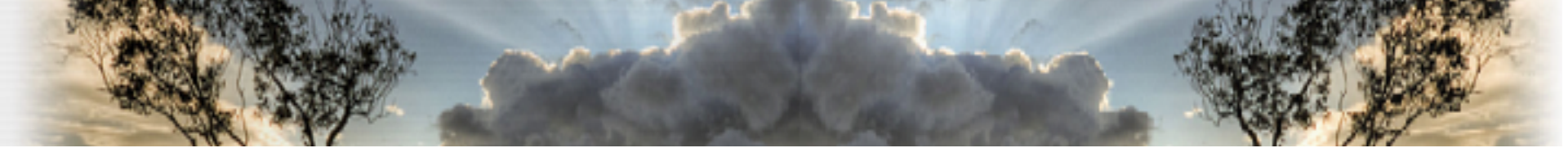


EBF

EBF Open Symposium

N° 13 From Cyberspace - Staying Connected

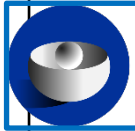
17-20 November 2020

A Chinese NMPA draft technical guideline on immunogenicity of therapeutic agents: similarities and differences to existing EMA and FDA Guidelines or a new global challenge for harmonisation?

Tobias Haslberger, on behalf of the EBF

Current Regional Guidelines/Guidances on Immunogenicity Assessment

De afbeelding kan niet worden weergegeven.



Immunogenicity Assessment of Therapeutic Proteins – EMA 2017

Immunogenicity Testing of Therapeutic Proteins Products – Developing and Validating Assays for Anti-Drug Antibody Detection – FDA 2019

A Draft Technical Guideline on Immunogenicity of Therapeutic Agents Issued by the National Medical Products Administration (NMPA) on 24 August 2020

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

新闻中心>>工作动态>>通知公告>>新闻正文

关于公开征求《药物免疫原性研究技术指导原则（征求意见稿）》意见的通知

发布日期：20200824

着国内新药，尤其治疗性蛋白药物研究与开发的日益增多，免疫原性相关研究越来越广泛。目前，我国尚无免疫原性研
技术规范，为鼓励和引导规范开展免疫原性相关研究，药审中心组织起草了本指导原则，经中心内部讨论，已形成征求
。
们诚挚地欢迎社会各界对征求意见稿提出宝贵意见和建议，并及时反馈给我们，以便后续完善。征求意见时限为自发布
1个月。
的反馈意见请发到以下联系人的邮箱：
系人： 闫莉萍 王寅
系方式：yanlp@cde.org.cn wangyin@cde.org.cn
谢您的参与和大力支持。

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

Current Location: News Center >>Work News>>Notice Announcement>>News Text

Notice on Publicly Soliciting Opinions on the "Technical Guidelines for Drug Immunogenicity Research (Draft for Comment)"

Release Date: 20200824

With the increasing research and development of domestic new drugs, especially therapeutic protein drugs, immunogenicity related research is becoming more and more extensive. At present, there is no relevant technical specifications for immunogenicity research in my country. In order to encourage and guide the development of immunogenicity-related research, the Center for Drug Evaluation organized the drafting of these guidelines. After internal discussions, a draft for comments has been formed.

We sincerely welcome all sectors of the society to put forward valuable comments and suggestions on the solicitation draft, and feedback to us in time for follow-up improvement. The time limit for soliciting opinions is 1 month from the date of publication.

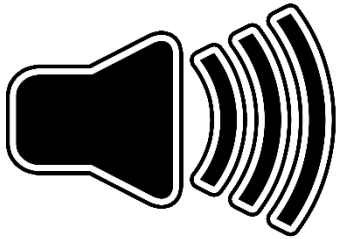
Please send your feedback to the following contact email:

Contact: Yan Liping Wang Yin

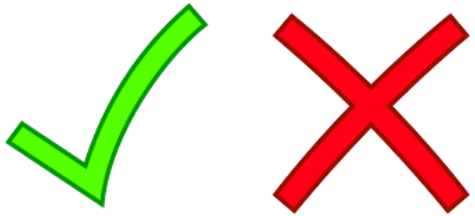
Contact: yanlp@cde.org.cn wangyin@cde.org.cn

Thank you for your participation and strong support.

