The assessment of immune responses against biological drugs

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Mastering Immunogenicity
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The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy

The immune response to therapeutic proteins
Why is it important?

It is desirable that vaccines elicit an immune response

Immune responses against non-vaccine protein-drugs on the other hand are detrimental:

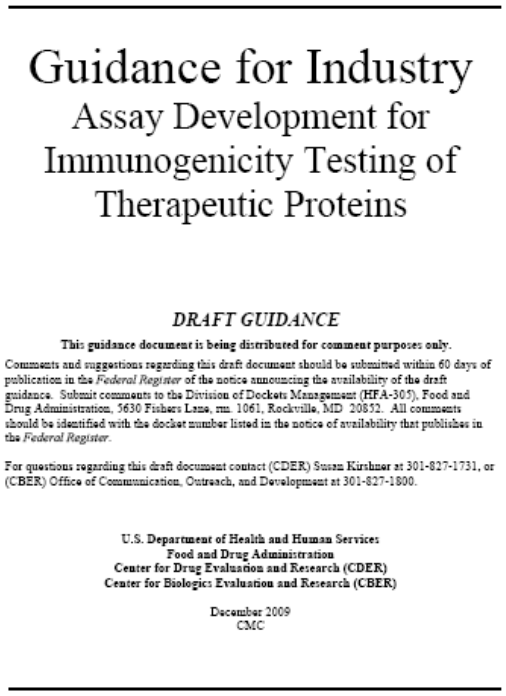
They affect both the efficacy and safety of the product

Result in adverse events which are occasionally life-threatening

Cause administration reactions such as hypersensitivity

Result in reduced efficacy and sometimes a complete lack of a clinical response

The immune response to therapeutic proteins
Why is it important to the FDA?



Guidance for Industry

Assay Development for Immunogenicity Testing of Therapeutic Proteins

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Susan Kirshner at 301-827-1731, or (CBER) Office of Communication, Outreach, and Development at 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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The FDA has been regulating biotechnology-derived protein products since the 1980s

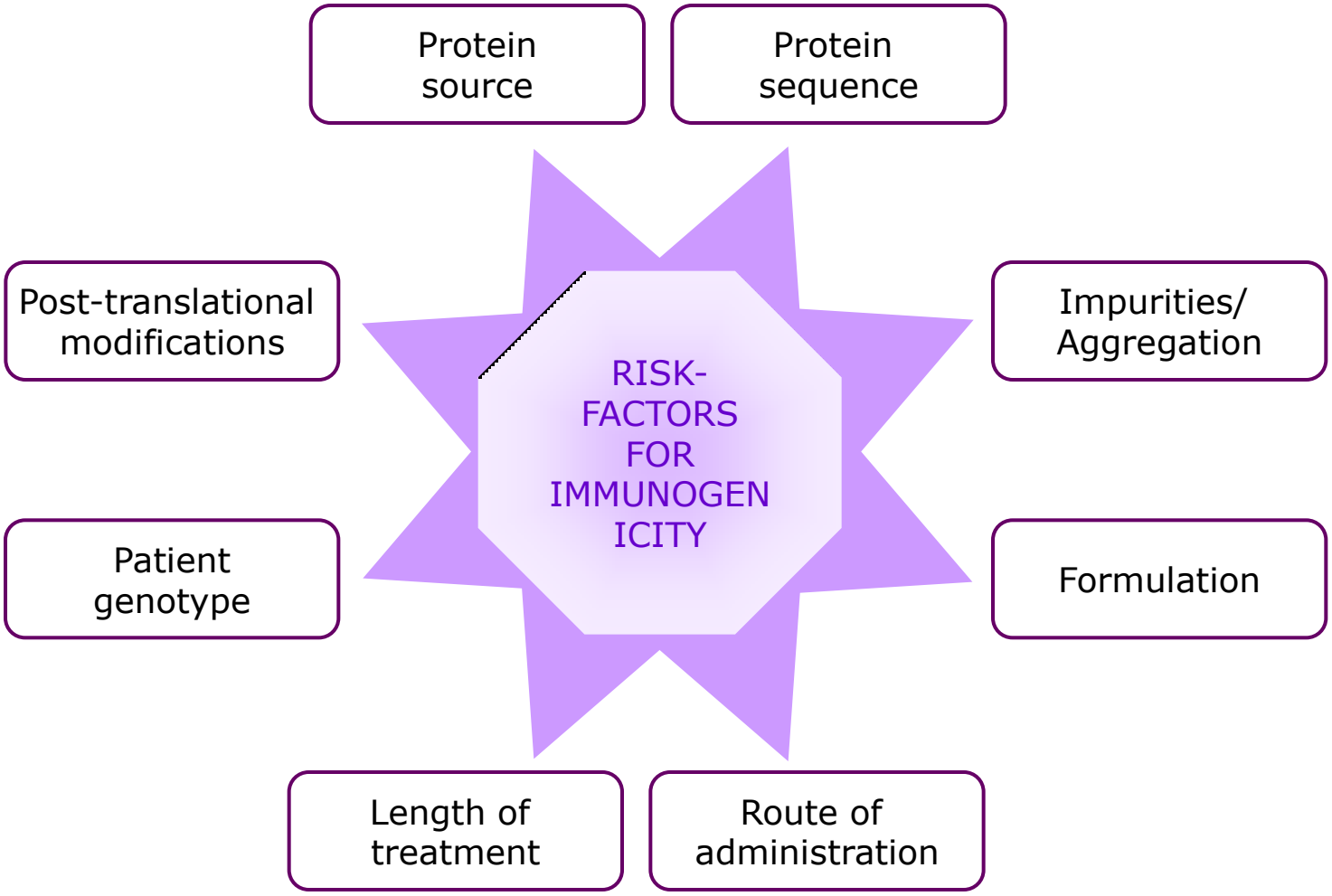
More than 200 biopharmaceutical proteins have now been approved

