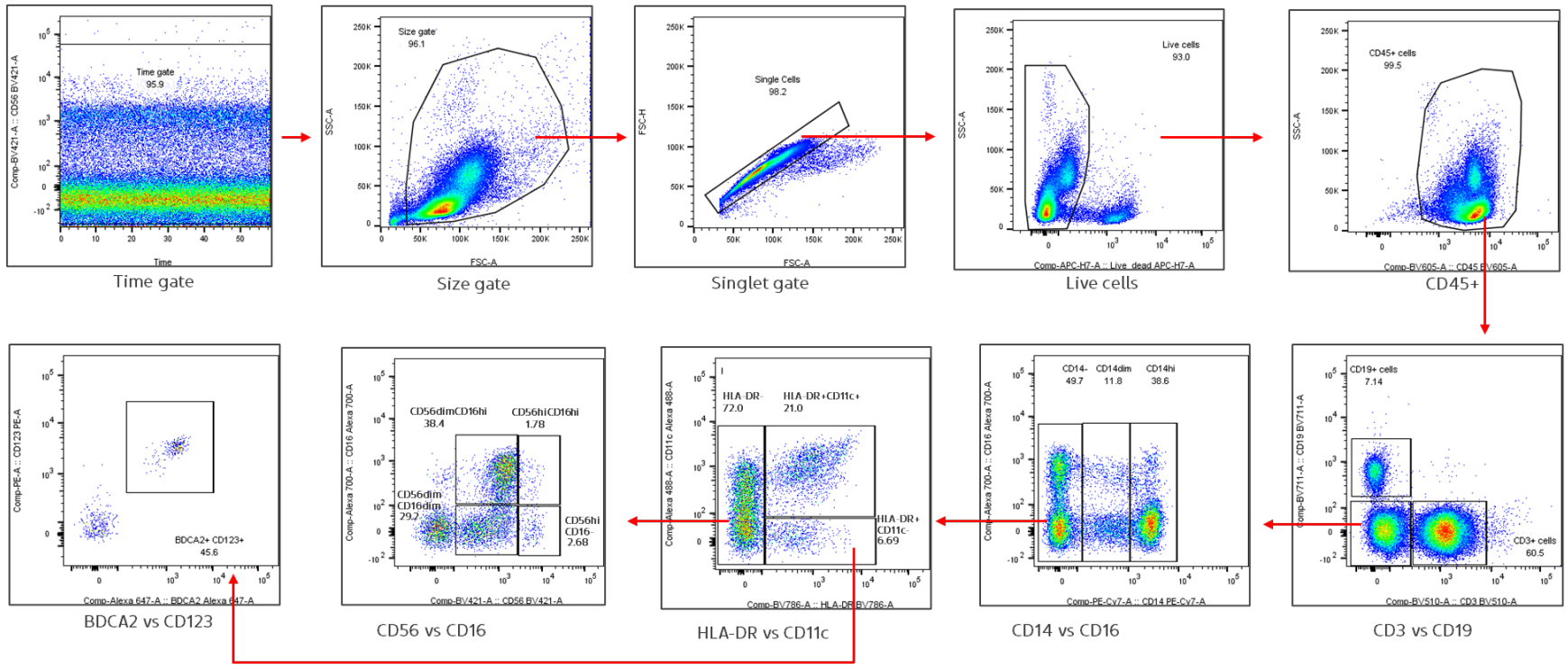
Assessing the innate immunogenicity risk of HCP



