Advice on Putting Together an Integrated Summary of Immunogenicity

Joint EIP / ABIRISK Scientific Symposium on Immunogenicity of Biopharmaceuticals, Short-course
13th November 2017

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NDA Advisory Board

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AGENDA: Part 2

1. Structure of the Integrated Summary of Immunogenicity
2. Relationship to other parts of the dossier
3. ***Examples: When, what, where & how?***

Intended only to ***exemplify*** for adaptation for specific product

- Intrinsic immunogenicity & systems biology
- Linkage to product Quality Control strategy
- Rationale for extent of evaluation
- Relationship of bioanalytical *vs*. clinical signals

PLEASE ASK QUESTIONS !

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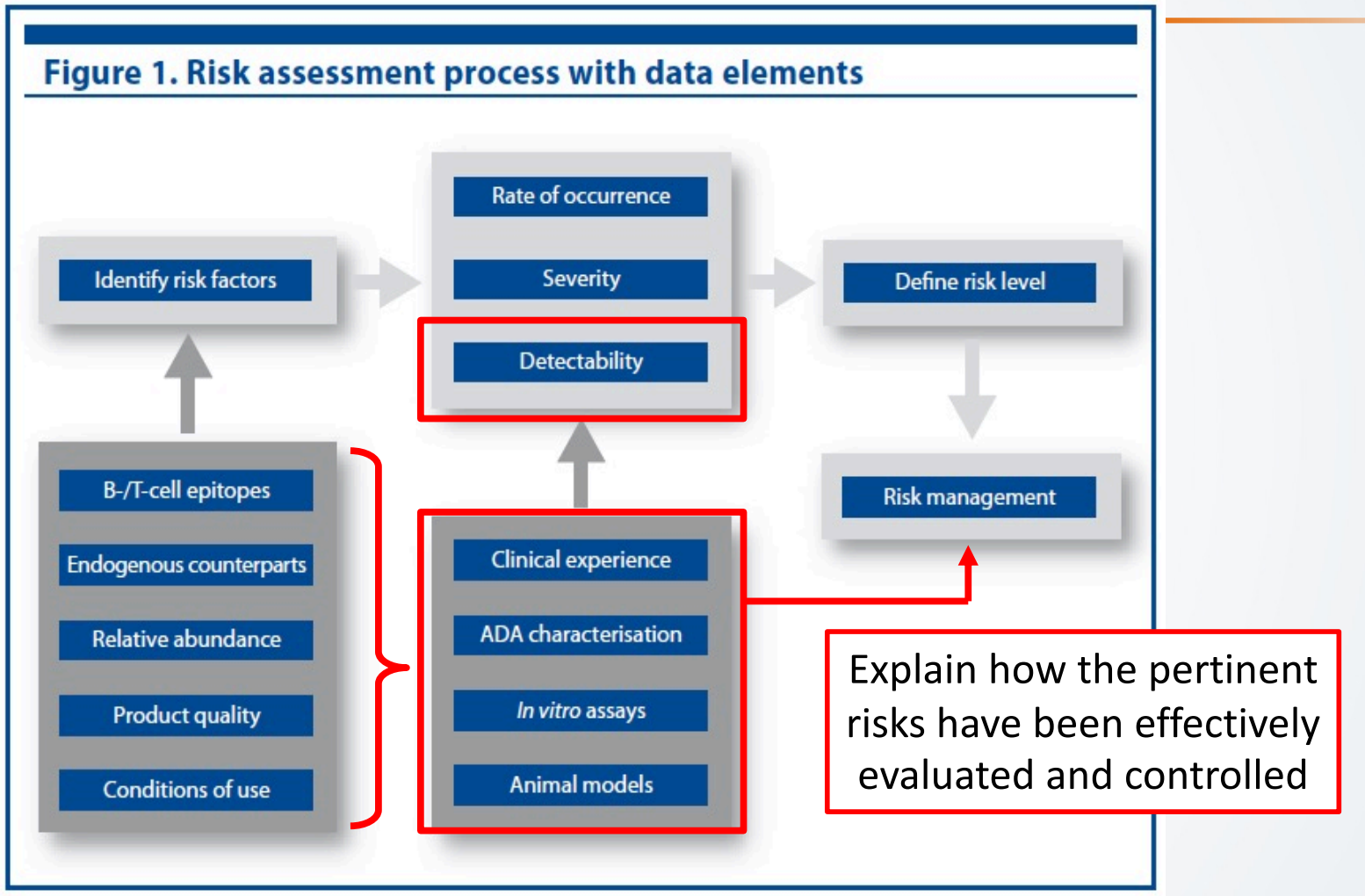
INTRODUCTION

Risk-based approach for immunogenicity assessment



Chamberlain P. Addressing immunogenicity-related risks in an integrated manner. *Regulatory Affairs Pharma*, Jan 2011, 10-15

Question-based approach to Immunogenicity Risk Assessment

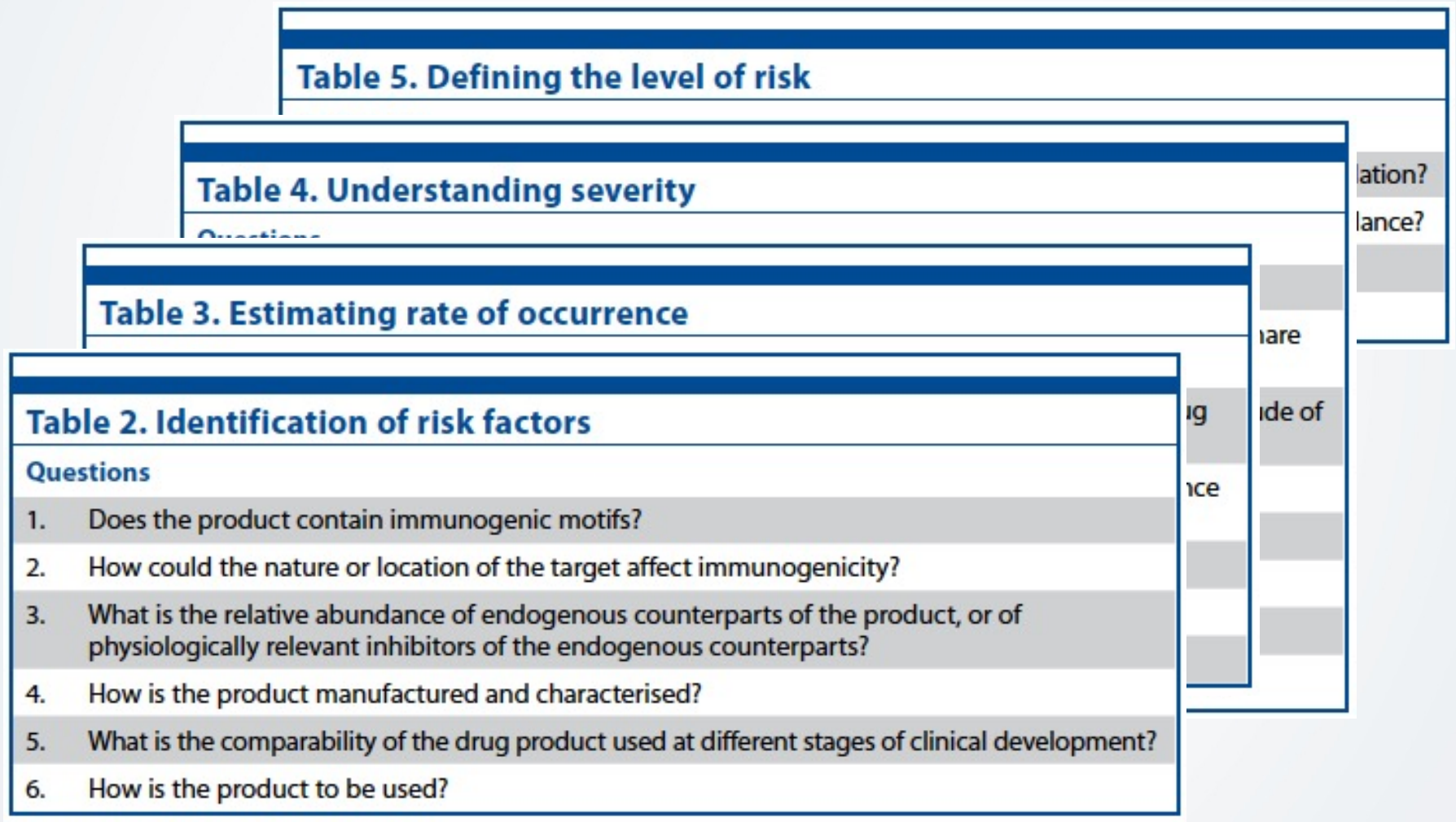


Table 5. Defining the level of risk

Table 4. Understanding severity

Table 3. Estimating rate of occurrence

Table 2. Identification of risk factors

Questions	
1.	Does the product contain immunogenic motifs?
2.	How could the nature or location of the target affect immunogenicity?
3.	What is the relative abundance of endogenous counterparts of the product, or of physiologically relevant inhibitors of the endogenous counterparts?
4.	How is the product manufactured and characterised?
5.	What is the comparability of the drug product used at different stages of clinical development?
6.	How is the product to be used?

Chamberlain P. Addressing immunogenicity-related risks in an integrated manner. *Regulatory Affairs Pharma*, Jan 2011, 10-15

Question-based approach to Immunogenicity Risk Assessment

Chamberlain P. Presenting an immunogenicity risk assessment to regulatory agencies. Chapter 13, p 239-258, in "Immunogenicity of biopharmaceuticals", edited by Marco van de Weert & Eva Horn MØller, Springer 2008

- *What is the structural relationship of the therapeutic protein to endogenous counterparts?*
- *What is the target of the drug product and how unique is its function?*
- *What is the abundance of endogenous counterparts of the drug product?*
- *How is the product manufactured and characterised?*
- *How is the product to be used?*
- *What is the extent of prior exposure to the product or to related products?*
- *What methods have been applied to measure anti-product immune responses?*
- *Are there any observations from non-clinical studies that indicate an impact of immunogenicity on pharmacodynamic markers?*
- *How is potential immunogenicity to be monitored/managed during clinical trials?*
- *What is the estimated probability of a clinical immune response to the product?*
- *What are the possible/likely consequences of a clinical immune response to the product?*
- *What is the overall risk for the target population, in balancing probability vs. consequences of an immune response to the product?*
- *How will this risk be managed?*

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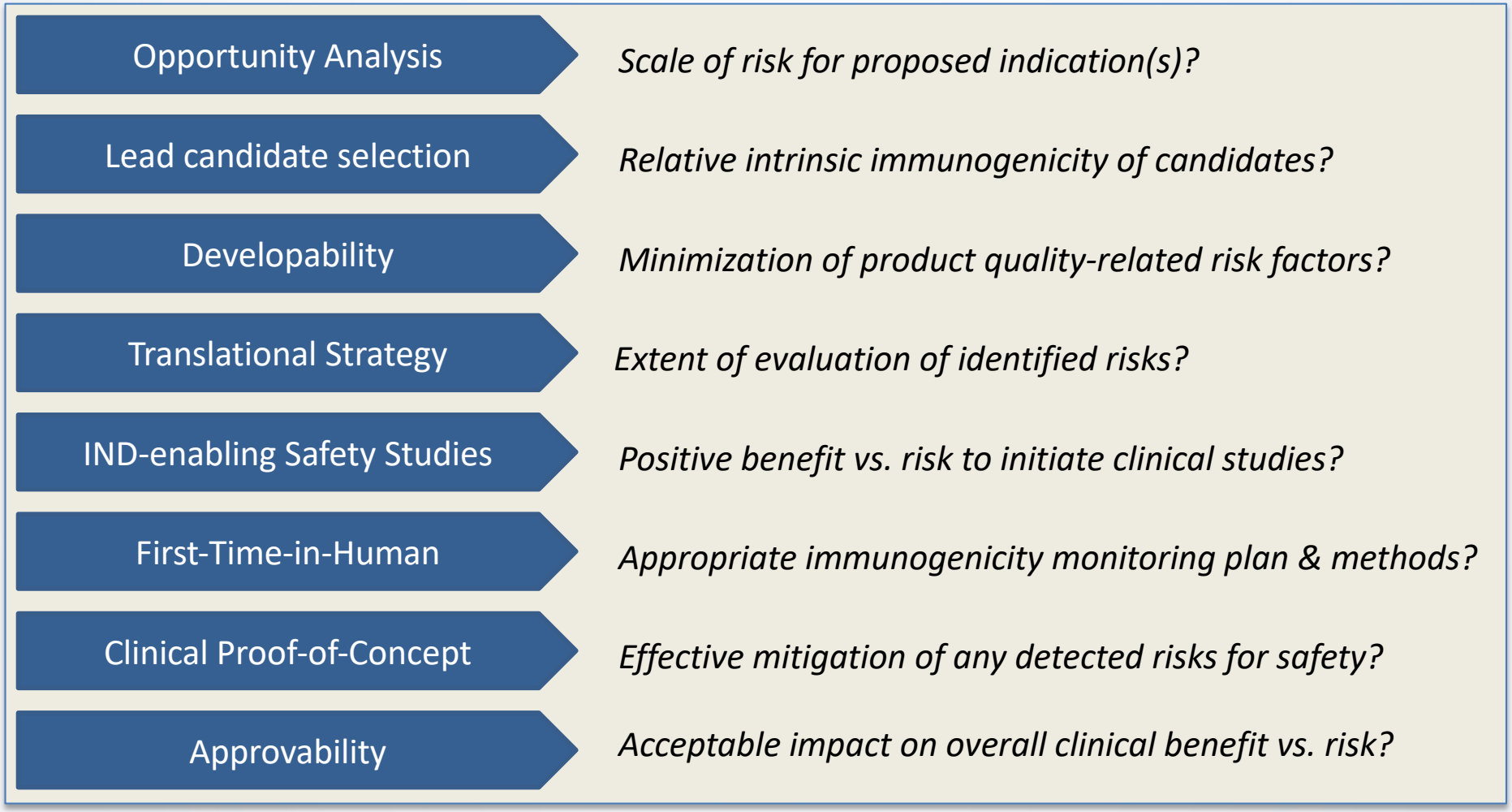
Immunogenicity risk assessment – Stage-gate approach