Widespread use of biopharmaceuticals has demonstrated that nearly all biologicals can elicit antibody responses

Antibodies to therapeutic proteins not only compromise efficacy but also cross-react with endogenous factors to cause serious toxicity

In non-clinical studies, anti-drug antibodies can complicate interpretation of the toxicity, pharmacokinetic and pharmacodynamic data

Immunogenicity is a complex phenomenon



For details see:
Rosenberg, A.S. & Worobec, A. Biopharm. Int. (2004) 17, 34–42

Immunogenicity: Managing risk

The risk of developing anti-drug antibodies cannot be eliminated but it can be managed

There is no prescribed method for risk determination; several variables must be considered to anticipate ADA incidence and ADA-mediated consequences. These variables may be:

- Product specific
- Host specific factors
- Related to the drug manufacturing process

Variables that affect incidence of anti-drug antibodies

Nature of the biological substance
Size and structural complexity
Sequence variation from endogenous protein (e.g. SNPs)
Post-translational & chemical modification (e.g. glycosylation, pegylation).
Conjugates

Nature of the formulated biologic
Formulation and storage conditions
Contaminants and impurities
Exposure of neoepitopes due to denaturation or fragmentation
Aggregates
Adjuvant potential of inactive ingredients

Target disease and population
Patient characteristics such as genetic background or concurrent illnesses
Natural tolerance to protein
Pre-existing immunodeficiency
Use of immunosuppressive drugs or chemotherapy
Concomitant medications (such as immunosuppressants like cyclosporin A)

Treatment regimen
Route of administration
Dose
Frequency of treatment
Length of treatment

Variables that affect the risk of adverse consequences due to anti-drug antibodies

The endogenous protein

Existence of an endogenous protein identical or similar in structure to the biologic.

If endogenous equivalent of the biologic exists, does it provide the sole activity or are there redundant endogenous molecules that can compensate or restore the mechanism of action?

Target disease and patient characteristics

Is the target indication a life-threatening disease?

Does the patient have endogenous protein?