3

Expansion

Assessing the innate immunogenicity risk of HCP

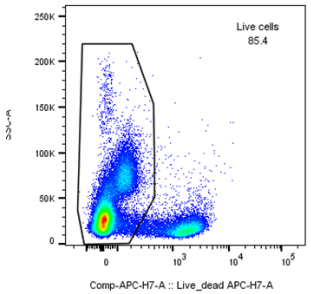


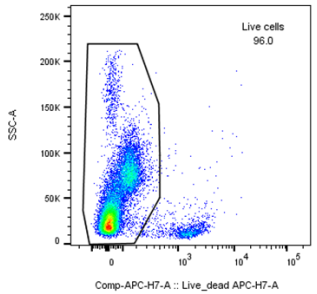
3

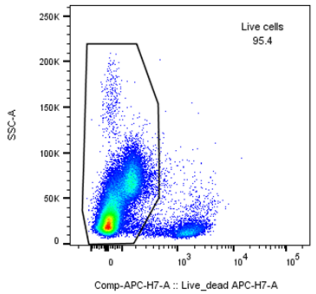
Expansion

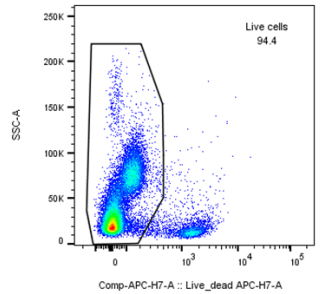
Assessing the innate immunogenicity risk of HCP