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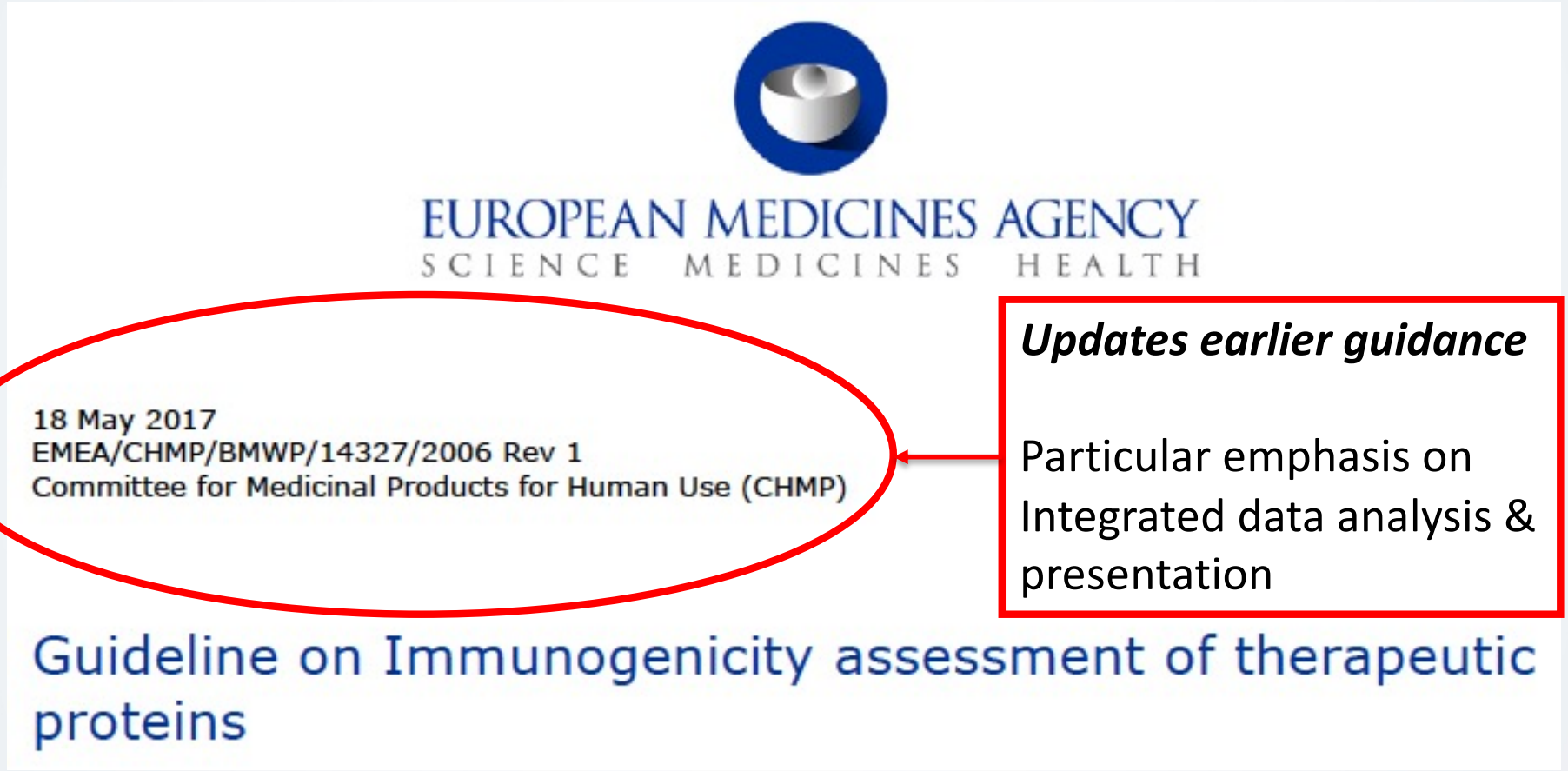
REGULATORY CONTEXT

Adopted revision of main CHMP Immunogenicity Guideline

Effective 01 Dec 2017



Updates earlier guidance

Particular emphasis on Integrated data analysis & presentation

Guideline on Immunogenicity assessment of therapeutic proteins

EMEA/CHMP/BMWP/42832/2005 Rev1, 18th May 2017 (effective 01 Dec 2017)

Section 10 = "Summary of Immunogenicity Program"

*"it is recommended that the applicant will include an **integrated summary of immunogenicity** in the application, including a **risk assessment** to support the selected immunogenicity program. It is recommended that this summary is placed in chapter 2.7.2.4 Special Studies or, if more detailed, in **chapter 5.3.5.3** of the CTD. The summary should be concise and contain links to the appropriate chapters of the application."*

*"This summary with risk assessment can evolve through the lifecycle of the product and may be used to **support applications** at various steps of product development."*

*"The risk assessment may have an **impact on additional characterization** of the immune response (e.g. isotyping and epitope mapping), frequency of sampling, timing of the analysis, and selection of the target population."*

- Integrated Summary of Immunogenicity is not mandatory, but recommended
- Risk assessment evolves through product development / can be used for CTA's
- Chapter 5.3.5.3 enables all relevant data to be presented in single location

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Guideline on Immunogenicity assessment of therapeutic proteins

EMEA/CHMP/BMWP/42832/2005 Rev1, 18th May 2017 (effective 01 Dec 2017)

Analysis of risk factors

1. Previous experience of the product/product class
2. Physicochemical and structural aspects
3. Does the route and/or the mode of administration raise concerns
4. Patient- and disease-related factors

Risk-based program

5. Assay strategy
6. Approach to immunogenicity in clinical trials
7. Impact of the risk assessment on the immunogenicity program

Immunogenicity results

8. Immunogenicity in clinical trials (relative immunogenicity in case of manufacturing changes and biosimilars)

Conclusions on the risk(s) of immunogenicity

9. Impact of the immunogenicity on the benefit/risk
10. Tools to manage the risk

Suggested minimum content, to be adapted according to product; *not* a mandatory format

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RELATIONSHIP TO OTHER PARTS OF THE DOSSIER

Relationship to other parts of MAA/BLA dossier

Module 5.3.5.3

Integrated Summary of Immunogenicity

➔ Risk Assessment

➔ Control of CMC variables

➔ ADA detection methodology

➔ Results from clinical evaluation

➔ Conclusions: Impact & Risk Management Plan

Module 1.8.2

Risk Management Plan

Module 2.7.1

Focus on PK assay methodology

Modules 2.7.3 & 2.7.4

Impact on overall clinical efficacy & safety

Module 5.3.1.4

Bioanalytical method validation reports

Modules 5.3.3 & 5.3.5

Clinical Study Reports, with raw ADA data from ADA testing

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ISI FORMAT

Organisation of ISI

There is no standard format

Principle = Tell the whole story, starting at the beginning…

- The beginning is the intrinsic immunogenic potential of the target molecule, *HOW* this might be modified by extrinsic factors and *WHAT* control measures have been applied to mitigate risks associated with these extrinsic factors
- Then, explain *HOW* the bioanalytical testing & clinical evaluation strategies have been aligned to the potential risks for the target population(s)
- Complete the story by summarising the evidence relative to the uncertainty about impact of undesirable immunogenicity on overall clinical benefit *vs*. risk

Objective of “integrated” summary is to provide a single source of the relevant information

4 main sections of ISI model

Introduction: Risk analysis	• Intrinsic immunogenic potential
	• Extrinsic factors:
	  • Product quality
	  • Patient / disease-related
	  • Conditions of use
		What are the risks?

Methodology for risk evaluation	• Bioanalytical methods (ADA & PK) • Clinical study design & data analysis • Relevance of non-clinical studies	*Detectability?*
Results	• ADA / nAb signal profiles • Impact on PK • Impact on PD/efficacy • Immune-mediated AE's (By study & overall)	*Probability & consequences?*
Conclusions	• Impact on overall clinical benefit & risk • Linkage to Risk Management Plan	*Effective risk mitigation?*

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SECTION 1 = INTRODUCTION

Introduction:
Risk analysis
	• Intrinsic immunogenic potential
	• Extrinsic factors:
	  • Product quality
	  • Patient / disease-related
	  • Conditions of use
		What are the risks?

Introduction (Risk analysis)

Why is this molecule potentially immunogenic?	• Intrinsic T- / B-cell epitopes
What extrinsic factors could modify potential immunogenicity?	• Immune tolerance / competence • Danger signals • Nature of target / mode of action • Manufacturing conditions • Physicochemical stability
How does the above impact on strategy for evaluating and mitigating risk for intended clinical populations?	• Molecular design • Choice of expression system • Formulation / presentation • Product Quality Control • Clinical study design / dose regimen • Bioanalytical strategy • Relevant non-clinical investigation

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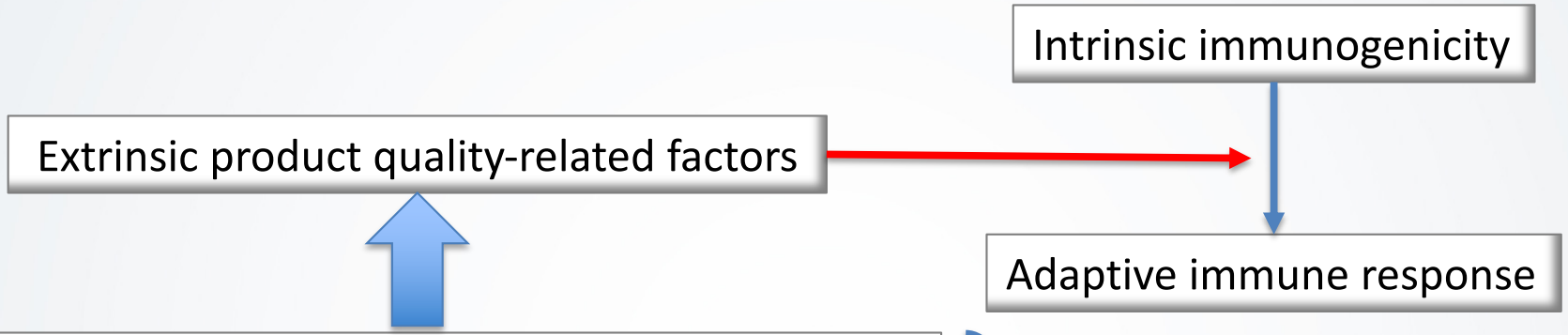
Linkage to CMC



- Expression system?
  - N-terminal modifications?
- Monomer stability?
  - Suitability of formulation?
  - Drug product at physiological pH / temp?
- Sub-visible particles?
- Truncated sequence?
- Conformational variants?
- Host cell-derived proteins?
- Non-human glycans?
- Leachates?
- Tungsten residuals in PFS?

Provide summary of control strategy for all of these factors & comment on comparability at different stages of clinical development

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CMC items to include for a *Pichia*-derived therapeutic protein

2.4 Product quality

2.4.1 Identification of risk factors for Product XXX

- Process-derived impurities (*Pichia* HCP & beta glucans, yeast extract-derived factors)
- Product-related variants:
  - Free cysteine
  - Dimer content
  - Sub-visible particles (DLS, MFI)
  - Visible particles
  - Batch-to-batch variability of α-1,2-linked mannose
- Formulation-primary container combination