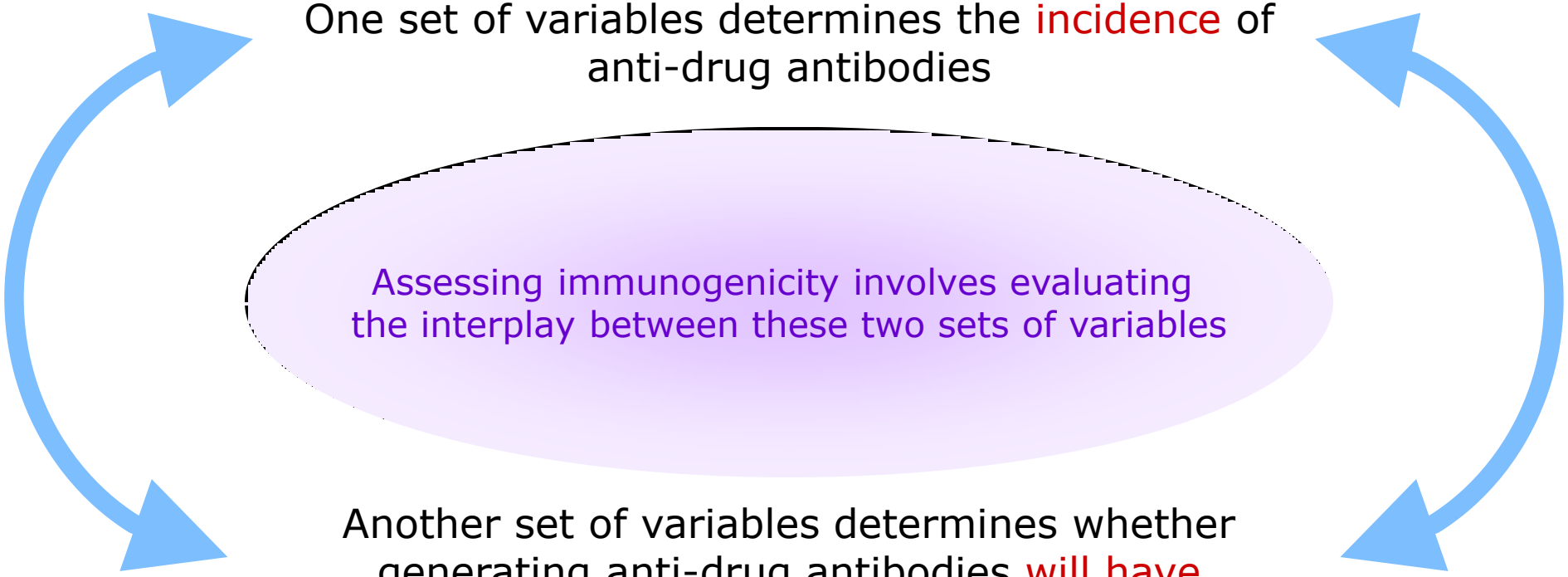
Will the patient be immunosuppressed (owing to pre-existing illness or use of concomitant drugs)?

Treatment

Does the product replace the endogenous version?

Will the product be the sole therapy in the market for that disease?

The development of anti-drug antibodies does not necessarily result in adverse consequences



Evaluating anti-drug antibody responses and what to do with the results

Regulatory authorities in the United States recommend that ADA responses be evaluated:

- U.S. Department of Health and Human Services/Food and Drug Administration. Guidance for industry: premarketing risk assessment, March 2005

FDA recommends that immunogenicity be approached from a safety (risk based) perspective:

- FDA DRAFT Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins
- Rosenberg, A.S. & Worobec, A. A risk-based approach to immunogenicity concerns of therapeutic protein products—Part 1—considering consequences of the immune response to a protein. *Biopharm. Int.* **17**, 22–26 (2004).
- Rosenberg, A.S. & Worobec, A. A risk-based approach to immunogenicity concerns of therapeutic protein products—Part 2—considering host-specific and product-specific factors impacting immunogenicity. *Biopharm. Int.* **17**, 34–42 (2004).
- Rosenberg, A.S. & Worobec, A. A risk-based approach to immunogenicity concerns of therapeutic protein products—Part 3—effects of manufacturing changes in immunogenicity and the utility of animal immunogenicity studies. *Biopharm. Int.* **18**, 32–36 (2005).