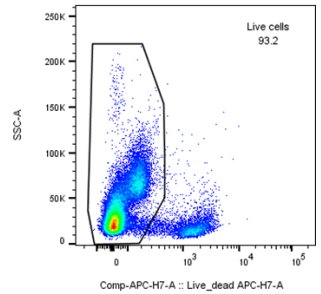
Pre-Treatment



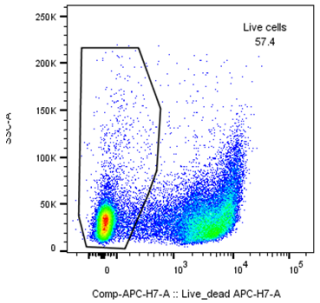




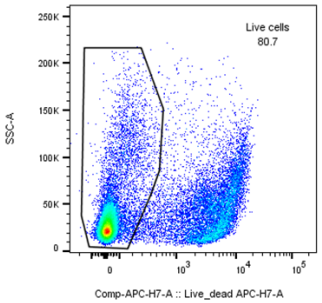




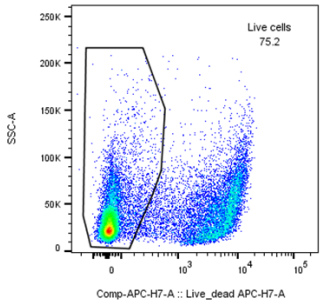
Post-Treatment



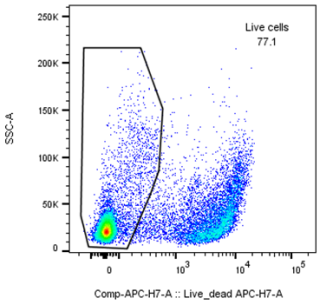
Donor 1



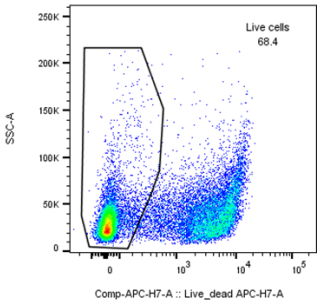