Goal of This Presentation



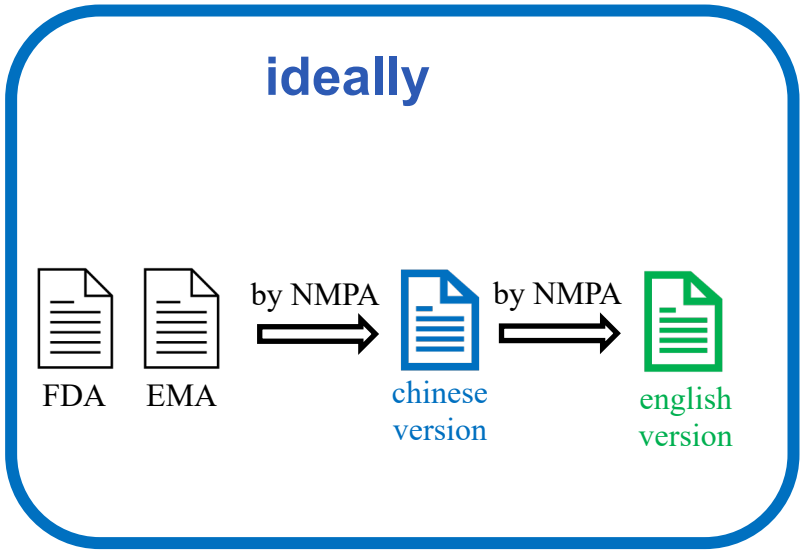
- **Raise awareness in the BA community of a new immunogenicity guideline on our horizon**
- **Impact/Challenge for us as an Industry**

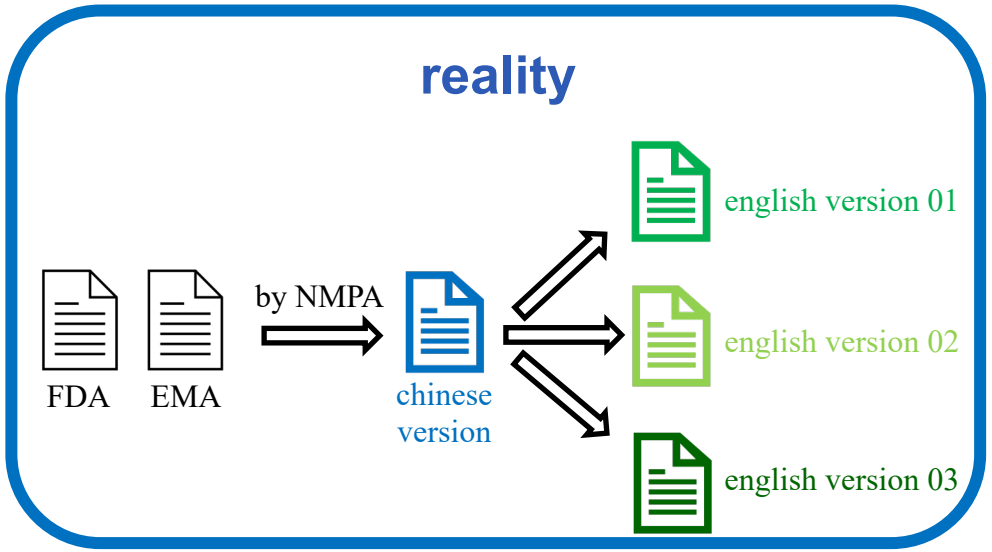


- **Share EBF perspective on this draft guideline**
- **Elaborating on ambi-guities, concerns and similarities/differences to existing guidelines**

How to Manage the Challenges as a Global BA Community – Timing & Translation

- **Timing**: published end Aug; EBF became aware mid Sep
- **Translation**: no official english translation available, rely on individual translations





