FDA Regulatory Perspectives on Immunogenicity Risk Assessment from Phase 1 IND to BLA and Beyond

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DISCLAIMER

The views and opinions expressed herein should not be used in place of regulations, published FDA guidances, or discussions with the Agency

- Presentation discusses primarily to 351 (a) and 351(k) biologics

Why do we need Immunogenicity Risk Assessments for biotherapeutics?

- Immunogenicity-related deficiency syndromes in patients treated with recombinant erythropoietin and thrombopoietin in the late 20th century resulted in increased regulatory and industry scrutiny
  - Historically immunogenicity assessments were performed “reactively”
  - Currently an immunogenicity assessment is considered a basic aspect of biotherapeutic development and is performed “proactively”

Immunogenicity- clinical concerns raised by Anti-drug Antibodies (ADA)

Clinical Concern	Clinical Outcome
Safety	• Hypersensitivity reactions •Neutralize activity of endogenous counterpart with unique function causing deficiency syndrome
Efficacy	Enhancing or decreasing efficacy by: • changing half life. • changing biodistribution.
Pharmacokinetics	• Changes to PK • Changes to PD
None	• Despite generation of antibodies, no discernable impact

Immunogenicity at the FDA

- Who reviews it?
  - Depends on the class of product
    - CDER - monoclonal antibodies, growth factors, fusion proteins, cytokines, enzymes, therapeutic toxins
    - CBER- allergenics, blood and blood components including clotting factors, cellular and gene therapies, vaccines

Office of Biotechnology Products (OBP)

- CMC for 351 (a) and 351 (k) biologics under CDER purview
  - Currently 4 product divisions with mixed portfolios

- Collaborate in immunogenicity risk assessments and review validation of clinical immunogenicity assays for 351 (a) and 351 (k) biologics at CDER
  - Involved in writing FDA Immunogenicity guidances
  - Immunogenicity Working Group

FDA Immunogenicity Guidances

- Guidance (2014): Immunogenicity Assessment for Therapeutic Protein Product
  - Discusses product and patient risk factors that may contribute to immune response rates.
- Draft Guidance (2016): Assay Development for Immunogenicity Testing of Therapeutic Proteins
  - Discusses the development and validation of immunogenicity assays
- Guidance (2016): Immunogenicity-Related Considerations for Low Molecular Weight Heparin
  - Provides recommendations on addressing impurities and their potential effect on immunogenicity for ANDAs
- Guidance (2015): Scientific Considerations In Demonstrating Biosimilarity To A Reference Product
  - Discusses immunogenicity assays in context of 351(k) pathway
- Guidance (2017): Considerations in Demonstrating Interchangeability to a Reference Product
  - Discusses immunogenicity studies required for interchangeability in context of 351(k) pathway
- Draft Guidance (2017): ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin
  - Discusses immunogenicity considerations for recombinant peptides under ANDA