Donor 2



Donor 3



Donor 4



Donor 5

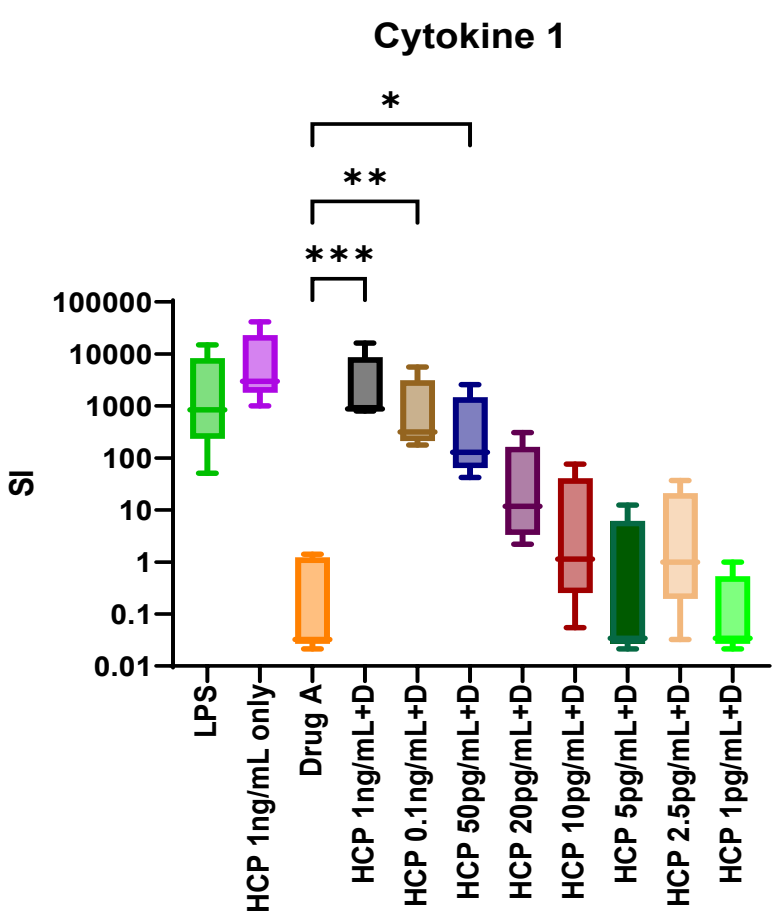
*HCP Treatment at 2.5µg/mL

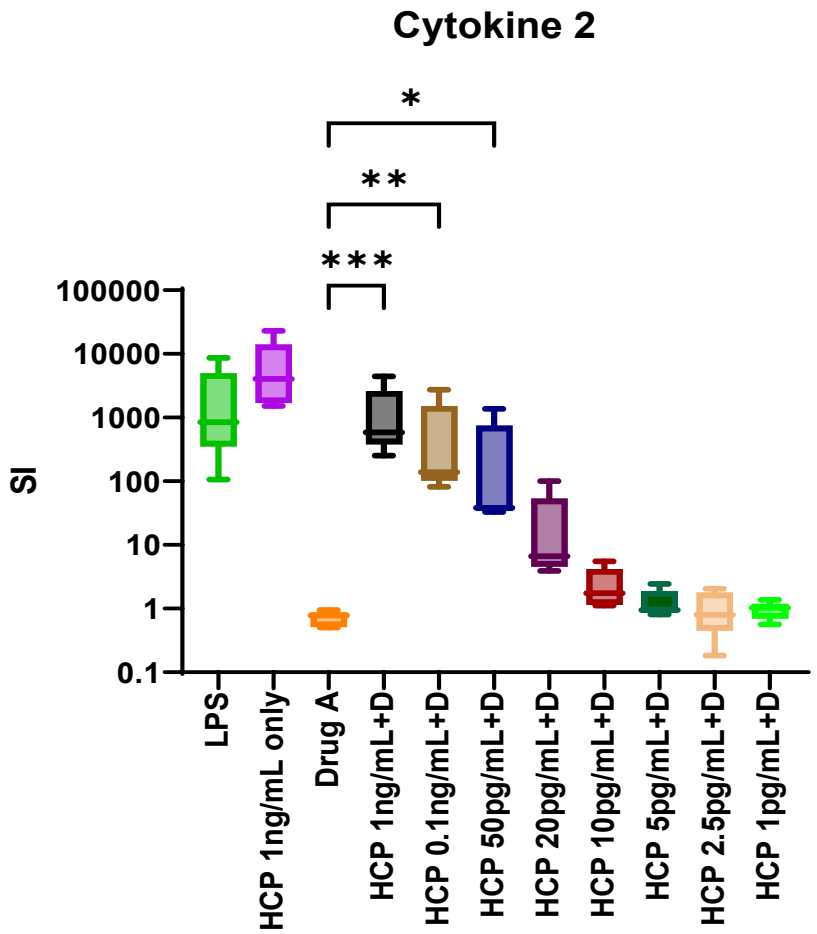
3

Expansion

Assessing the innate immunogenicity risk of HCP

E coli HCP in presence of Drug A

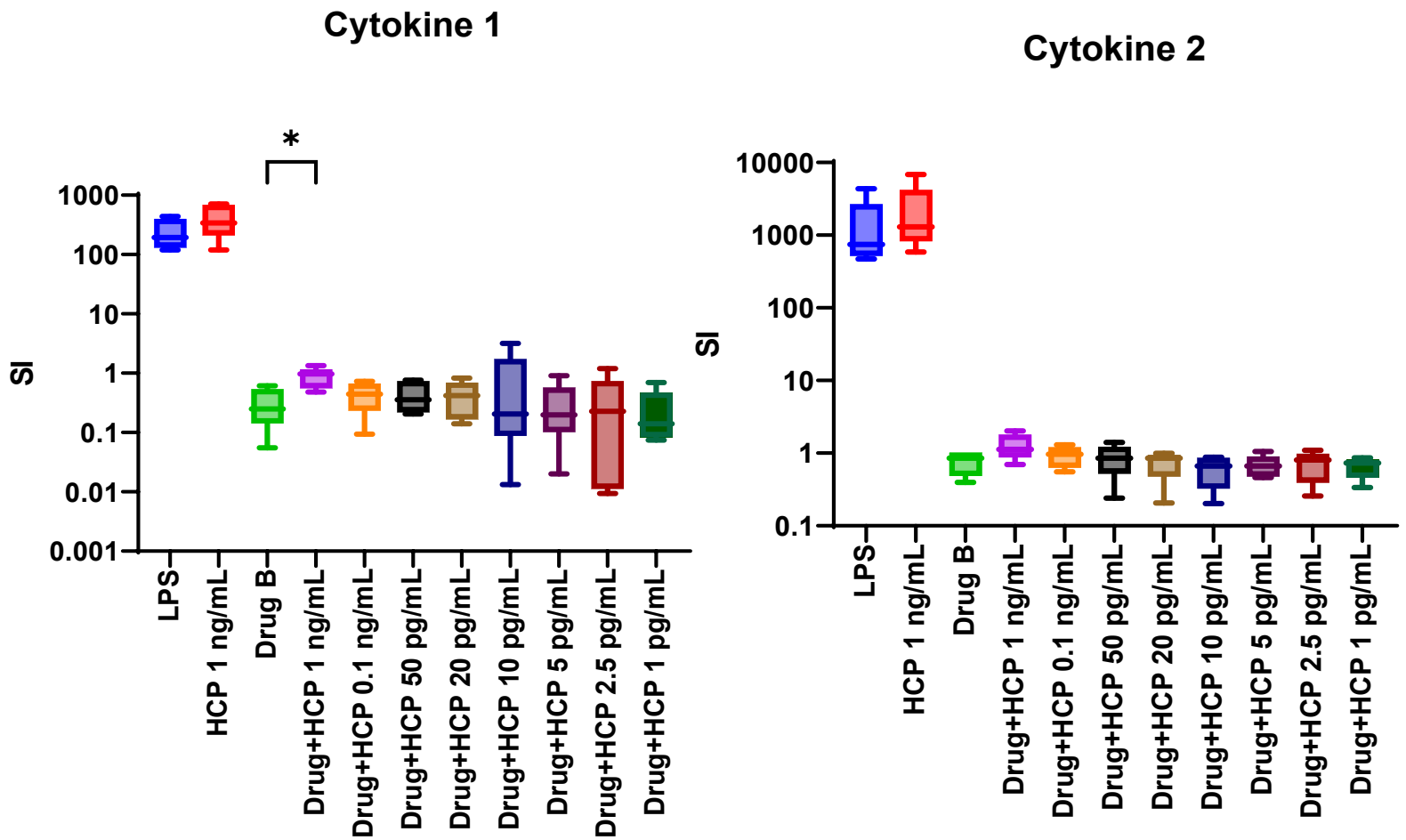