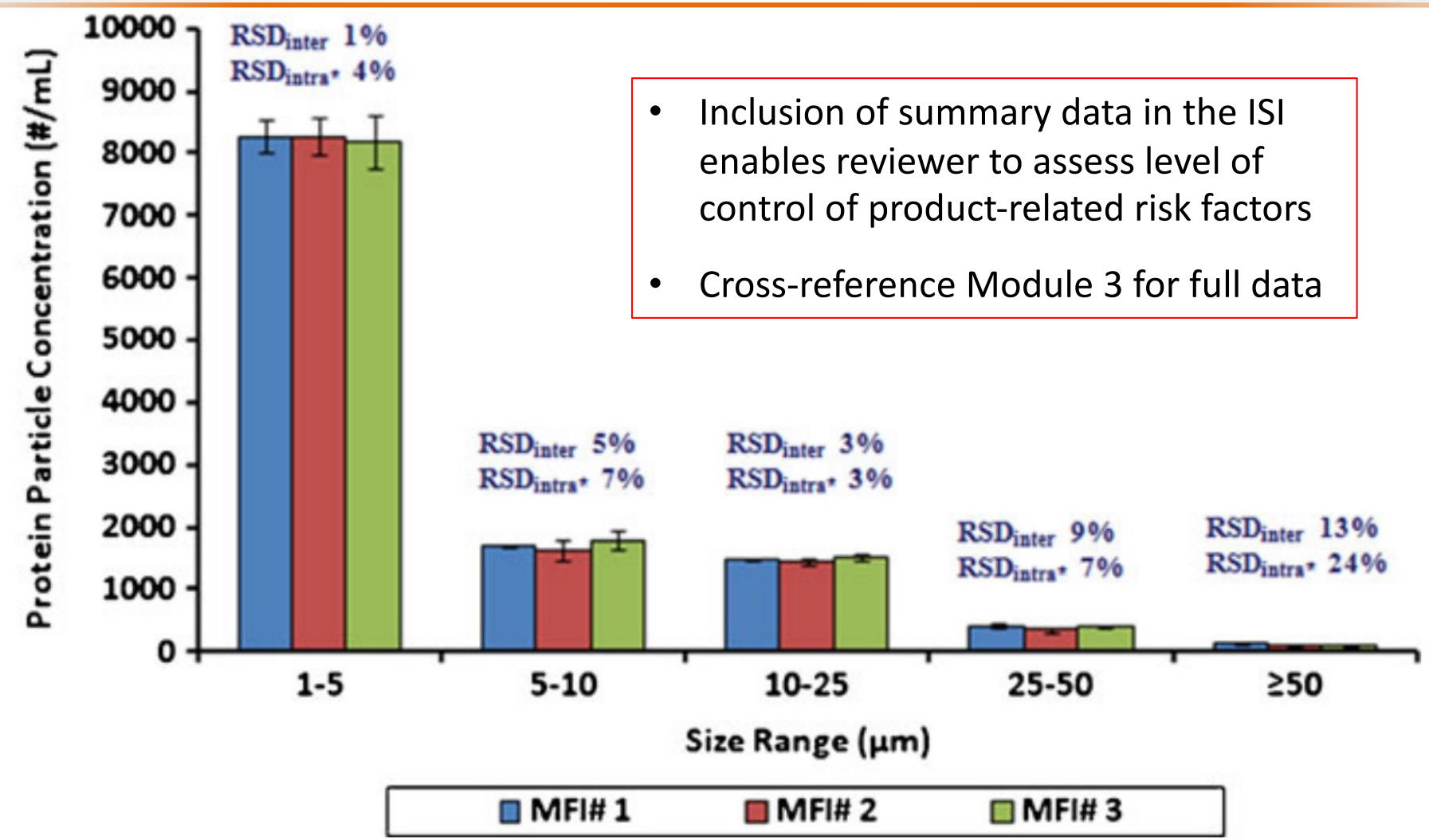
2.4.2 Evaluation results

- DSP clearance of process-related impurities
- DS & DP batch testing data
- Extended analytical characterisation
- DP stability testing (including thermal & agitation stress, and in-use stability)
- Comparability of clinical trials *vs*. commercial DS/DP
- Analytical method suitability

2.4.3 Conclusion

Justification for effective mitigation of risks via manufacturing process control and product specifications, product storage and handling, and exclusion of incremental risks for commercial material compared to product evaluated in clinical studies.

Sub-visible particle analysis



- Inclusion of summary data in the ISI enables reviewer to assess level of control of product-related risk factors
- Cross-reference Module 3 for full data

Sharma DK et al: The AAPS Journal, Vol. 12, No. 3, September 2010

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SECTION 2 = METHODOLOGY

Methodology for risk evaluation	• Bioanalytical methods (ADA & PK) • Clinical study design & data analysis • Relevance of non-clinical studies	*Detectability?*

Bioanalytical methodology: ***How?***

- Schematic diagram of assay format
- Tabular summary of validated performance characteristics
- Impact of methodological changes
  - Include tabular summary of changes *vs*. clinical studies
- Critical control reagents
- Minimum Required Dilution
- Specificity & Selectivity
- Relative sensitivity, including drug and matrix interference
- Statistical methods used to calculate assay cut-points
  - Include tabular summary of screening and confirmatory assay cut-points by clinical study

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Linking assay documentation in ISI to CSR's

Table X: Linkage of Bioanalytical Method Documents to Clinical Studies / CSR's for Product X

Clinical Study #	Phase / Objective	Clinical Study Report #	Screening assay SOP #	NAb assay SOP #
CT-01	1	*XXX*	*YYY*	*ZZZ*
CT-02	2a			
CT-03	2b			
CT-04	2b			
CT-05	3			
CT-06	3			

Use as navigational guide in CTD module 2.7.2.4 - ISI

Explicit linkage of method description to the results of the sample analyses reported in the respective CSR's

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Illustrating evolution of method / controls

Table X: Impact of changes in SOP for homogeneous bridging format used for screening, confirmatory & titer anti-drug antibody assays

Document No. / Date	Applicable clinical studies	Impact
SOP-XXX-v1 Aug 2008	CT-01	Baseline for clinical development of Product X Fixed screening assay cut-point = 112 ECL units Sensitivity in undiluted serum = 125 ng/ml
SOP-XXX-v2 Jan 2009	CT-02	*Change in antigen labelling procedure to increase sensitivity* Fixed cut-point remained at 128 ECL units CPM Sensitivity in undiluted serum = 75 ng/ml
SOP-XXX-v3 Oct 2011	CT-03 & CT-04	*Change from Fixed to Floating Assay Cut Point* *Reduced Low QC from 150 to 100 ng/ml* Negligible impact on assay sensitivity
SOP-XXX-v4 Jan 2012	CT-05 & CT-06	*Reduced dilution factor for titration stage to increase accuracy of titer estimate* No impact on sensitivity to detect positive samples in screening assay

Provides explicit linkage between methodology *vs*. stage of clinical development

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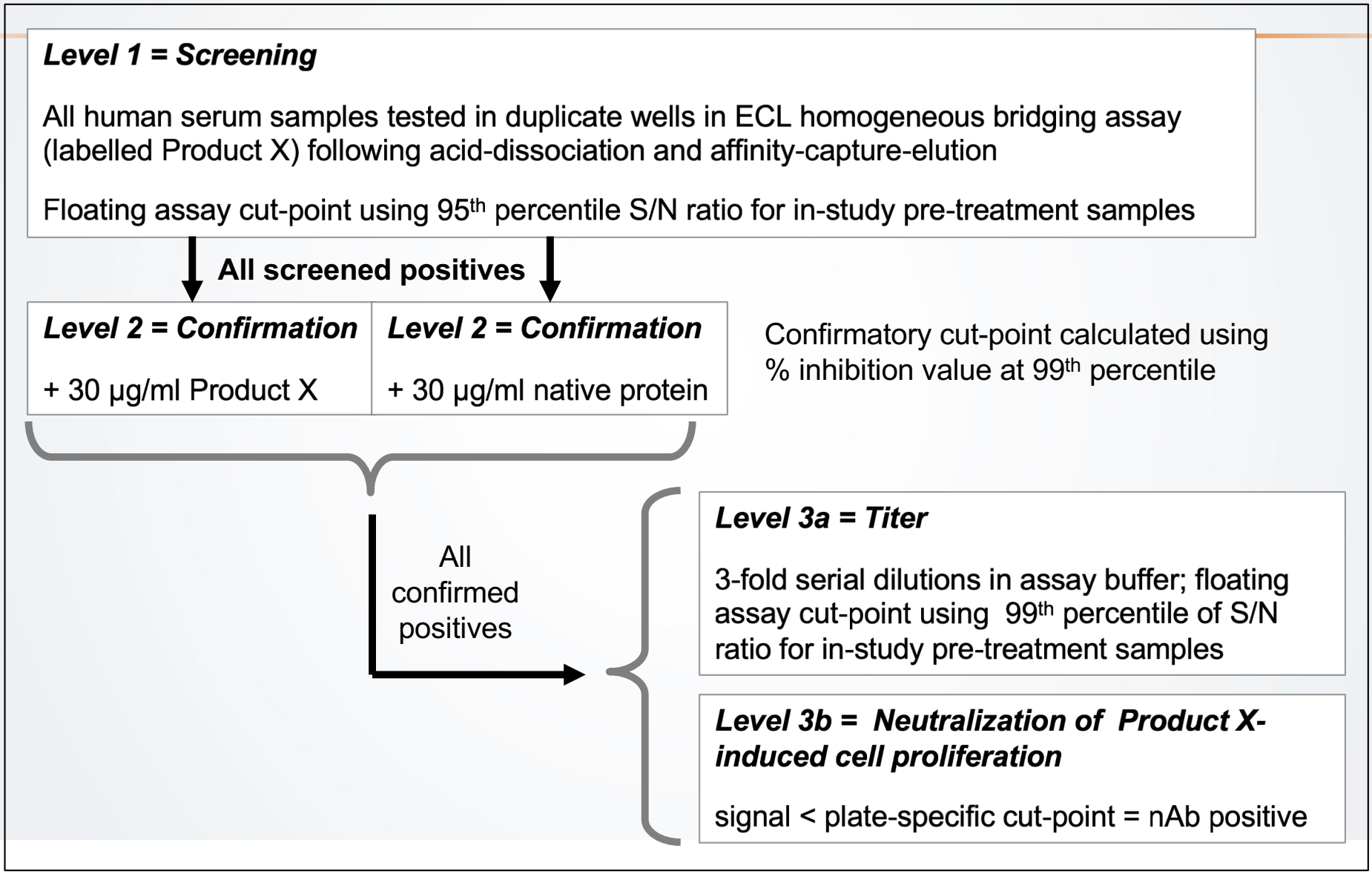
Hierarchical test scheme



ADA assay: Tabular summary

Assay format	
Plate coating	
Assay & Blocking buffer	
Wash buffer	
Labelled antigens	
Test matrix	
Sample pre-treatment, e.g. acid-dissociation, affinity capture	
Sample volume	
Dilution of test matrix (MRD)	
Positive control description	
LOD for positive control	
QC concentrations	
Threshold for drug interference at LPC	
Negative Control matrix	
Screening assay cut-point factor for clinical sample analysis	
Confirmatory assay cut-point (+ 30 μg XXX/ml)	
Titer assay cut-point factor	
Selectivity / Matrix interference	
Validation Report No.	

Aim is to consolidate information from the Method Validation Reports in a single location

Specificity & Selectivity

It is a regulatory requirement to:

- Validate the specificity & selectivity of anti-drug antibody assays to detect pre-existing and treatment-emergent antibodies to *all* components of the drug product;
- Determine the specificity of signals detected in clinical samples

- Endogenous molecules with cross-reactive potential
- Each component of fusion protein or conjugate & linker
- Non-human glycans / glycosidic linkages
- Non-native product conformer
- Process-related impurities, e.g. *E.coli*-derived HCP
- Soluble target ligand
- Other, e.g. Rheumatoid Factor or heterophilic Abs

Demonstration of signal inhibition by solution-phase competing antigen is the most effective way to confirm signal specificity

Advisable to present sufficient data, ***as relevant for the product***, in the assay validation & CSR's to confirm specificity of the signals detected

Assay cut-points

- Explain how these were calculated for *each* clinical study:
  - Population used (healthy *vs*. disease matrix)
  - Outlier exclusion
  - Pre-study *vs*. in-study
  - Fixed *vs*. floating
  - 95th *vs.* 99th percentile
- Indicate % false positive rate for pre- and post-treatment samples
  - Provides index of accuracy for test matrix

Critical reagents

Use ISI narrative to explain rationale for bioanalytical strategy

- Choice of assay format
- Qualification of critical reagents
- Signal-to-noise ratio *vs.* sample dilution
- Matrix interference
- Drug tolerance
- Need for sample pre-treatment?
- Selection of QC levels

- Negative Control matrix
- Positive Control antibodies
- Labelled antigens
- Ligands for cross-reactivity testing

Minimum Required Dilution

100 % Serum							
Verdünnung	c [ng/mL]	RLU 1	RLU 2	Mean RLU	SD	% CV	S/B
S1	100	2277	2183	2230	66	3.0	25.8
S2	50	1187	1158	1173	21	1.7	13.6
S3	25	662	675	669	9	1.4	7.7
S4	12.5	376	375	376	1	0.2	4.3
S5	6.25	249	235	242	10	4.1	2.8
S6	3.125	185	183	184	1	0.8	2.1
S7	1.5625	141	137	139	3	2.0	1.6
S8	0	88	85	87	2	2.5	1.0
HPC	750 ng/ml	10602	10883	10743	199	1.8	

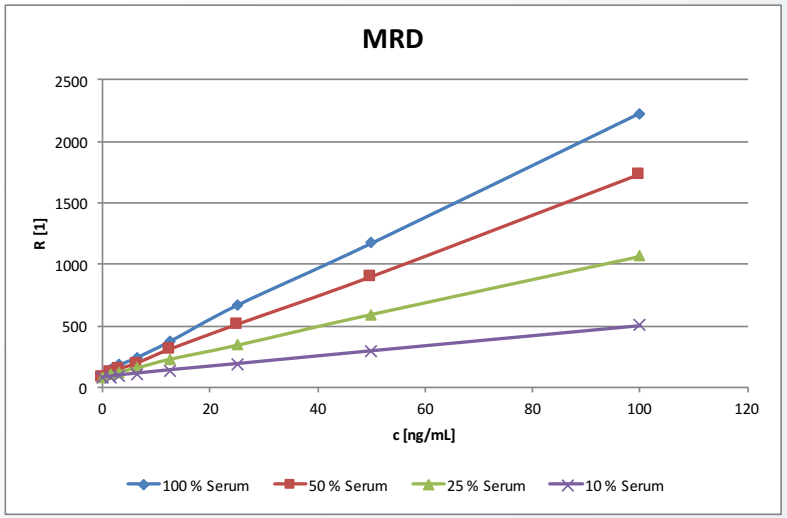
50 % Serum							
Verdünnung	c [ng/mL]	RLU 1	RLU 2	Mean RLU	SD	% CV	S/B
S1	100	1790	1670	1730	85	4.9	20.0
S2	50	886	907	897	15	1.7	10.4
S3	25	499	517	508	13	2.5	5.9
S4	12.5	299	314	307	11	3.5	3.5
S5	6.25	194	191	193	2	1.1	2.2
S6	3.125	150	145	148	4	2.4	1.7
S7	1.5625	120	115	118	4	3.0	1.4
S8	0	81	80	81	1	0.9	0.9