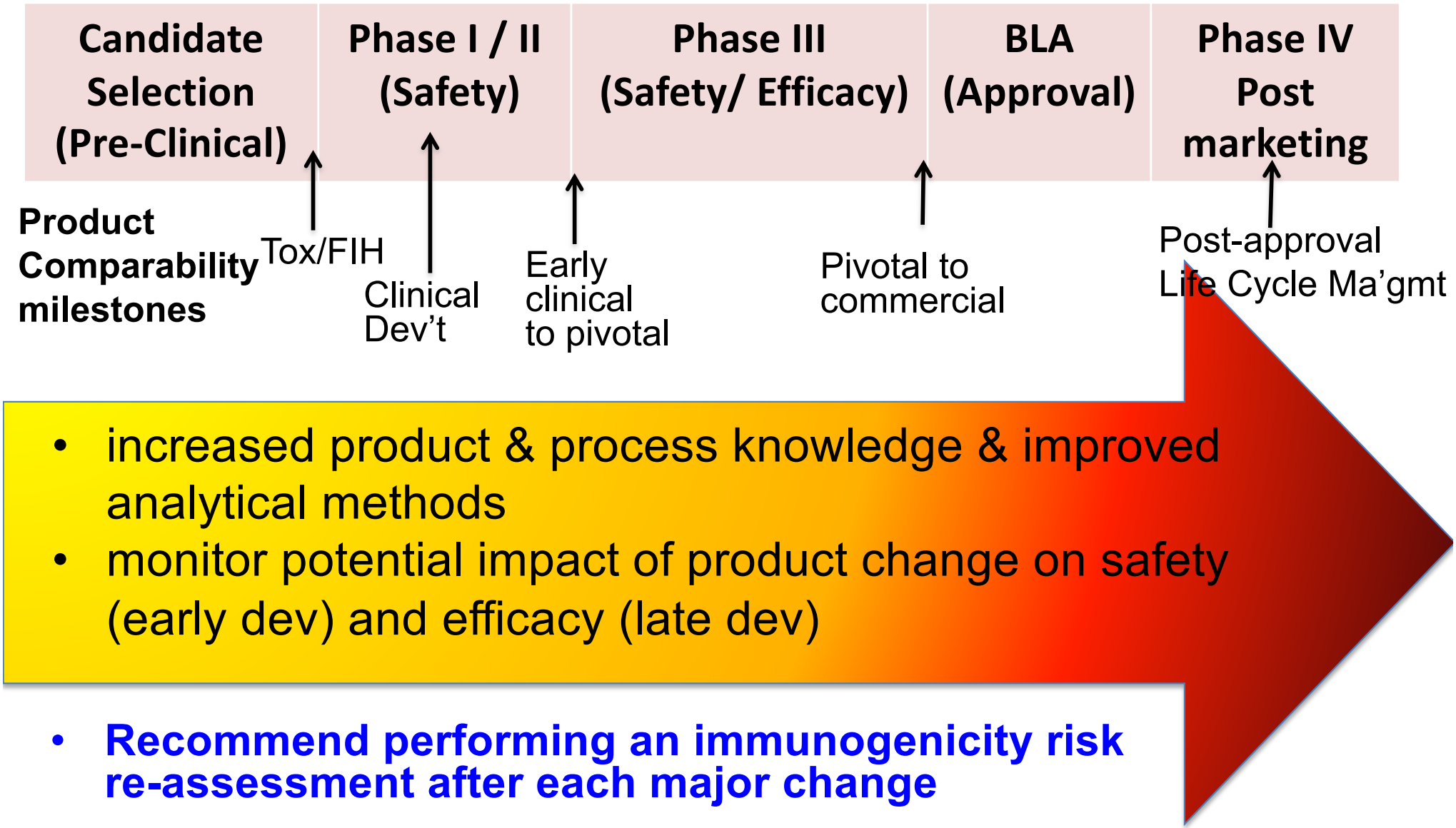
CDER Immunogenicity Review Committee

- IRC is a new cross-center committee with members from:
  - Office of Pharmaceutical Quality's Office of Biotechnology Products (OBP)
  - Office of Translational Sciences' Office of Clinical Pharmacology (OCP), Office of Scientific Integrity and Surveillance (OSIS) and Office of Bioequivalence (OB)
  - Office of New Drugs' clinical review divisions (DPARP, OHOP, DGIEP, DMEP, DBRUP)
  - Office of Statistics and Epidemiology (OSE)
  - Office of Generic Drugs (OGD)
  - Office of Medical Policy (OMP), Office of Regulatory Policy (ORP), and Office of Chief Council (OCC)
  - Observers from CBER and CDRH