3

Expansion

Assessing the innate immunogenicity risk of HCP
E Coli HCP in presence of Drug B

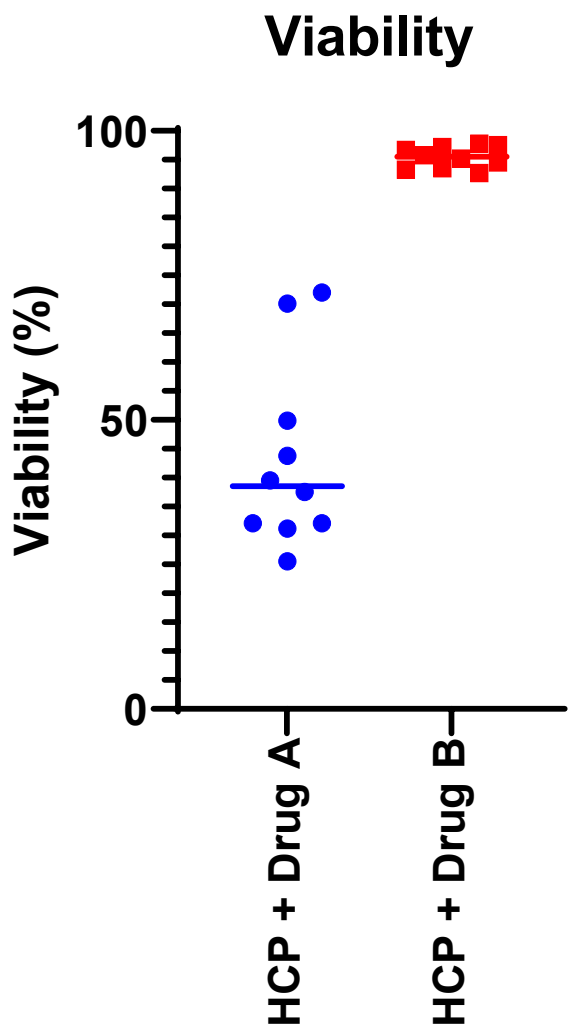


3

Expansion

Assessing the innate immunogenicity risk of HCP

Inhibitory effect of Drug B protects cell viability at higher concentrations of HCP