25 % Serum							
Verdünnung	c [ng/mL]	RLU 1	RLU 2	Mean RLU	SD	% CV	S/B
S1	100	1057	1083	1070	18	1.7	12.4
S2	50	589	599	594	7	1.2	6.9
S3	25	351	332	342	13	3.9	3.9
S4	12.5	230	223	227	5	2.2	2.6
S5	6.25	152	158	155	4	2.7	1.8
S6	3.125	124	125	125	1	0.6	1.4
S7	1.5625	104	106	105	1	1.3	1.2
S8	0	79	86	83	5	6.0	1.0

10 % Serum							
Verdünnung	c [ng/mL]	RLU 1	RLU 2	Mean RLU	SD	% CV	S/B
S1	100	507	506	507	1	0.1	5.9
S2	50	297	296	297	1	0.2	3.4
S3	25	191	188	190	2	1.1	2.2
S4	12.5	138	138	138	0	0.0	1.6
S5	6.25	110	109	110	1	0.6	1.3
S6	3.125	94	96	95	1	1.5	1.1
S7	1.5625	84	86	85	1	1.7	1.0
S8	0	78	79	79	1	0.9	0.9

Compare signal-to-noise ratio at increasing serum matrix dilution

Select dilution that yields optimal S/N vs. sensitivity



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Reporting ADA titers

- *"The MRD should be factored in the calculation of titers and provided when reporting titers"*
  - FDA draft April 2016
- *"Titer is defined as the reciprocal of the highest dilution of the sample (including MRD) that yields a positive result.."*
  - Shankar et al 2014
- *"During bioanalysis, confirmed positive patient samples that fall between the screening cut-point and titration cut-point can be assigned a titer value equal to that of the MRD."*
  - USP 1106

FDA is requesting Companies to re-calculate reported ADA titer to include MRD

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Assessment & reporting of the clinical immunogenicity of therapeutic Proteins & Peptides – harmonized terminology and tactical recommendations

Shankar G, Arkin A, Cocea L, Devanarayan V, Kirshner A, Kromminga A, Quarmby V, Richards S, Schneider CK, Subramanyman M, Swanson S, Verthelyi D & Yim S

AAPS Journal 2014

Encourages application of:

- Consistent terminology
- Integrated approach to testing and data interpretation / presentation

Improved understanding of:

- ADA incidence, magnitude, onset, duration & neutralizing capacity
- Cross-reactivity with endogenous molecules / other products
- Clinically relevant thresholds

Acknowledges that:

"*determinations of clinically relevant ADA thresholds may be unnecessary until after completion of the pivotal studies supporting registration*"

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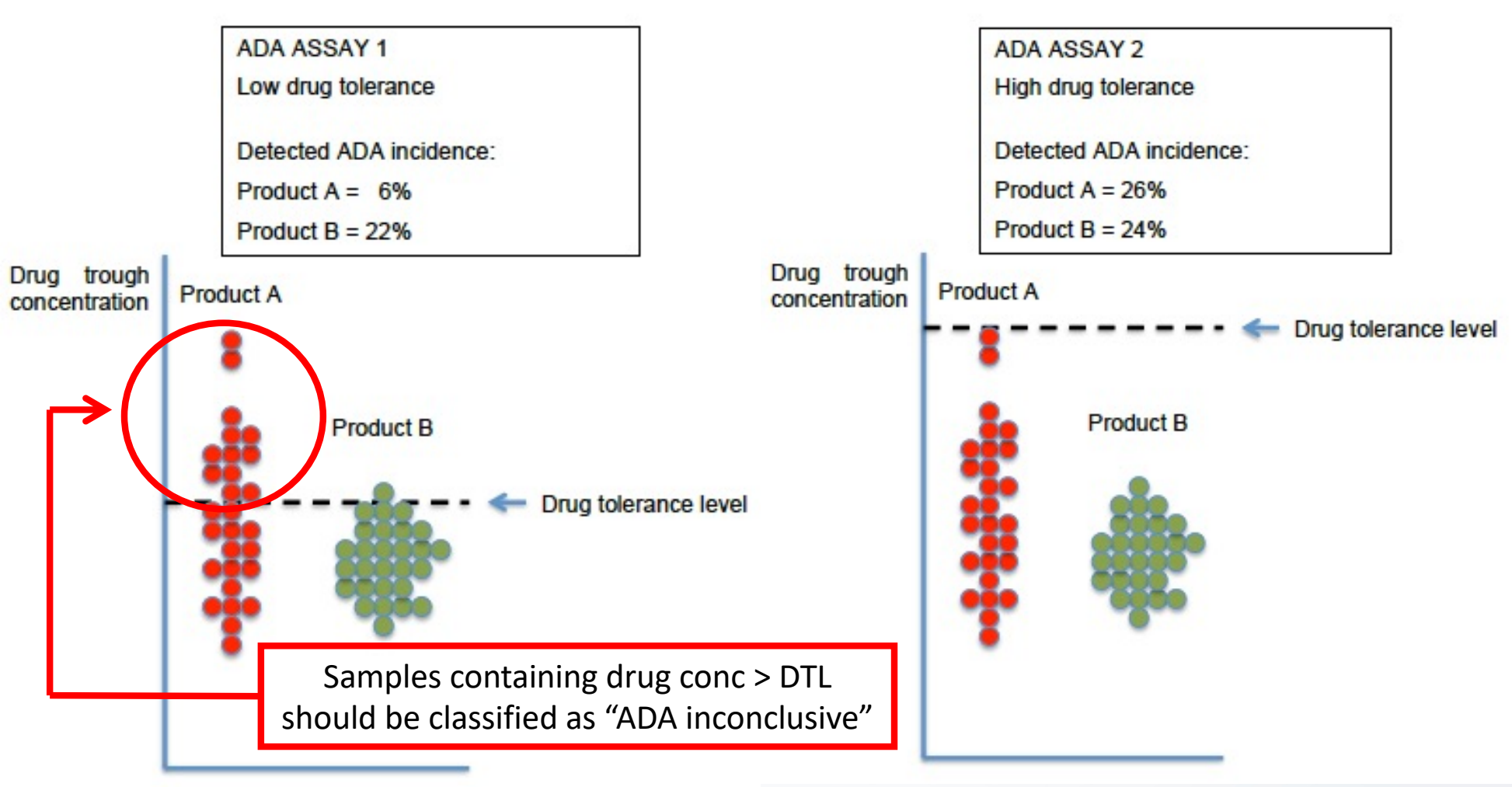
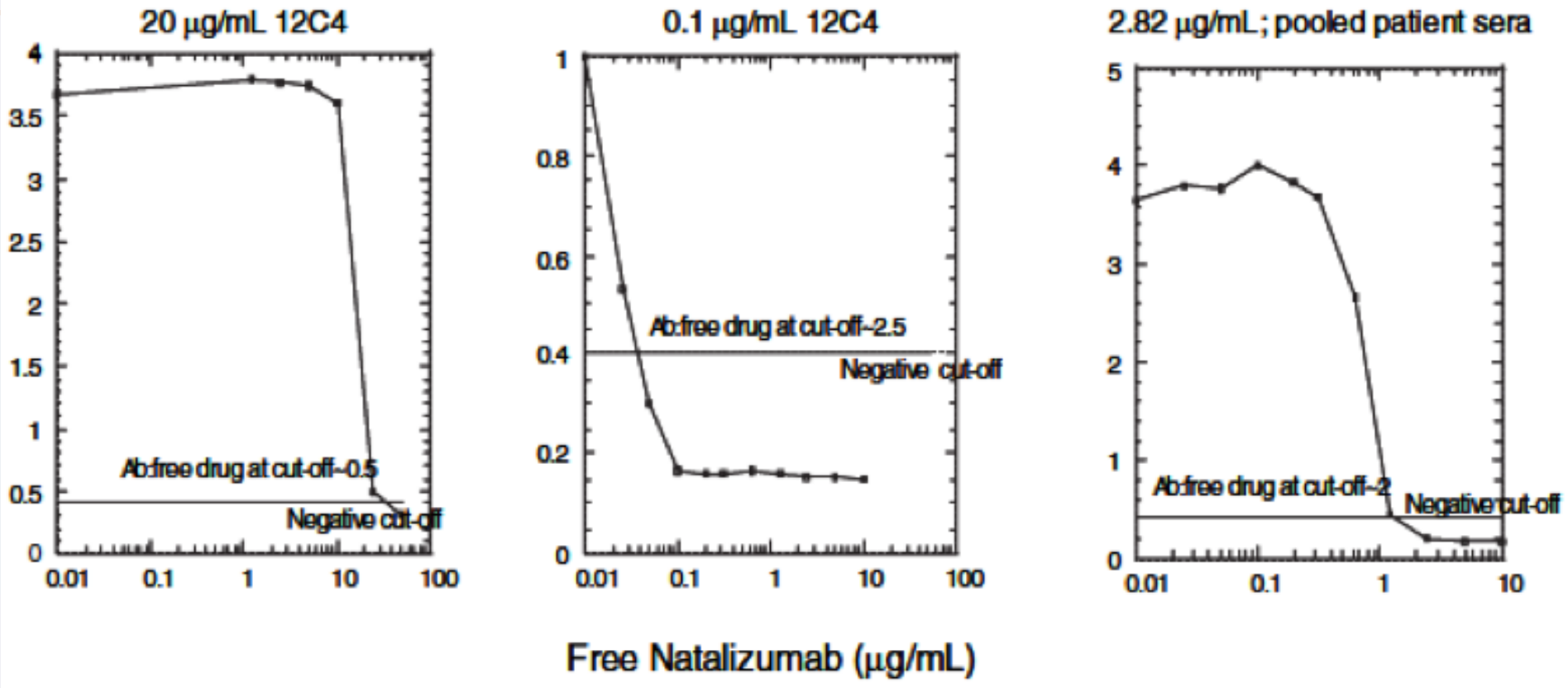
Results of comparative immunogenicity evaluation depend on drug concentration relative to drug tolerance level of ADA assay



Need critical analysis of potential impact of residual drug levels

Drug tolerance

Subramanyam M, 2008. Case Study: Immunogenicity of natalizumab; Chapter 10, p 173-187, in "*Immunogenicity of Biopharmaceuticals*", Ed. van de Weert & Moller, Springer.



Drug interference occurred when drug concentration was approximately two-fold above the anti-natalizumab antibody concentration

SECTION 3 = RESULTS

Results	• ADA / nAb signal profiles • Impact on PK • Impact on PD/efficacy • Immune-mediated AE's	*Probability & consequences?*

Relevant parameters

BIOANALYTICAL PARAMETERS

Humoral immune response

ADA
Incidence & Titer
Neutralizing capacity
Time-course of formation

Specificity:
Biosimilar *vs*. Reference
Process-related impurities

Pre-existing *vs*. post-treatment

IgE ADA only if suspected Type I hypersensitivity ADRs

CLINICAL PARAMETERS

Cmax, T½, drug trough concentration	PK
Biomarkers of response	PD
1° & 2° clinical endpoints	Efficacy
Timing & severity of immune-mediated AE's	Safety

Example of format for clinical results

Overview of clinical studies performed

Tabular summary / Figure to orient the reviewer

Summary by study#

- Diagram of study design & ADA & drug conc. sample time-points
- Drug product batches / presentations used
- Sample handling / missing samples
- Concomitant immune-suppressive medications
- ADA & nAb assay results
- ADA *vs*. PK / drug levels
- ADA / nAb *vs*. efficacy
- Immune-mediated TEAE's
- Conclusions