CDER Immunogenicity Review Committee

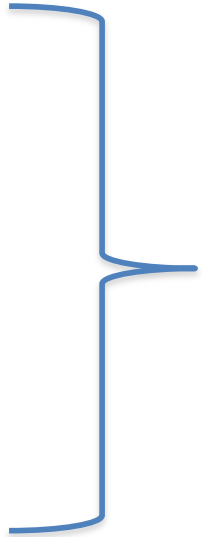
- The IRC provides a multi-disciplinary space to:
  - Develop and maintain risk-based frameworks for evaluating immunogenicity risk
  - Provide advice and expertise to review programs evaluating BLAs, NDAs, and ANDAs with product-specific immunogenicity concerns
  - Internally and externally communicate interdisciplinary product-specific immunogenicity evaluations, as well as broader immunogenicity-related issues and initiatives

Typical Biotech Product Development



Stages of Immunogenicity Risk Assessment

- *PreIND/ biotherapeutic candidate selection*
- IND support
  - Initial IND/Phase 1 (FIH)
  - Mid-development (Phase 2 and Pivotal)
- BLA submission
- Post-Aproval/life-cycle management



Reviewed by FDA

Immunogenicity Risk Assessment for IND Support

- Analysis of program and product risk factors as per FDA Guidance (2014*) Immunogenicity Assessment for Therapeutic Protein Product*:
  - Product/CMC related factors
    - What is the immunogenic potential of the product?
  - Patient related factors
    - How likely is the patient population and clinical indication to produce an immune response to the product?
  - Trial design-related factors
    - How likely are the study conditions to facilitate an immunogenic response?

Product/CMC-Related Factors

- Essential to understand the critical quality attributes (CQA) of the biotherapeutic:
  - Degree of “foreignness” and molecular size
  - Chemical composition and molecular complexity
  - Stability/degradability/impurities
    - Purity on release, storage and handling
    - Upon contact with biological matrices

Preclinical Immunogenicity:

- Biotherapeutics are frequently immunogenic in animals.
  - Immunogenicity in animal models is not predictive of immunogenicity in humans.
  - Assessment of immunogenicity in animals may be useful to interpret nonclinical toxicology and pharmacology data.
  - Immunogenicity in animal models may reveal potential antibody related toxicities that could be monitored in clinical trials.

Additional Utility:

- Pre-clinical immunogenicity studies as part of comparability exercises- pre and post-change material
  - When analytical data reveals changes in CQA
- Pre-clinical immunogenicity studies as part of Biosimilar development programs
  - Comparisons between biosimilar and US-licensed product

Recommendations

A RISK-BASED approach is required to balance the potential harm with potential good of a new biotherapeutic throughout clinical development

- Likelihood of developing an immune response
- Risk of immune response to patient
- Are there therapeutic alternatives
- Reversibility of response