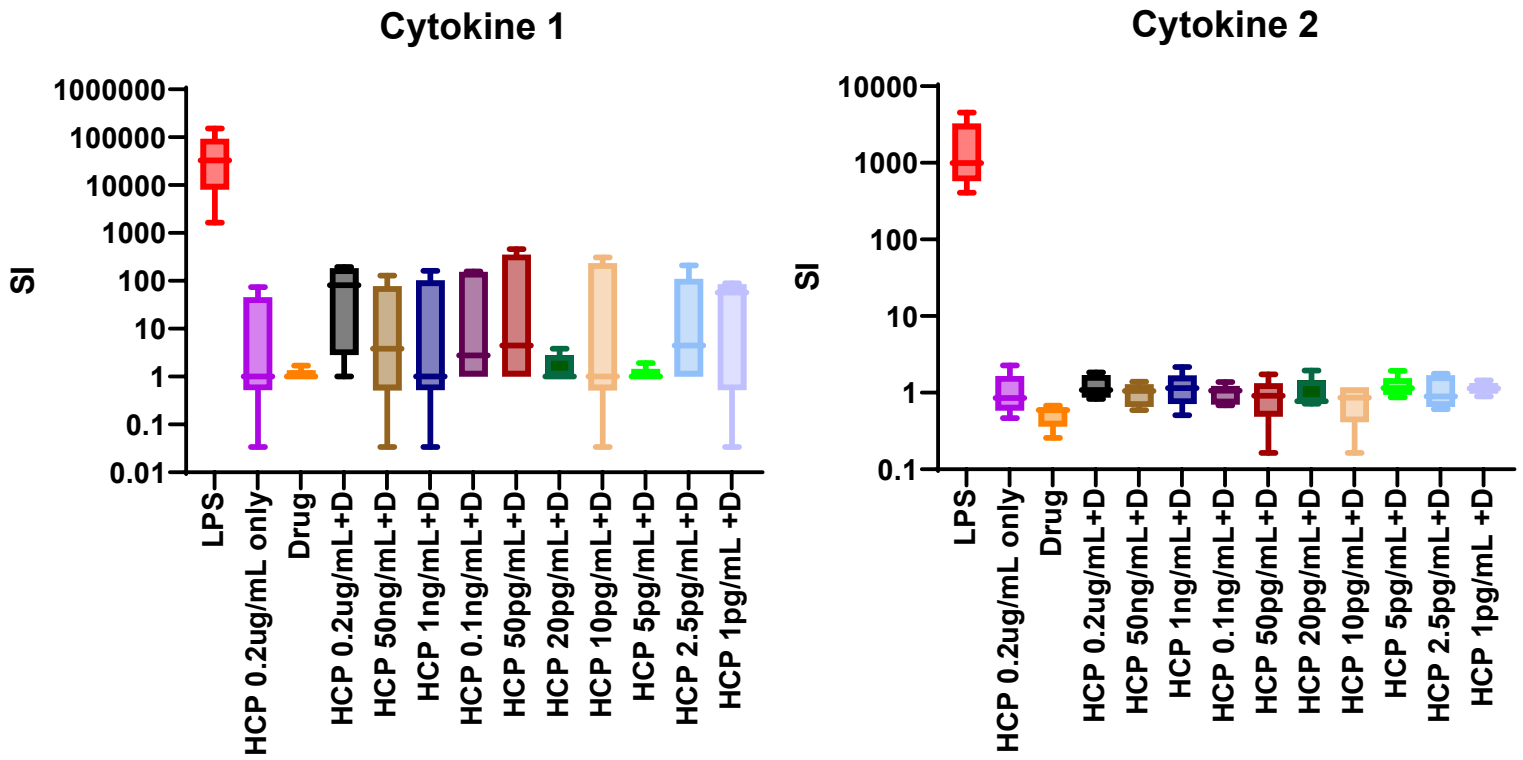


3

Expansion

Assessing the innate immunogenicity risk of HCP

CHO HCP in presence of Drug A



3

Expansion

- We believe that adaptive immunogenicity risk of HCP in recombinant generic peptides can be adequately assessed between established *in silico* platforms and *in vitro* assays

- Our early experiments suggest that innate immunogenicity platforms, such as our PBMC cytokine release platform demonstrated here, can provide adequate assessment of the innate immunogenicity risk of HCP present in generic drug products. In particular:

    - We have demonstrated that our assay can detect increased immunogenicity potential in response to low levels of E coli HCP

    - As expected, sensitivity to HCP is affected by the nature of the drug as well as the type of HCP present
        - Suppressive drugs hinder the sensitivity of the assay while also increasing cell tolerance to higher levels of HCP
        - Given its mammalian origins, CHO HCP triggers undetectable levels of innate cytokine release compared to similar concentrations of E coli HCP

3

Expansion

- **RESEARCH OPPORTUNITY:**
  - Additional work and controls will be required for thorough evaluation of innate immunogenicity platforms and their suitability for supporting 505(j) submissions for recombinant peptides
  - Must establish expectations for industry to leverage *in silico* and *in vitro* platforms for supporting recombinant submissions, including appropriate controls, levels of sensitivity, and statistical approaches
  - Opportunity to leverage learnings from BsUFA III research aimed at enabling quicker approval of biosimilars through supportive *in silico* and *in vitro* assessments
  - **Ideal outcome is guidance or white papers on employing *in vitro* immunogenicity assays for 505(j) submissions of recombinant peptides (and/or other classes of generic drugs)**

1

Background

2

Standardization & Harmonization

3

Expansion

4

Conclusions

4

Conclusions

- Substantial and combined research by FDA and industry has led to the continued maturation of *in silico* and *in vitro* platforms that are now used to support 505(j) submissions for synthetic generic peptides
- Despite the maturation of these platforms, many types of platforms and many different approaches make it difficult to assess the validity of an assay or compare results across assays or sponsors
- Now is the time for FDA to support research initiatives to standardize, harmonize, and expand the utility of these assays, creating an environment where industry has confidence in their submissions while simultaneously allowing for a clearer, more thorough, and standardized approach to submission evaluation for the Agency reviewers

Acknowledgments

Specialty Bioanalytics

Michele Rasamoelisolo

Kate Nukunya

Weimin Kong

Marella Angello

Samantha Carroll

Samantha Warmkessel


teva