In order of weight of evidence, i.e. starting with pivotal clinical studies

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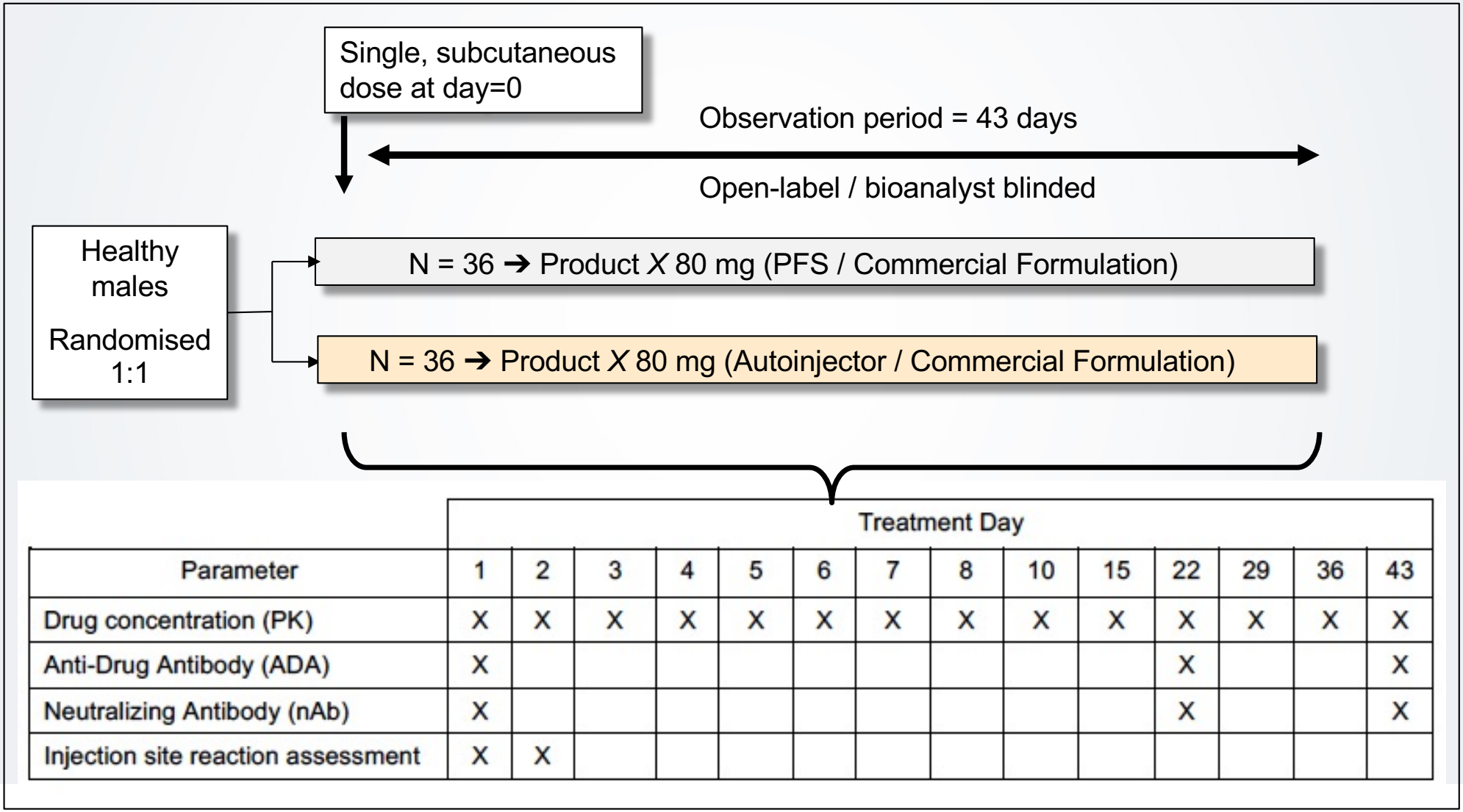
Illustrate study design with sampling time-points



	Treatment Day													
Parameter	1	2	3	4	5	6	7	8	10	15	22	29	36	43
Drug concentration (PK)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Drug Antibody (ADA)	X										X			X
Neutralizing Antibody (nAb)	X										X			X
Injection site reaction assessment	X	X												

ADA assay data granularity

ITEM
Patient ID/Code
Assay run no.
Assay run date
Age
Gender
Treatment Group
Sampling Time Point
Corresponding Low QC value in screening assay (RLU)
Corresponding High QC value in screening assay (RLU)
Corresponding Negative control value in screening assay (RLU)
Plate-specific screening assay cut-point
Screening assay result (RLU)
Screening assay assignment: Positive / Negative
Low QC value in confirmatory assay (RLU)
High QC value in confirmatory assay (RLU)
Negative control value in confirmatory assay (RLU)
Confirmatory assay result (RLU)
Percent inhibition in the confirmatory assay
Confirmatory assay assignment: Positive / Negative
Titer of confirmed positive samples
Concentration of on-board drug at time of sampling

Include sufficient data granularity to enable reviewer to perform an independent analysis

Ideally in Excel spreadsheet format

Appendix to:

- CSR *or*
- Sample analysis report *or*
- ISI

Request CRO to provide these outputs in Excel format following unblinding of clinical study

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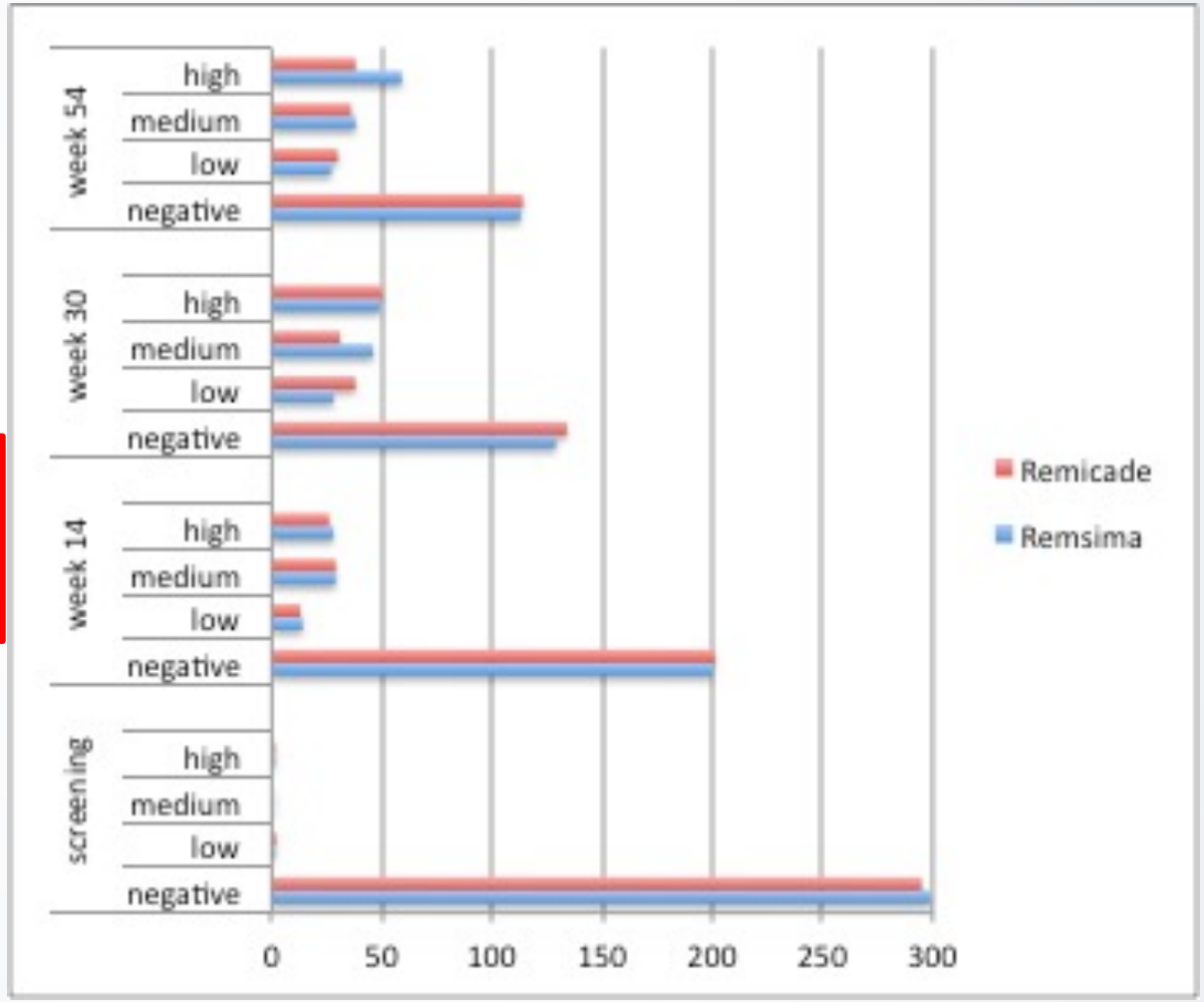
ADA response dynamics: Infliximab

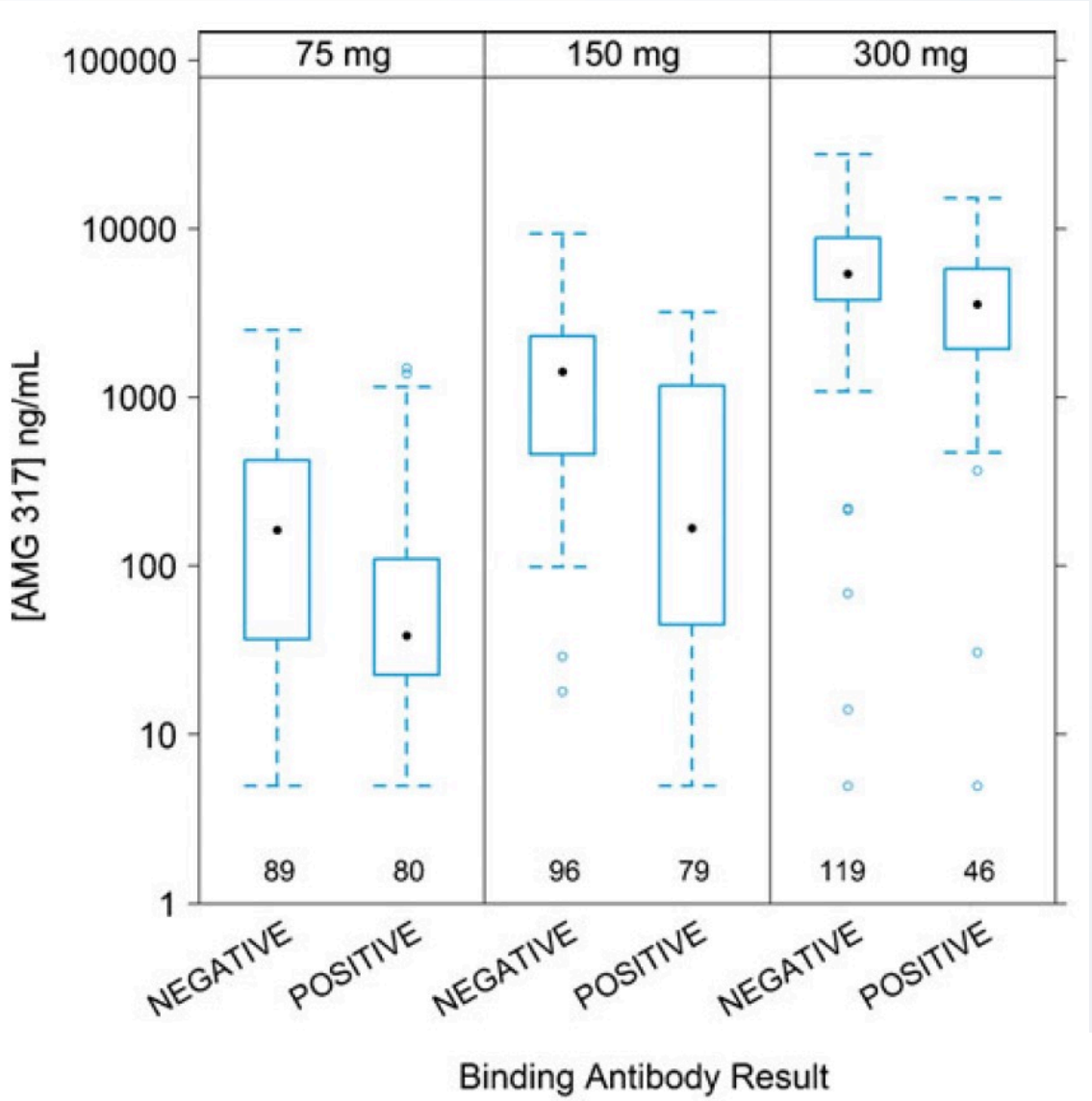
EPAR for REMSIMA™
Study CT-P13 3.1
Rheumatoid Arthritis

Highly similar ADA response dynamics for Remsima™ *vs.* Remicade™



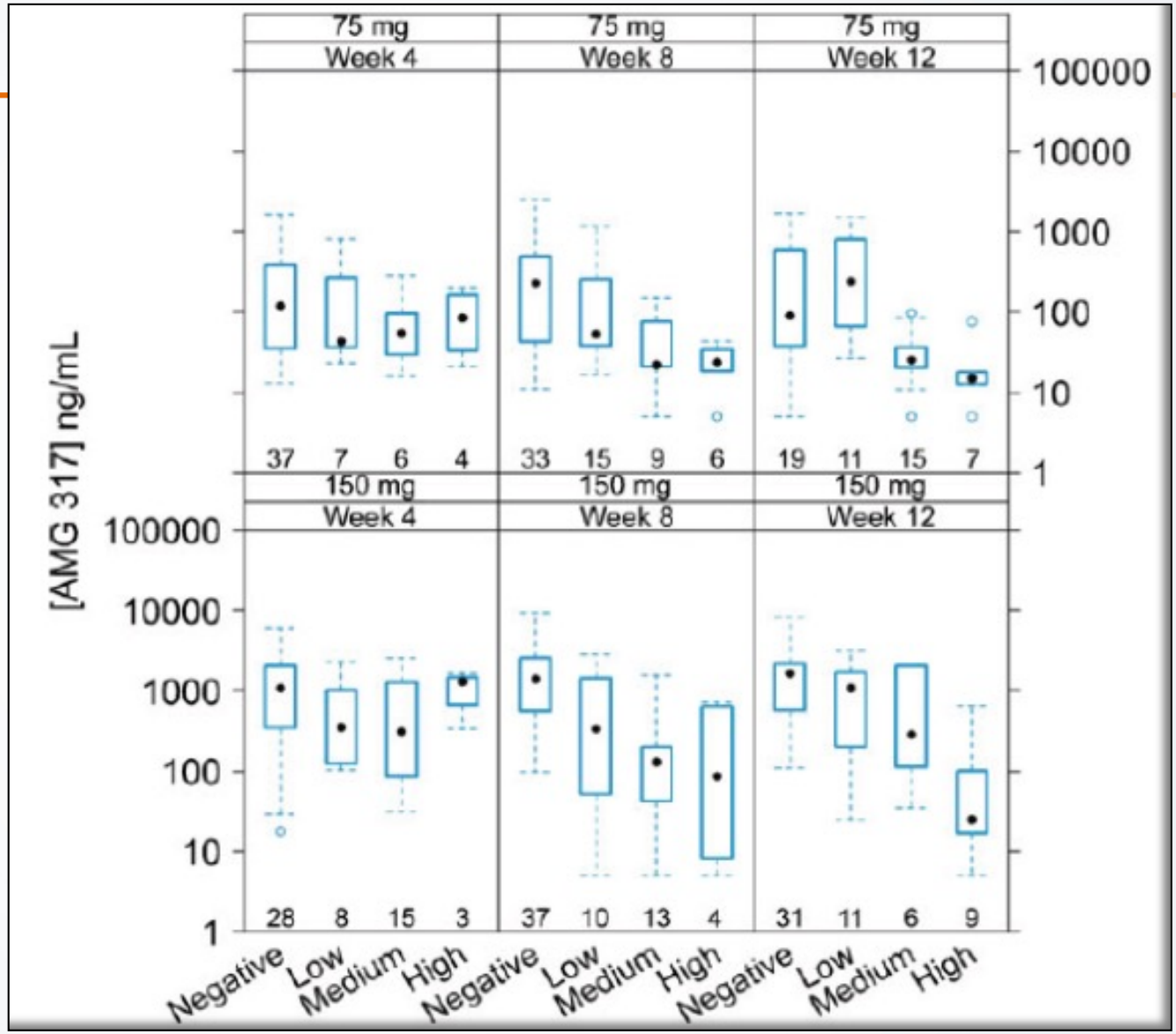
PK as a sensitive correlate of ADA formation