Current Challenges for FDA reviewers

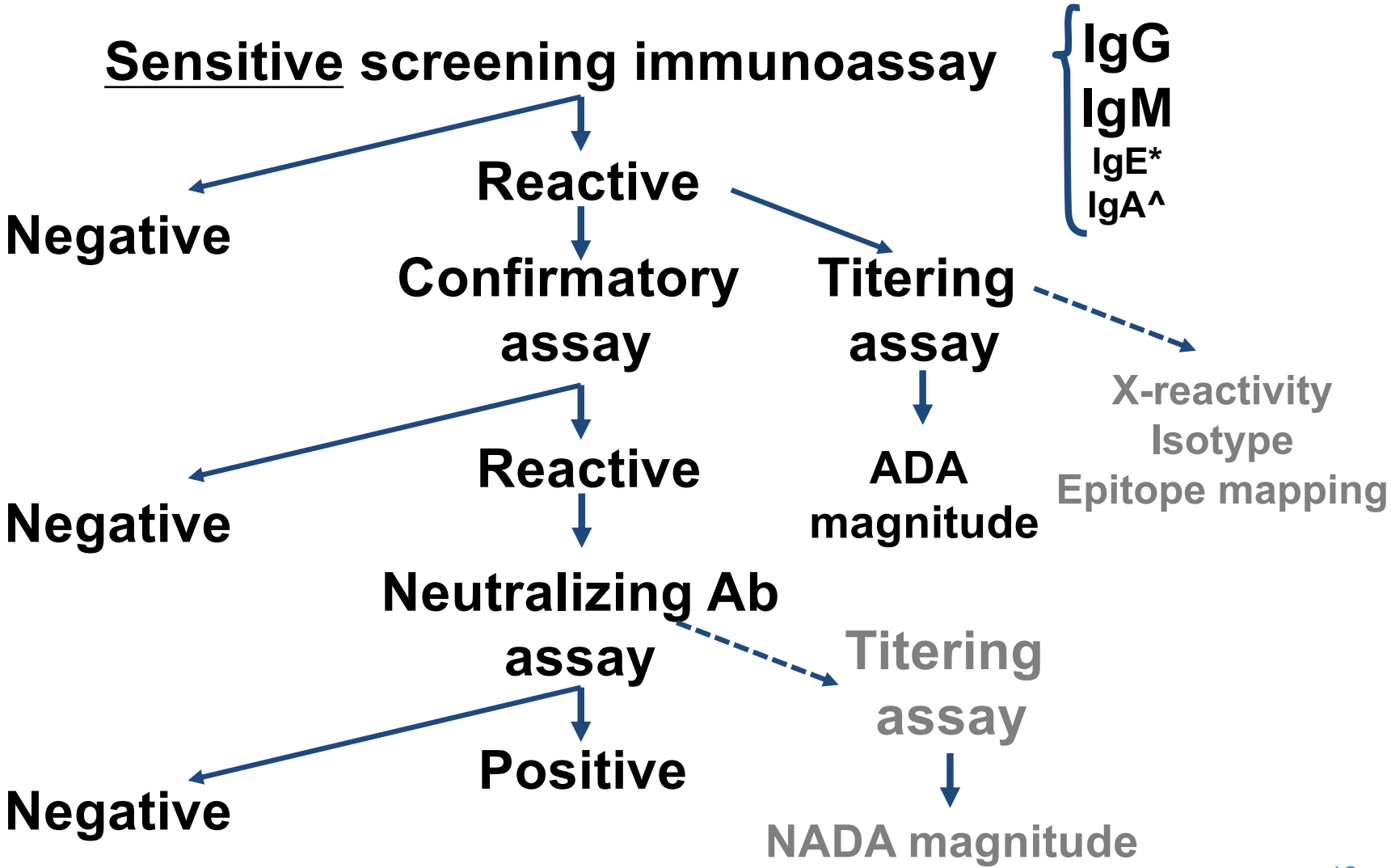
- IND Stage
  - Lack of clearly delineated immunogenicity risk assessment section with summary sampling plans for clinical studies with an immunogenicity component during IND stage.

Suggestion: eCTD 5.3.1.4 Reports on Biopharmaceutical Studies

Additional Information to Support IND

- Follow FDA Draft Guidance (2016): *Assay Development for Immunogenicity Testing of Therapeutic Proteins:*
  - Description of tiered approach
  - Description of Bioanalytical Methods
  - Provide stage-appropriate information concerning the assays
  - Include immunogenicity sampling plans for each new trial
  - Provide immunogenicity updates for individual trials as they become available
    - Inappropriate to pool data from trials that used different assays

Multi-Tiered Immunogenicity Approach



Risk-based Approach to Immunogenicity Assay Development

- Provide a rationale for immunogenicity testing strategy at IND stage, preferably during phase 1

- Assays are critical when neutralizing immunogenicity poses a high-risk therefore real time data concerning patient responses are needed
  - Part of risk mitigation
  - Preliminary validated assays should be implemented early (preclinical and phase I)

For Other Risk Level Products

- Sponsor may store patient samples to be tested when suitable assays are available
- Phase 1 and phase 2 study samples may be tested using “fit-for purpose” assays
- Pivotal study/phase 3 samples need to be tested using fully validated assays
- Provide data supporting full validation of the assays at license