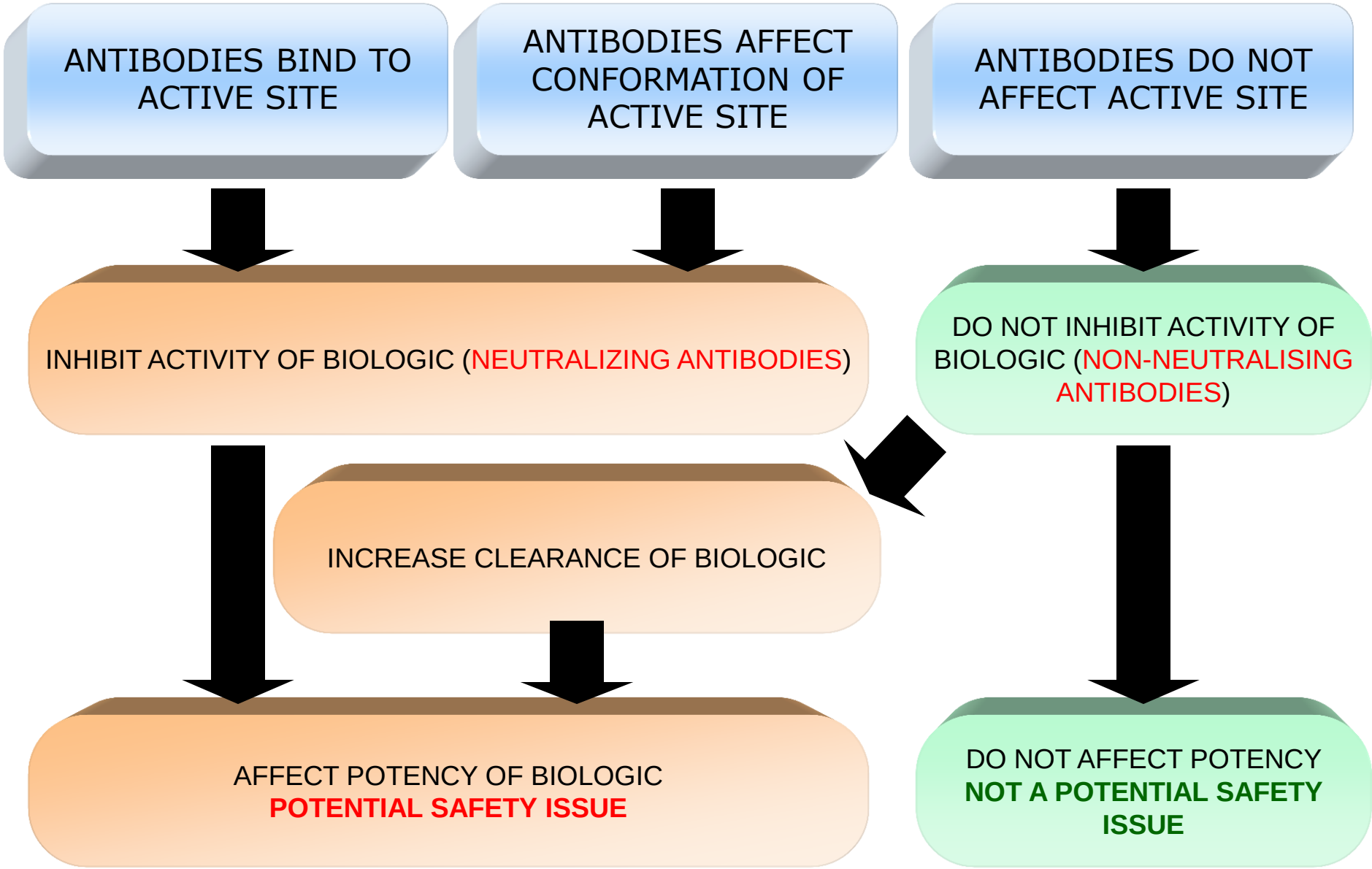
The measurement of anti-drug antibodies

Immunoreactivity assays such as radioimmunoassay, surface plasmon resonance or enzyme-based solid-phase immunoassays, to detect anti-drug antibodies