Zhou L et al; AAPS Journal 2013, 15 (1), 30-40



PK *vs* ADA

Zhou L et al; AAPS Journal 2013, 15 (1), 30-40



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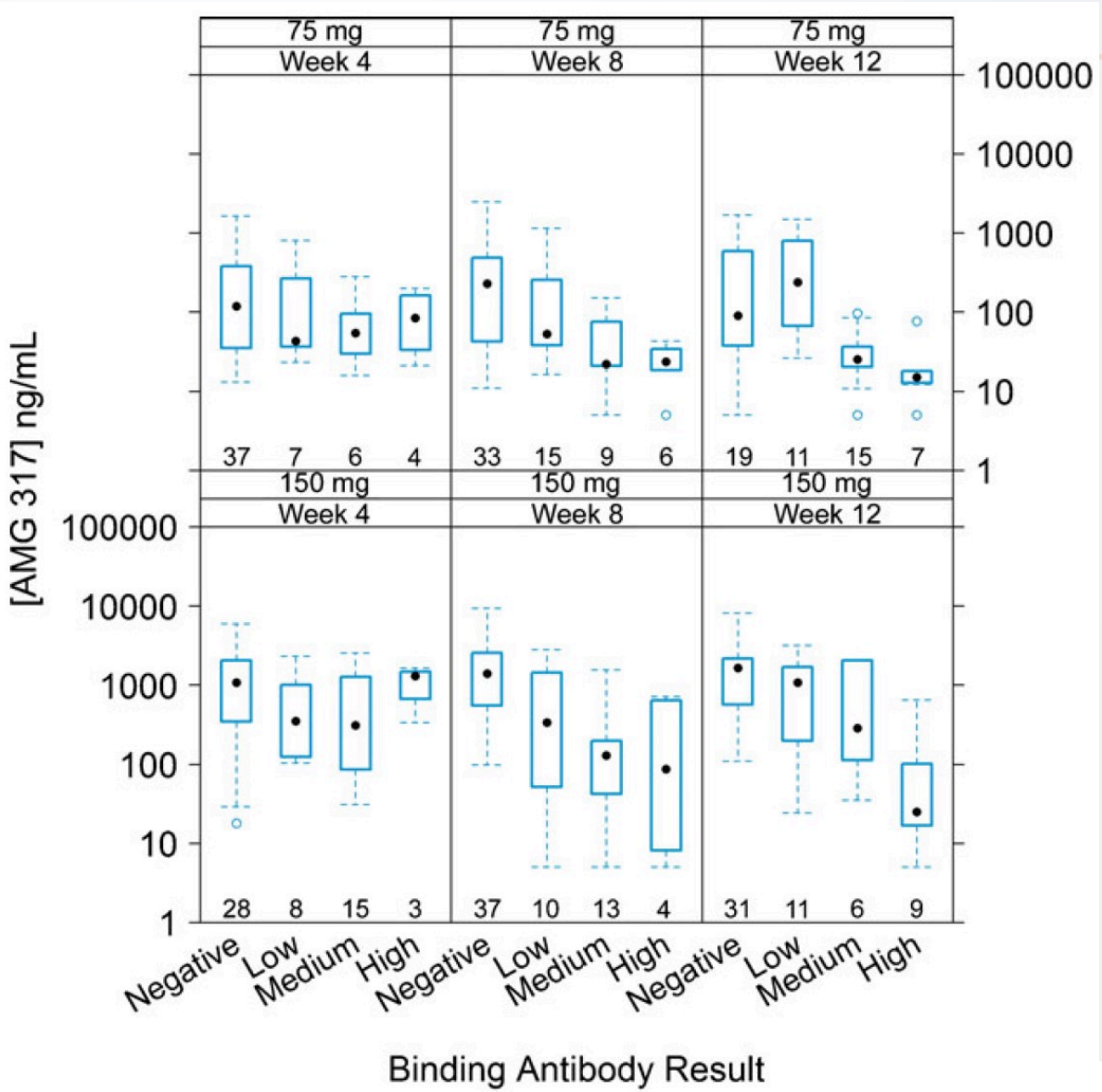
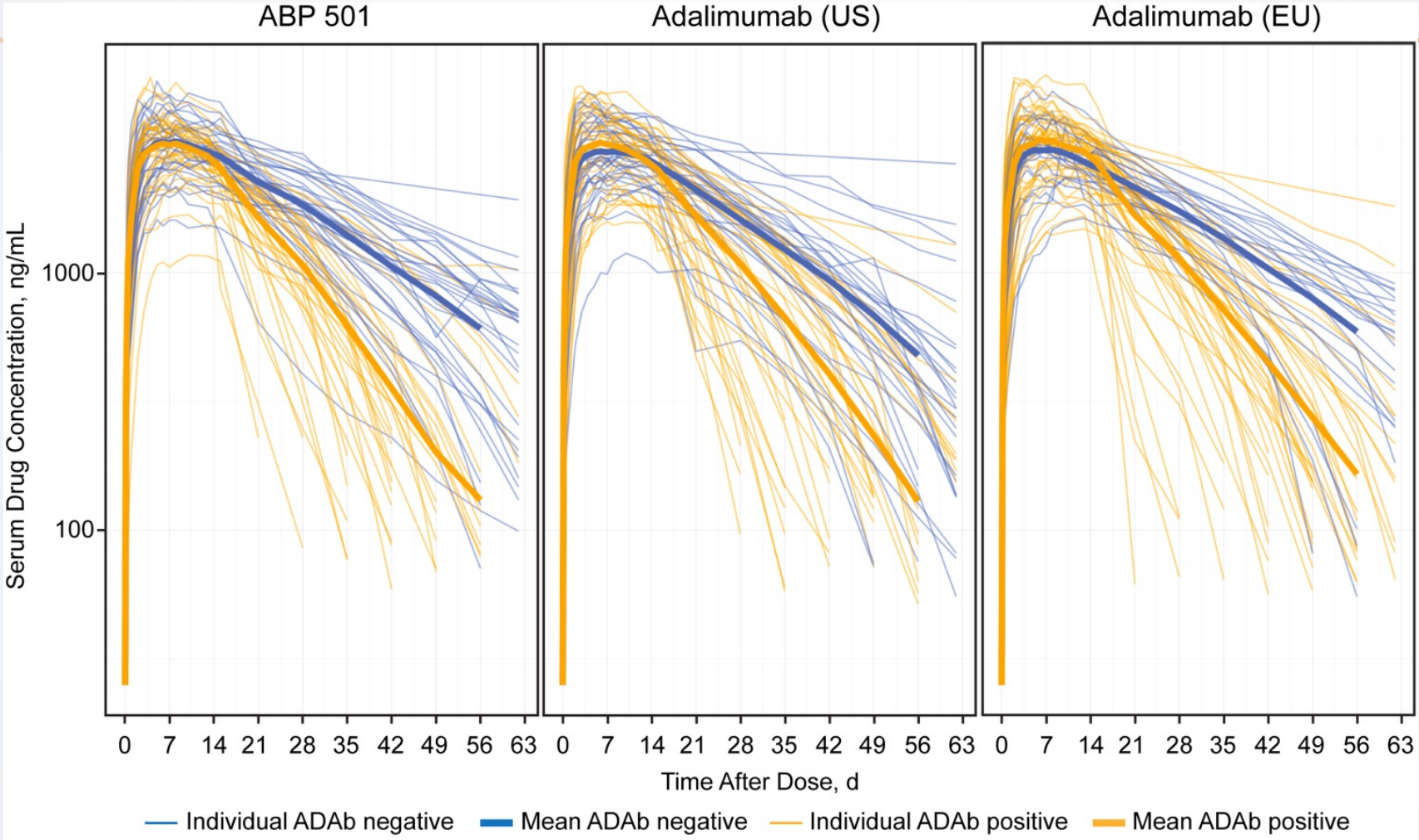


PK vs. ADA

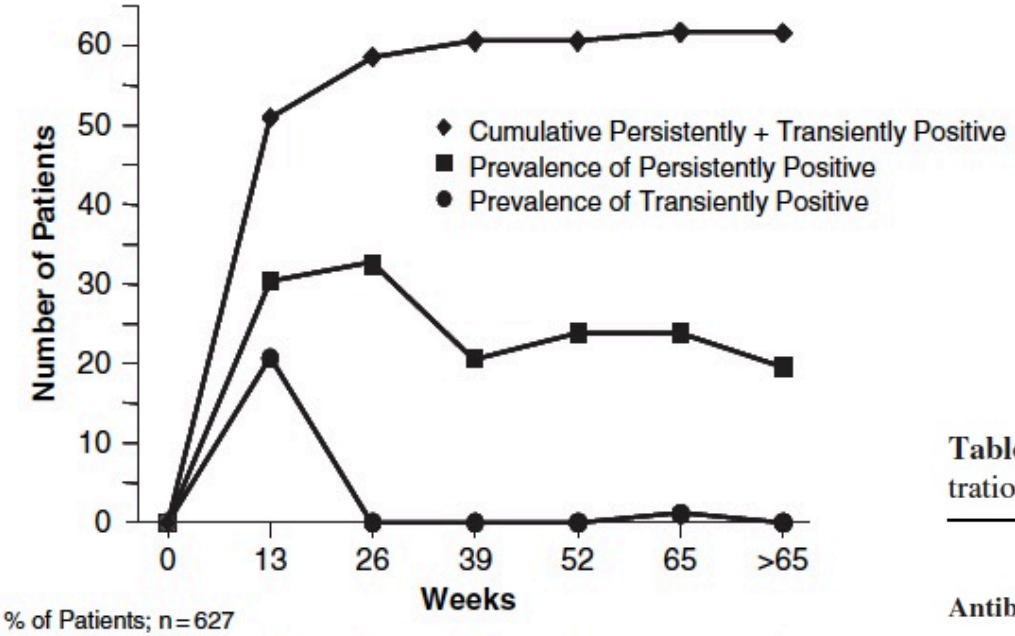
Kaur P, et al. Ann Rheum Dis 2017;76:526–533



Individual PK profiles depicting longer t1/2 in ADAb-negative subjects for all three test products: ABP 501, adalimumab (USA) and adalimumab (EU). ADAb, antidrug antibody

Subramanyam M, 2008. **Case Study: Immunogenicity of natalizumab**; Chapter 10, p 173-187, in "*Immunogenicity of Biopharmaceuticals*", Ed. van de Weert & Moller, Springer.

Time-course of detected ADA in monotherapy study



% of Patients; n = 627							
Cumulative	0	7	9	9	9	9	9
Persistent	0	4	5	3	4	4	3
Transient	0	3	0	0	0	<1	0

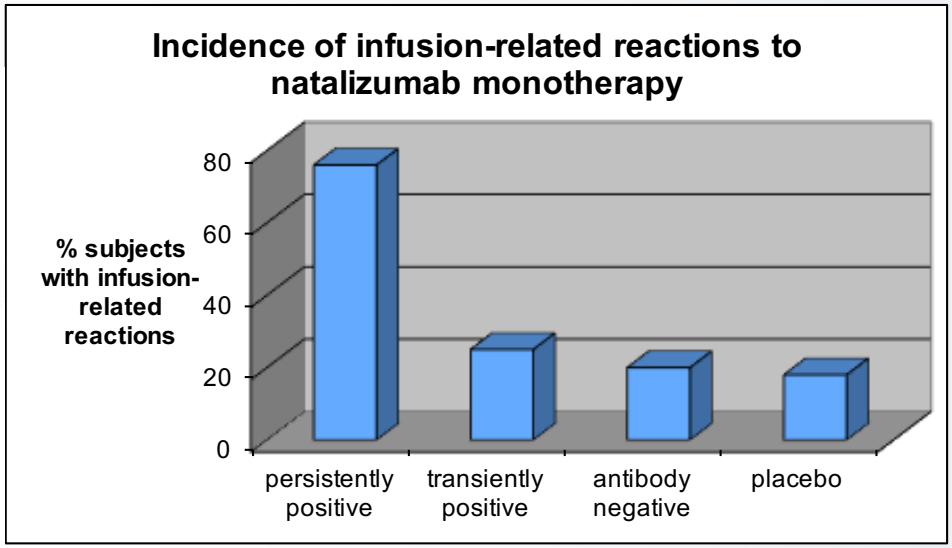


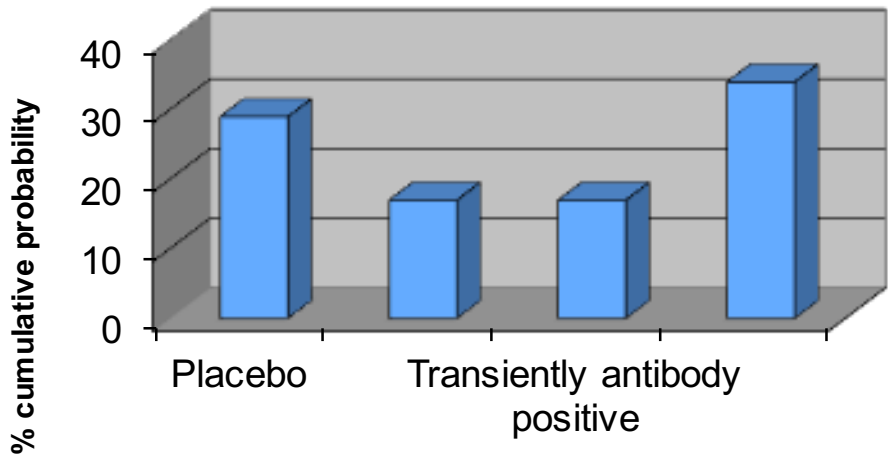
Table 10.1 Effect of anti-natalizumab antibodies on trough serum concentration of natalizumab in the monotherapy study.