Similarities Between FDA/EMA Guidelines and NMPA Draft Guideline Draft

- NMPA draft is certainly not a completely new guideline!
- NMPA draft has sections that are taken 1:1 from FDA **and/or** EMA
- Key elements are in: IRA, limited predictive value of non-clinical results on clinical immunogenicity, multi-tiered approach, detailed information on key assay elements (e.g. PC and NC) and individual validation parameters

But ...
... there is **ambiguity** and **concerns**

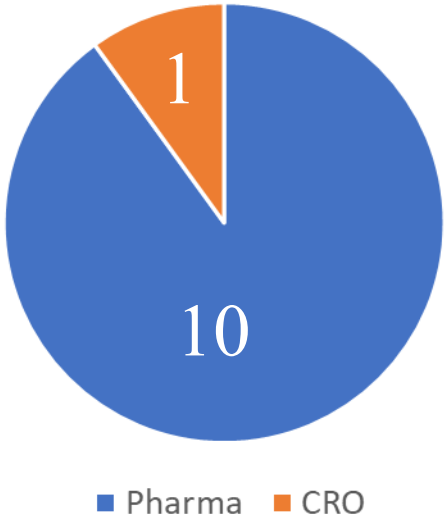
EBF Survey on NMPA Draft Guideline

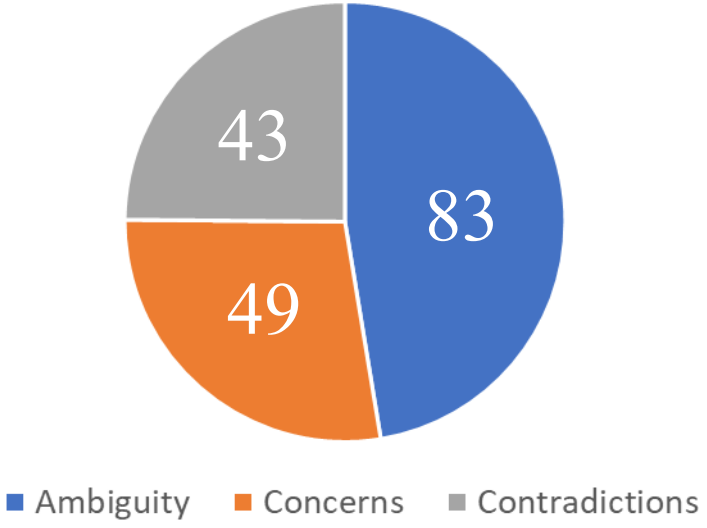
- Translated document was divided into 65 paragraphs
- Asked EBF community to highlight areas of
  - Ambiguity
  - Concerns
  - Differences/Contradictions to existing (EMA/FDA/ICHS6) guidelines

Chapter	Paragraph	Original Text	I agree, no comments	I see ambiguity in the current wording. Please specify where you see ambiguous statements and/or rephrase accordingly.	I see concerns with this requirement. Please specify where/why you see concerns	I see differences/contradictions to current guidelines. Please specify where you see differences/contradictions and to which guideline they relate to (e.g. FDA/EMA/ICHS6)
1. Introduction		For the purposes of this guidance, the immunogenicity of therapeutic agents is defined as the propensity of a therapeutic agent and/or its metabolites to generate immune responses or immune-related event to itself or to related proteins. The consequences of an immune reaction are extensively ranging from transient appearance of ADAs without any clinical significance to severe life-threatening conditions. Potential clinical consequences of an unnecessary or unexpected immune response may lead to loss of the biological activity of therapeutic protein or cross-reactivity with the endogenous counterpart, and serious adverse events such as anaphylaxis				
		For most drugs, adverse immune reactions are usually caused by an immune response to therapeutic agent mediated by humoral immune				

- Could only allow for short time period (10 days) for providing feedback

Some Survey Statistics





- Being mindful of (i) short review timeline and (ii) not each company running business in China
- 11 responses (10 Pharma, 1 CRO), total of 175 comments

NMPA Draft Guideline:

Ambiguities

NMPA Draft Guideline: Ambiguities at a Glance

- Whole sentences/chapters are **difficult to read/understand**
  - Translation issue: English → chinese → english
  - Lack of consistent use of one word for “drug” throughout the doc (drug vs antigen vs therapeutic agent vs product)
  - Some sections were taken only partially 1:1 from EMA/FDA, thereby generating risk of putting things out of context, e.g. (i) single-assay concept for Biosimilars is not mentioned at all or (ii) ambiguity on how to deal with manufacturing changes

- Document could benefit from **better structuring/differentiating** dedicated sections:
  - section on risk-factors (product-/study-/patient-specific)
  - sections on consequences of unwanted immunogenicity (PK/PD/efficacy/safety)
  - ISI/IRA only briefly mentioned and might need more guidance/details
  - Text jumps from topic to topic, e.g. describe potential add. validation for Biosimilar assays in one sentence, describing SPR and the need to check surface stability after chip regeneration in the next sentence

- Consider elaborating more/better on **assay limitations**:
  - Positive control (PC) is a surrogate and not fully reflective of the study population → suggest removing the statement "Ideally, the PC antibody reflects the anticipated immune response that will occur in humans”.
  - ADA assays are non-quantitative: consider to avoid using words like “STD curve” or “assessment of Ab content”

FDA/EMA Guidelines and NMPA Draft Guideline:

Concerns/Differences

Scope: Emphasis on Clinical **AND** Non-Clinical Immunogenicity Assessment

"Therapeutic proteins show species differences in most cases, and there are limitations in predicting human immunogenicity based on animal immunogenicity studies."

"… immunogenicity studies are always an important part of the chain evidence for non-clinical safety studies of therapeutic protein drugs."

→ Seems to be not well aligned with principles of ICH S6(R1):

Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies.
Measurement of anti-drug antibodies (ADA) in non-clinical studies should be evaluated when there is 1) evidence of altered PD activity; 2) unexpected changes in exposure in the absence of a PD marker; or 3) evidence of immune-mediated reactions (immune complex disease, vasculitis, anaphylaxis, etc.).

Non-Clinical Immunogenicity Assessment

- **Concern**: clear differentiation is obviously missing on WHAT is required WHEN for non-clinical vs clinical immunogenicity assessment. Also, leaner approaches for non-clinical assays are not discussed, like e.g. running only a screening assay, using a 1% FPR.

- **Differences**:

- NMPA draft is the first guideline that is specific/prescriptive on how to assess some (but not all) validation parameters for non-clinical assays, e.g.:
  - CP: at least 15 individual samples, at least 2 variables, run 3 batches, at least 3 days
  - Precision: at least 2 variables
  - LPC determination: 1.5-2x NQC or CP
  - Sensitivity: 250-500 ng/mL (Mire-Sluis: 500-1000 ng/mL)

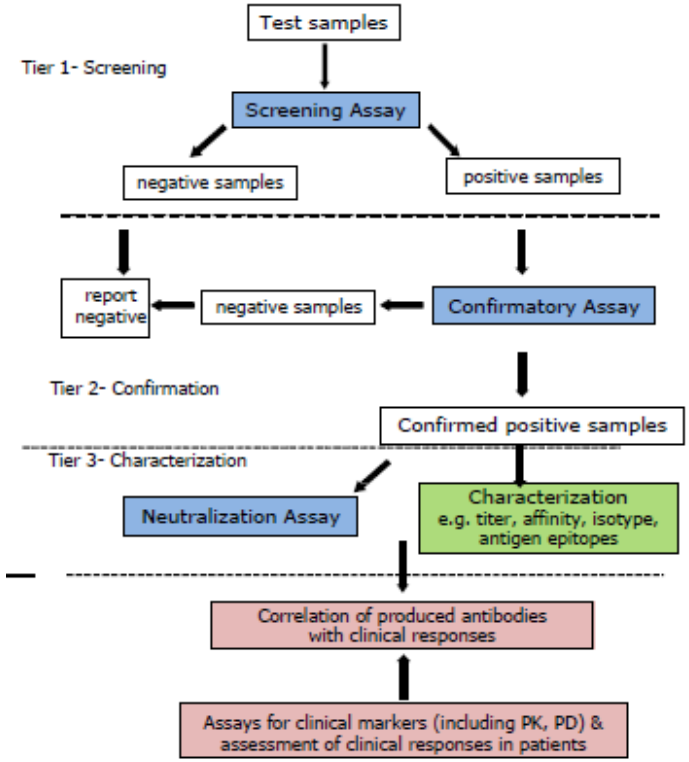
- NMPA draft is the first immunogenicity guideline expecting/explicitly mentioning *in vitro* cytokine release tests in addition to *in vivo* animal cytokine measurements for immune-related adverse reactions as part of a full non-clinical data package.