Functional cell-based bioassays or target binding (receptor recognition) inhibition-based immunoassays for the characterization of the neutralizing antibodies subset of the anti-drug antibodies

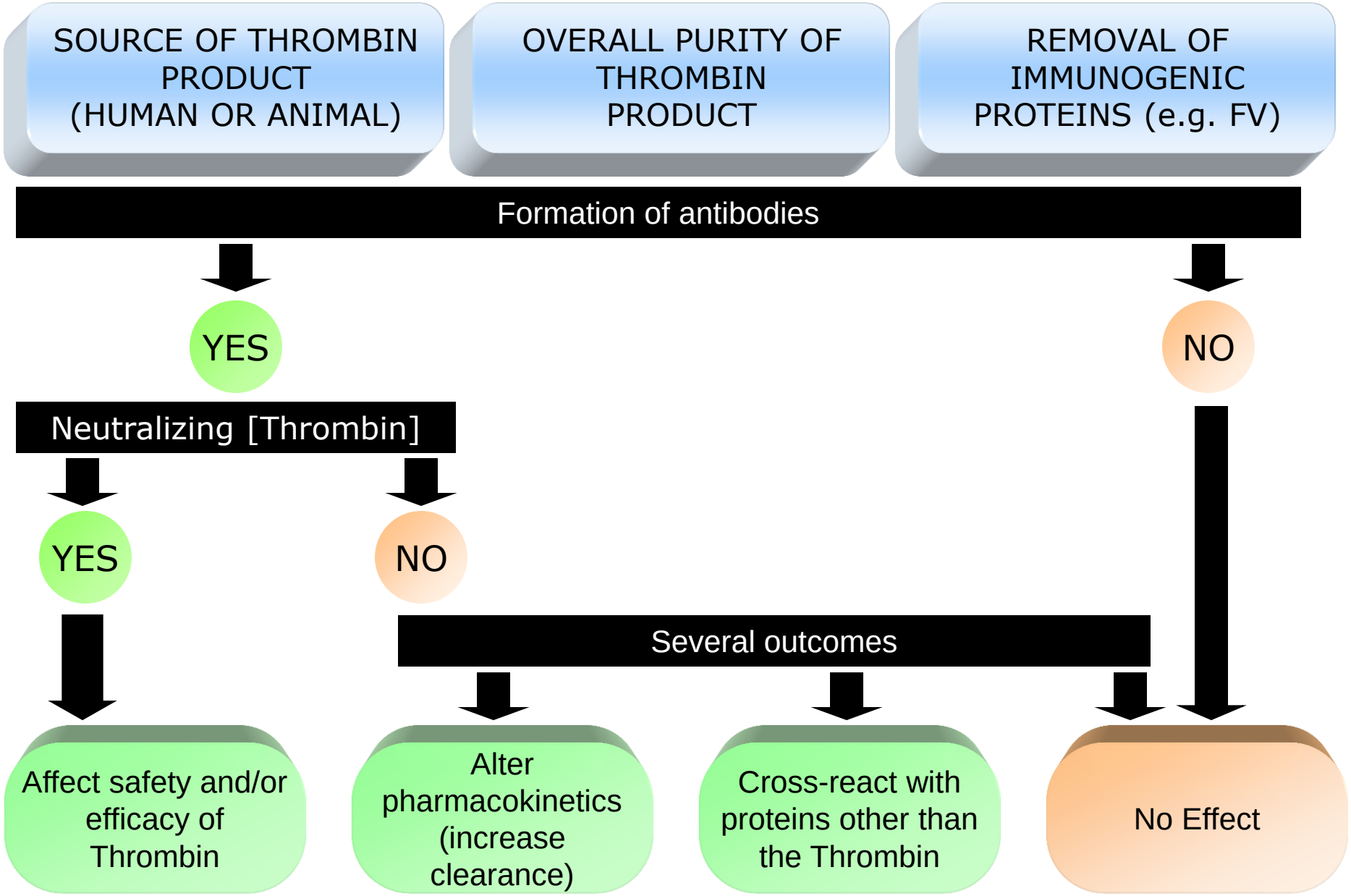
Thes assays when used together allow a determination of whether an anti-drug antibody is a neutralizing antibody