To Support A BLA:

Applicants should provide:

- An immunogenicity risk assessment specific to their product,
- Details on the tiered immunogenicity strategy followed
- Immunogenicity sampling plan(s) for all supporting clinical studies with suitable justification
- Method development and validation reports for all immunogenicity assays used
  - Particularly those used to test immunogenicity samples from pivotal clinical study(ies)

To Support a BLA

Applicants should also provide:

- Tabular summary identifying which immunogenicity assays were used to test samples from individual clinical studies
- Results of immunogenicity analysis for clinical studies having immunogenicity component
  - Correlation of ADA with PK/PD/efficacy/safety (adverse-events)
  - Traceability of drug product lots used in the clinical studies
    - » Study and individual patient level

Current Challenges for FDA Reviewers

- BLA Stage
  - Immunogenicity information is scattered throughout the eCTD in the BLA file.
    - 2.7.4 Summary of Clinical Safety
      - Summary of immunogenicity results
    - 5.3.1.4 Reports on Biopharmaceutical Studies
      - The rationale and information about the chosen immunogenicity testing strategy
      - Assay Validation Reports
    - 5.3.5 Reports of Efficacy and Safety Studies
      - Immunogenicity data set

Integrated Summaries of Immunogenicity

- OBP is currently encouraging Integrated Summaries of Immunogenicity prepared as per EMA guidelines for BLAs
  - Has made immunogenicity reviews less time-consuming
  - Revised FDA Draft Guidance (2016): "Assay Development for Immunogenicity Testing of Therapeutic Proteins" will likely include a section discussing recommendations for Integrated Summaries of Immunogenicity

Post-Aproval/life-cycle management

- How will immunogenicity be monitored post-marketing?
  - Tied to life-cycle management of immunogenicity assays
    - REMS and adverse event reporting
    - Efficacy supplements
    - Post-Approval Manufacturing Supplements
    - Support cross-referencing IND(s) / clinical Investigator IND(s)?

Immunogenicity Risk Assessment for Biosimilars

Immunogenicity Assessment for Biosimilars

- The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the US-licensed product in the incidence and severity of human immune responses
  - Remember that ADAs to either product can have an effect on clinical safety and/or efficacy

Immunogenicity Assessment for Biosimilars

- Structural, functional, and animal data are generally not adequate to predict immunogenicity in humans
- At least one clinical study that includes a comparison of the immunogenicity of the proposed biosimilar to that of the US-licensed product will be expected
  - Parallel arm study for "biosimilarity"
  - Switching arm study(ies) for "interchangeability"

Immunogenicity Assessment for Biosimilars

- The extent and timing of the clinical immunogenicity assessment will vary depending on a range of factors including
  - The extent of analytical similarity between the proposed product and the US-licensed product
  - The incidence and clinical consequences of immune responses for the reference product

Immunogenicity Assessment for Biosimilars

- Considerations for the immunogenicity risk assessment
  - the nature of the immune response (e.g., anaphylaxis, neutralizing antibody)
  - the clinical relevance and severity of consequences (e.g., loss of efficacy of life-saving therapeutic and other adverse effects)
  - the incidence of immune responses, and the population being studied

Biosimilarity and Immunogenicity

- Immunogenicity study(ies) are part of the totality of evidence required to establish “biosimilarity” and “interchangeability” between a 351 (a) licensed product and 351 (k) biosimilar applicant.
  - A key element to demonstrate there are “no clinically meaningful differences”.
  - Follow a tiered approach for immunogenicity assessment

Biosimilarity and Immunogenicity

- Immunogenicity study(ies) are part of the totality of evidence required to establish "biosimilarity" and "interchangeability"
  - The design of any study to assess immunogenicity between a biosimilar and a US-licensed product and acceptable differences in ADA incidence and other parameters of immune response should be discussed with FDA before initiating the study.

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