  → Better placed in a tox guideline?

Consolidated EBF Feedback on Concerns & Differences: Multi-Tier Assays

Screening Assay	Confirmatory Assay	Titer Assay
Detect rapidly dissociating ADAs → challenging/impossible based on availability of key reagents like e.g. low affinity IgM	*„Confirmatory assays are expected for confirming the positive results and eliminating any false positive results…".* → A confirmatory will not eliminate FP as the CCP is typically set to provide a 1% FPR	Different definition of titer: NMPA: maximal dilution where a sample gives a value above the CP FDA/EMA: reciprocal of the highest dilution that gives a value at/above the CP
Carry out screening and confirmatory cut point determination on the same plate		Titer Cut Point concept is missing: Consider 99.9% TCP to facilitate titer determination in case SCP falls on the lower plateau of the positive control dilution curve.
Analysis strategy in duplicates, w/o providing any rationale		Good description of concepts to differentiate titers is missing (e.g.minimum significant ratio)

Need for Additional Characterization of Positive Anti-Drug Antibody Responses



- Consider mentioning that potential characterization (e.g. isotyping, domain specificity, neutralization activity) of ADA responses should occur based on:
  - Overall risk assessment
  - Stage of drug development

- Neutralization Assay:
  - Provide a clear statement, as early as possible in the document, that NAb assays are not required for non-clinical and early clinical phases when (i) risk is low and (ii) appropriate PK/PD assays are in place and indicative for the presence of NAbs
  - Mention that NAb assays may not achieve the sensitivity of an ADA assay
  - Provide more details on when CLBA is sufficient

Consolidated EBF Feedback on Similarities & Differences for Selected Validation Parameters

Parameter	EMA/FDA	NMPA
Negative Control (NC)	NC should match characteristics of study samples (collected from treatment-naïve subjects, consider disease condition, gender, age, co-medication)	
Positive Control (PC)	Human ADAs are preferred, but mentioning „where available (NMPA) or „often not available“ (FDA) → pAb via animal immunization, mAb Low, mid, high PC for Dev/Val to monitor assay performance; no mid QC for routine sample analysis	
Precision	Not prescriptive on how many/which variables except for days and analysts	non-clinical ≥ 2 variables clinical ≥ 4 variables: day, plate, analyst, instrument
Selectivity	FDA: spike different amounts of PC antibodies in buffer and matrix and compare ADA recovery	Spike ≥ 10 blank individual matrices with PC samples at 2 concentration levels all blank matrix controls should be < SCP ≥ 80% of the PC samples should be > SCP and meet precision criterion
Drug Tolerance (DT)	FDA: DT in presence of expected drug levels EMA: if DT doesn‘t exceed drug level, justify	DT has to exceed the drug levels in the sample

Conclusions

- While sharing basic concepts of immunogenicity assessment with EMA/FDA, the NMPA draft has its own flavour and shows differences to EMA/FDA, e.g. emphasis on non-clinical immunogenicity analysis
- Guideline differences …
  - … cause challenges when filing in different regions
  - … result in increased demands on resources/cost/time
- How can we as EBF still share our comments with NMPA in light of having missed the due date for public consultation? → via EFPIA?
- **Risk** (of e.g. increasing the non-clinical package for submissions in China) vs **Opportunity** (for harmonization via ICH) ?

Acknowledgements

- Joanna Grudzinska-Goebel and Rob Nelson … for bringing this topic into EBF
- EBF community … for giving input on the draft guideline on very short notice

Contact Information

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European Bioanalysis Forum vzw

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