Non-neutralizing antibodies are not necessarily benign

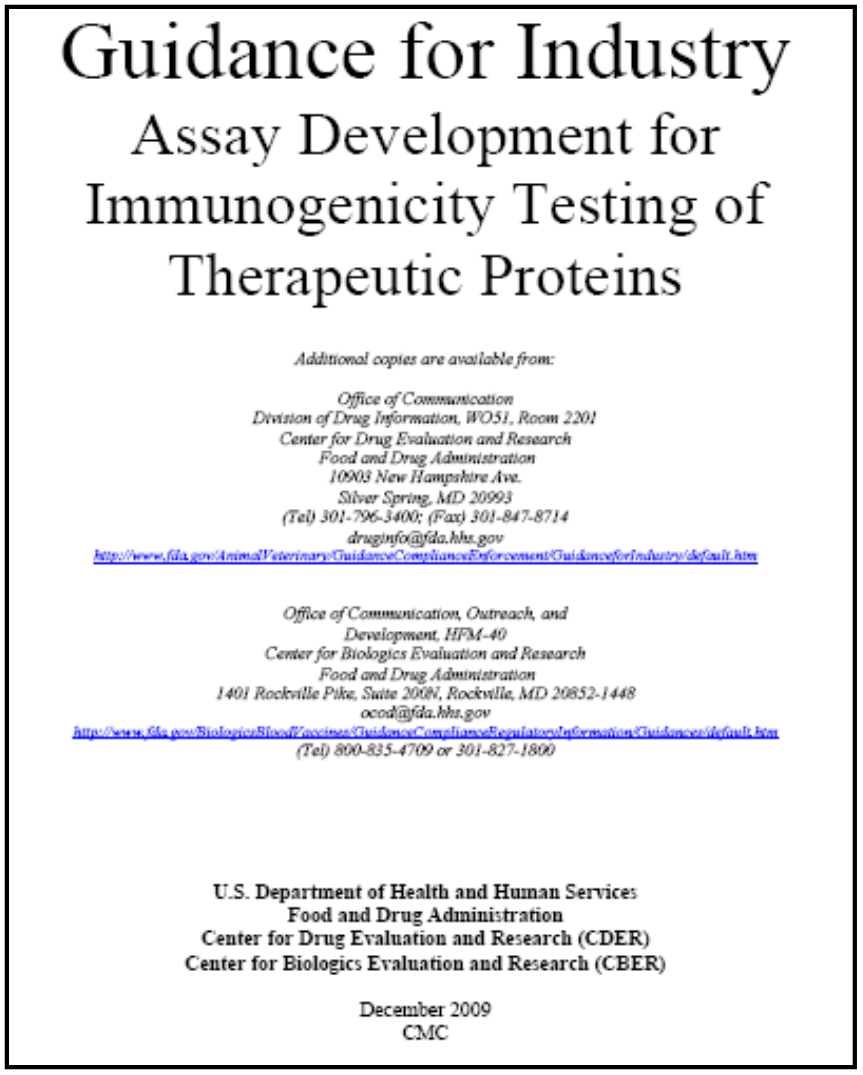


Neutralizing antibodies: The example of thrombin

(For details see: ***Kessler & Ortel Thromb Haemost (2009) 101: 15–24***)



DRAFT Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins



Guidance for Industry

Assay Development for Immunogenicity Testing of Therapeutic Proteins

Additional copies are available from:

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druginfo@fda.hhs.gov
http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

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http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
(Tel) 800-835-4709 or 301-827-1800

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This is a draft document NOT finalized policy

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WEB LINK:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf

DRAFT Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins (contd.)

SCOPE

This guidance provides current considerations to facilitate industry's development of immune assays for assessment of the immunogenicity of therapeutic proteins during clinical trials. This document includes guidance for binding assays, neutralizing assays, and confirmatory assays. While the document does not specifically discuss the development of immune assays for animal studies, the concepts discussed are relevant to the qualification and validation of immune studies for preclinical evaluation of data.