	Mean serum natalizumab concentration (μg/mL)			
Antibody status	**Week 12**	**Week 24**	**Week 36**	**Week 120**
Persistently positive	1.3	BLQ*	1.4‡	2.9–7.9§
Transiently positive	1.3	6.4†	17.5	~20
Negative	14.9	21.2	24.3	~23

*Below limit of quantitation.
†2 out of 15 transiently antibody-positive subjects tested BLQ at week 24.
‡16 out of 20 persistently antibody-positive subjects tested BLQ at week 36.
§50–70% persistently antibody-positive subjects tested BLQ at week 120.

Subramanyam M, 2008. **Case Study: Immunogenicity of natalizumab**; Chapter 10, p 173-187, in "*Immunogenicity of Biopharmaceuticals*", Ed. van de Weert & Moller, Springer.

Probability of disability progression *vs.* ADA status for natalizumab monotherapy



	Placebo	Antibody negative	Transiently antibody positive	Persistently antibody positive
Cumulative probability (%)	29	17	17	34*,†

*$p \leq 0.05$ vs. antibody-negative patients.
†$p = 0.66$ vs. placebo.

Defining a clinically meaningful ADA level

Steenholdt C et al. Scandinavian Journal of Gastroenterology, 2011; 46: 310–318

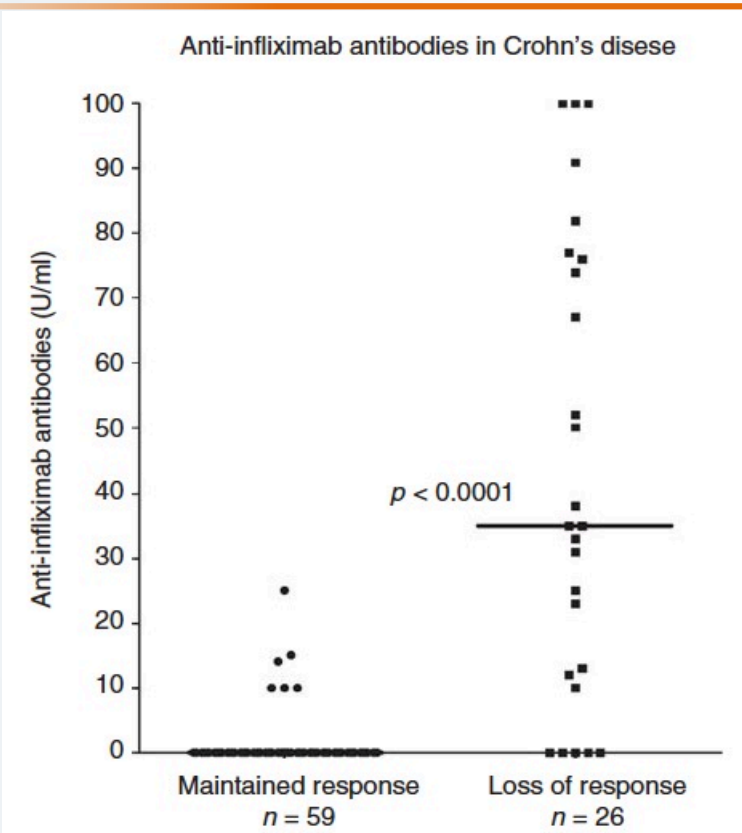


Figure 3. Anti-infliximab antibody concentrations in serum of patients with Crohn's disease with maintained response and loss of response to infliximab maintenance treatment. Horizontal lines indicate median values.

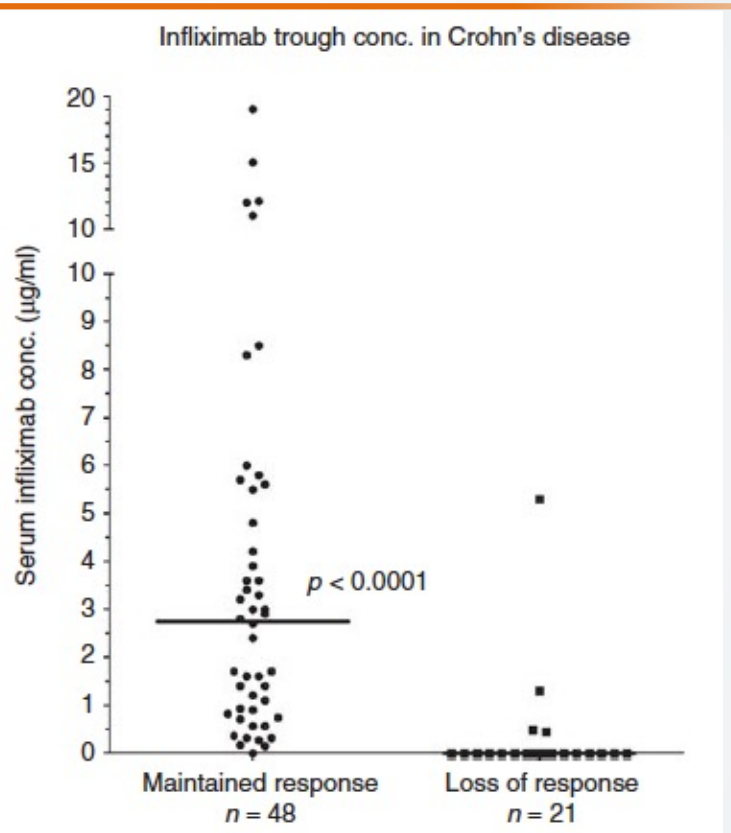


Figure 1. Infliximab trough serum concentrations in patients with Crohn's disease with maintained response and loss of response to infliximab maintenance treatment. Horizontal lines indicate median values.

Combined measurements of infliximab and anti-infliximab antibodies using cut-off levels provided high accuracy for discriminating between clinical response types to infliximab maintenance therapy

NDA

Defining a clinically meaningful ADA level

Steenholdt C et al. Scandinavian Journal of Gastroenterology, 2011; 46: 310–318

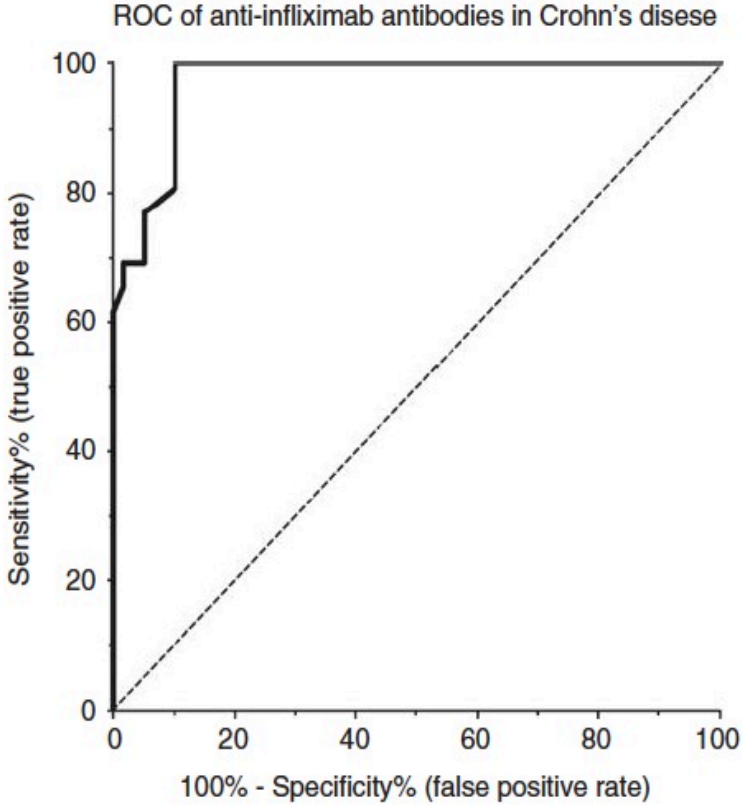


Figure 4. Receiver operating characteristic (ROC) curve of anti-infliximab antibody trough serum concentrations in patients with Crohn's disease to determine cut-off levels associated with clinical response type to infliximab maintenance treatment.

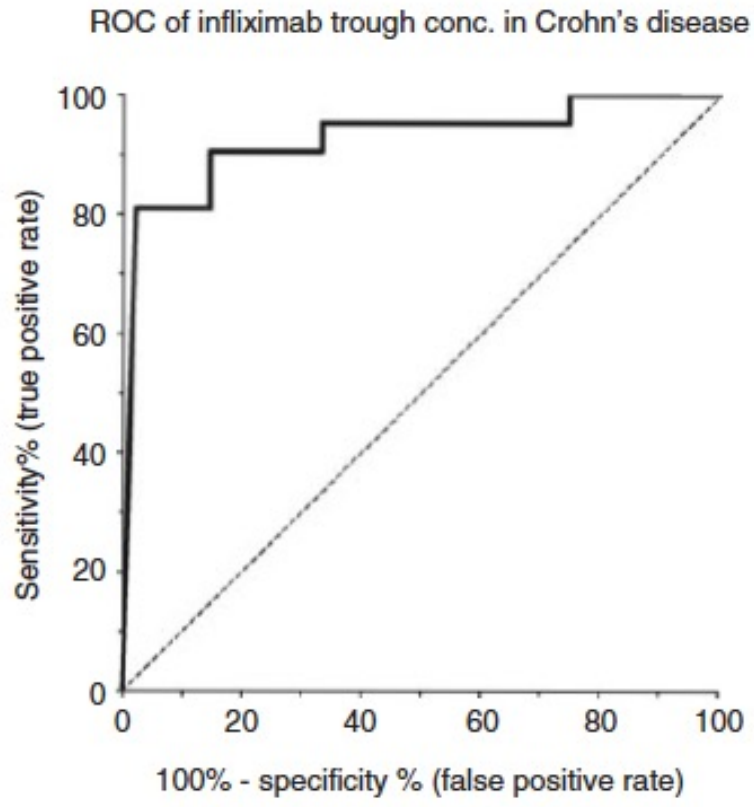
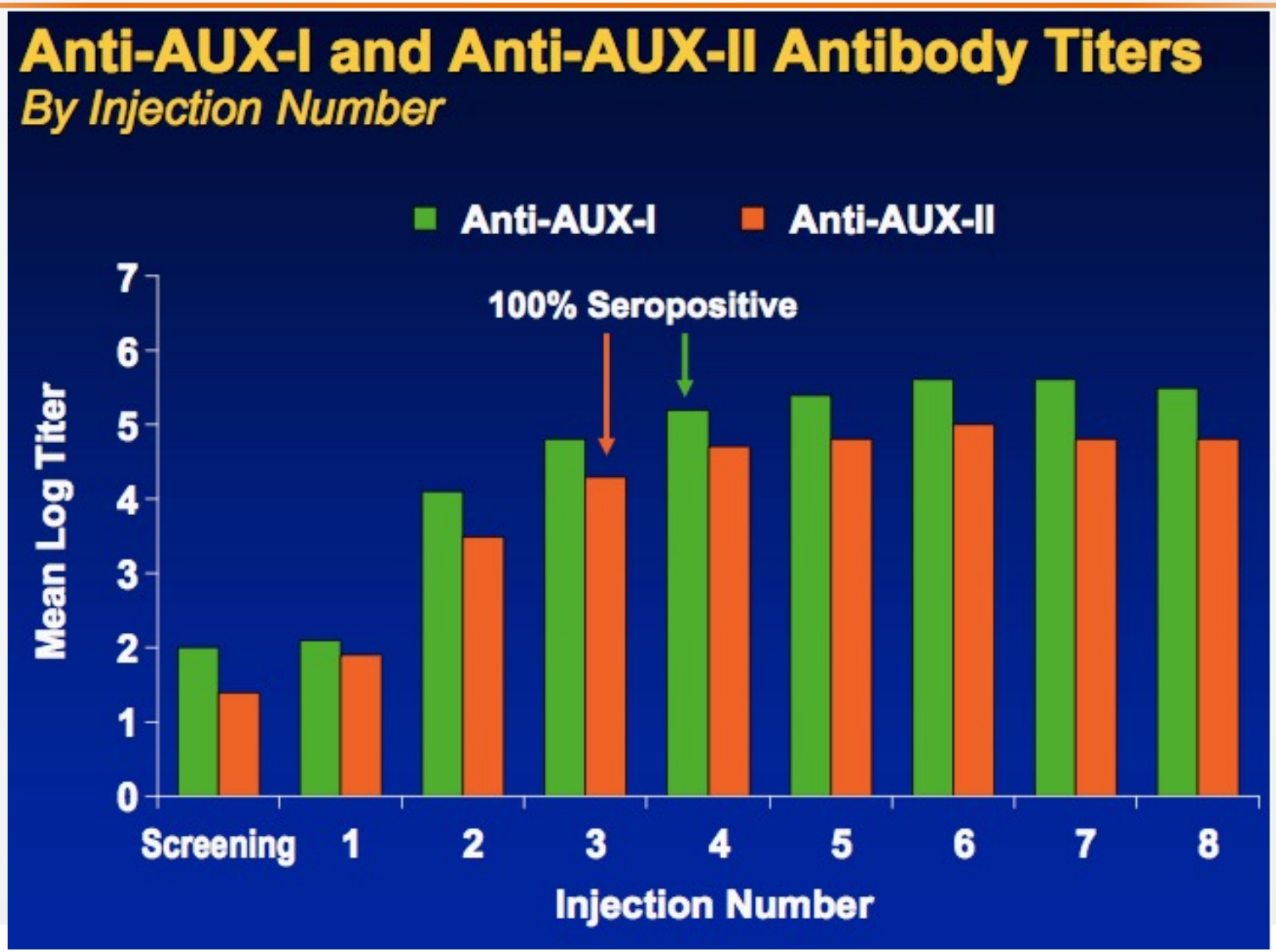