This document does not discuss the product and patient risk factors that may contribute to immune response rates (immunogenicity).

Product life cycle and assay development

- FDA supports an evolving approach to assay development and validation during product development

- when immunogenicity poses a high-risk and real time data concerning patient responses are needed, the applicant should implement preliminary validated assays early (preclinical and phase 1)

- Applicant should bank patient samples so samples can be tested when suitable or improved assays become available

- FDA expects that the assays will be refined during product development

- At the time of license application, the applicant should provide data supporting full validation of the assays

Comparing the immunogenicity of different products

- Even though different companies developing similar products employ fully validated assays to assess immunogenicity, such assays will differ in a number of parameters

- These differences can make immunogenicity comparisons across products in the same class invalid

- A true comparison of immunogenicity across different products in the same class can best be obtained by conducting head-to-head patient trials using a standardized assay that has equivalent sensitivity and specificity for both products

- When such trials are not feasible, FDA recommends the applicant develop assays that are highly optimized for sensitivity, specificity, precision, and robustness

- In the product labeling, FDA does not recommend comparing the incidence of antibody formation between products when different assays are used

Designing an immunogenicity assay

- Sensitivity:

The assays should have sufficient sensitivity to detect clinically relevant levels of antibodies.

- Interference:

Assays results may be affected by interference from the matrix this potential effect should be evaluated.

- Functional or physiological consequences:

Immune responses may have multiple effects including neutralizing activity and ability to induce hypersensitivity responses, among others. Immunogenicity tests should be designed to detect such functional consequences.

- Risk based application:

The risk to patients of mounting an immune response to product will vary with the product.

Continuing immunogenicity assessments post-approval

Often the incidence of anti-drug antibodies and neutralizing antibodies in controlled clinical studies may not reliably reflect that seen during the post-approval stage due to:

- Larger numbers of exposed subjects
- More concomitant medications
- Repeated drug re-exposures
- Reduced patient treatment compliance

The risk assessment & management plan

- A sponsor should prepare a risk assessment and management plan in advance of human clinical trials
- Immunogenicity risk assessment should be decided case by case
- Extent of anti-drug antibody characterization should depend on the potential risk associated with anti-drug antibodies
- Several variables must be considered to anticipate the incidence and consequences of anti-drug antibodies
- There is no prescribed method for risk determination [some basic criteria can however be helpful in classifying therapeutic proteins into distinct safety risk categories]

Classification of therapeutic proteins into risk categories

ORIGIN	In general human or humanized protein therapeutics pose a lower risk than those of non-human origin
TARGET	If the target of the antibody is a non-human protein it poses a lower risk (this is not always true see example of bovine thrombin)
STRUCTURE	If the structure of the protein targeted by inhibitory antibodies is identical or similar to that of an endogenous protein there is a higher safety risk

Immunogenicity & regulatory documents

Review TRENDS in Biotechnology Vol.24 No.6 June 2006

Scientific and regulatory considerations on the immunogenicity of biologics

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[2]Division of Therapeutic Proteins, CDER, FDA, N29A RM2A01 HFM-538, 8800 Rockville Pike, Bethesda, MD 20892, USA
[3]Product Quality and External Affairs, MS 92-2-B, One Amgen Center Drive, Amgen Inc., Thousand Oaks, CA 91320, USA

Explicit or implicit references to immunogenicity can be found in many regulatory documents this reference provides an exhaustive listing of quotes from such documents

Summary

Evaluation of immunogenicity is required for the licensure of almost all biologics

Immunogenicity is a complex phenomenon and a ‘one size fits all’ approach cannot be advocated

FDA advocates a risk-assessment and risk-management approach to immunogenicity during drug development

FDA recognizes that assay development poses challenges to applicants and supports an evolving approach to assay development and validation during product development

Early communication and ongoing interactions with FDA is encouraged

Draft Guidance available for download at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf

Amanda Turner or I can also e-mail you a copy:
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