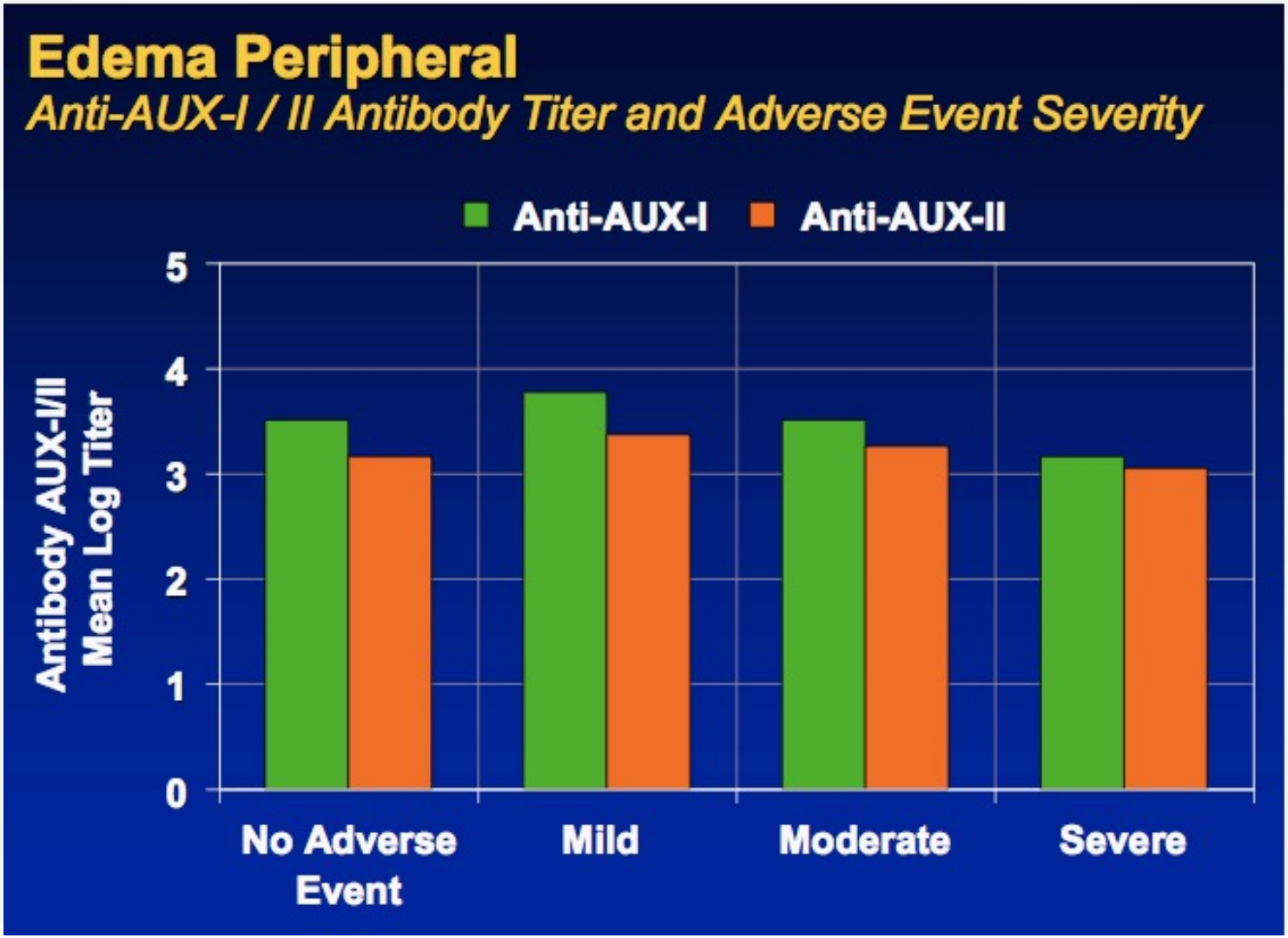
Figure 2. Receiver operating characteristic (ROC) curve of infliximab trough serum concentrations in patients with Crohn's disease to determine cut-off levels associated with clinical response type to infliximab maintenance treatment.

Receiver operating characteristic (ROC) analysis identified optimal cut-off values: infliximab <0.5 mg/ml, combined with anti-infliximab antibodies ≥10 U/ml

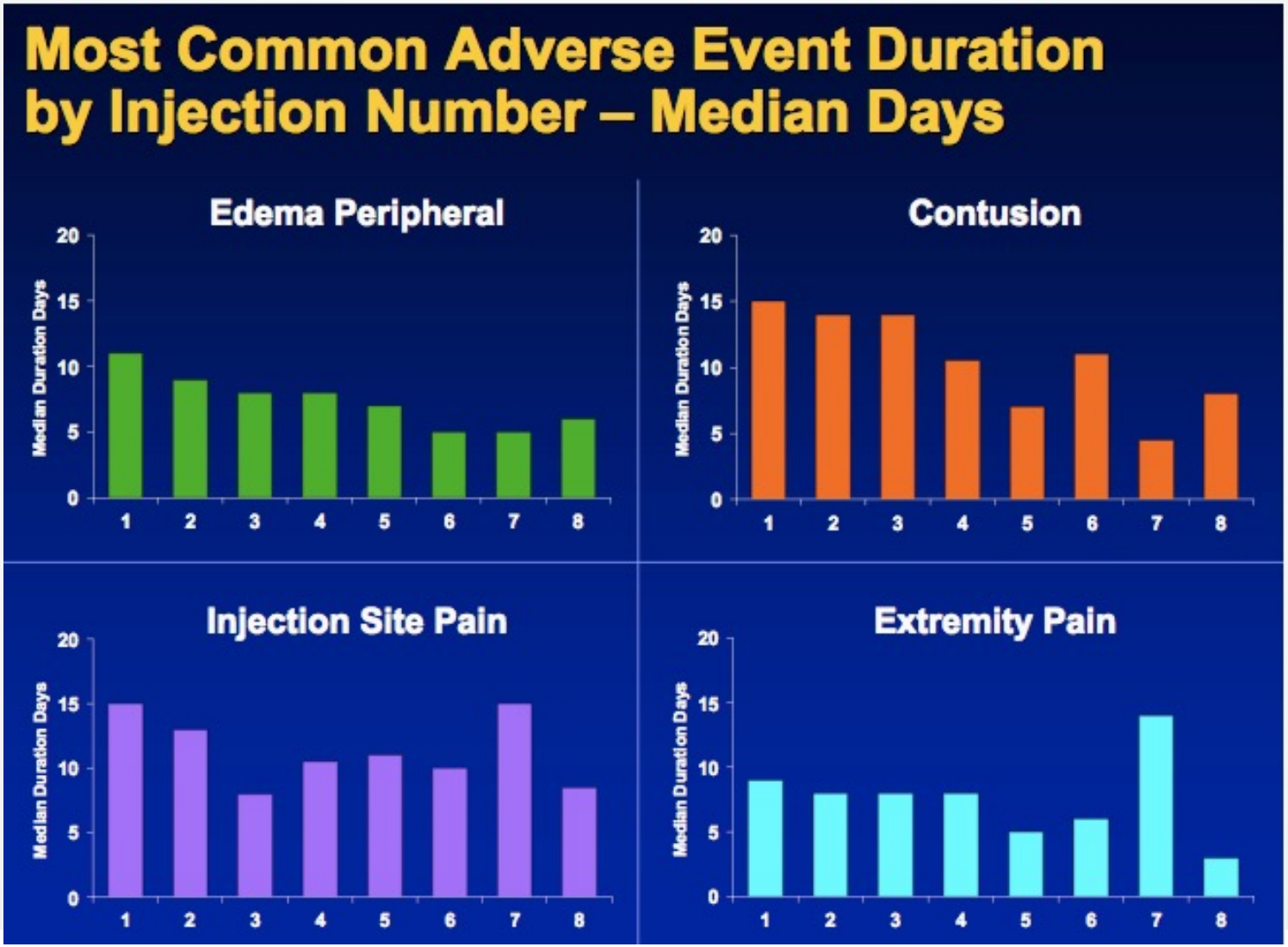
FDA Arthritis Advisory Committee, 16 Sep 2009
Xiaflex® for Dupuytren's contracture



FDA Arthritis Advisory Committee, 16 Sep 2009
Xiaflex® for Dupuytren's contracture



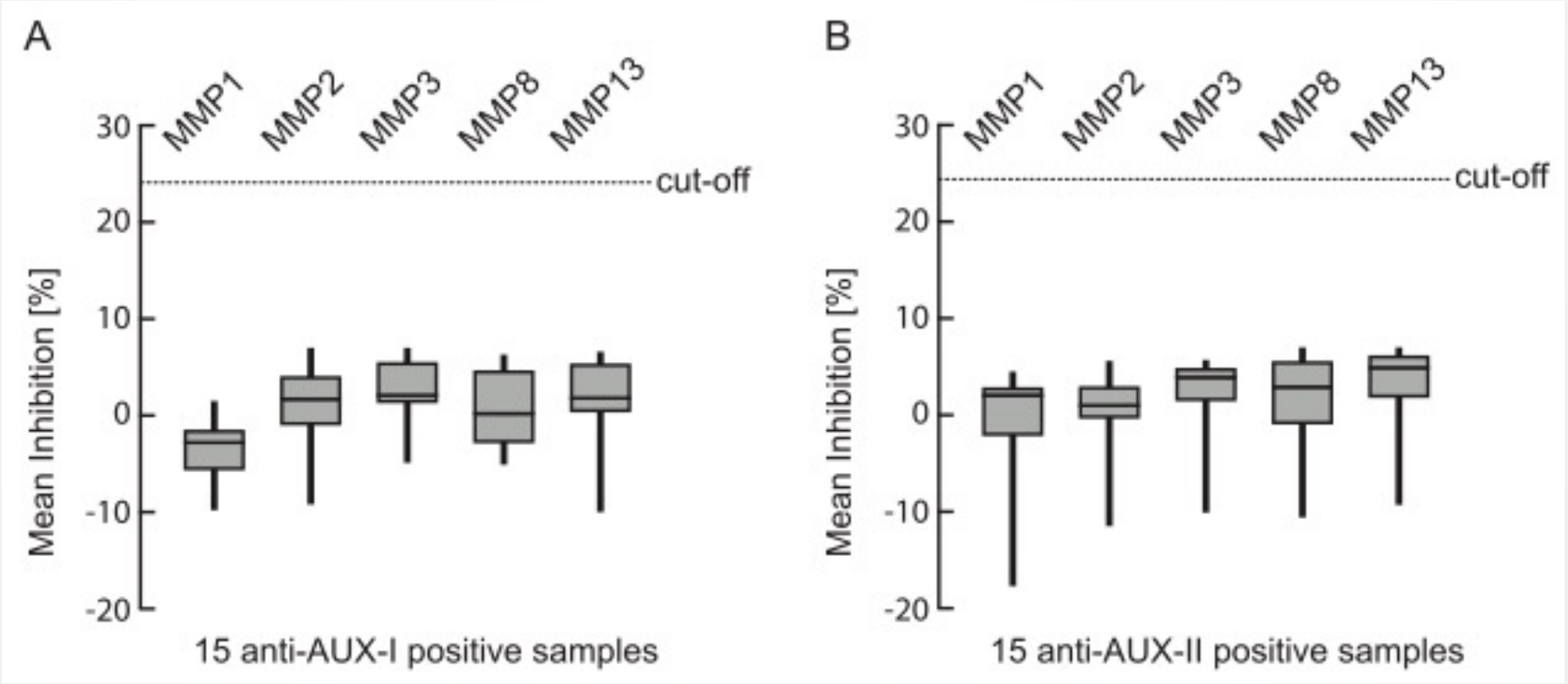
FDA Arthritis Advisory Committee, 16 Sep 2009
Xiaflex® for Dupuytren's contracture



Example: Xiaflex®

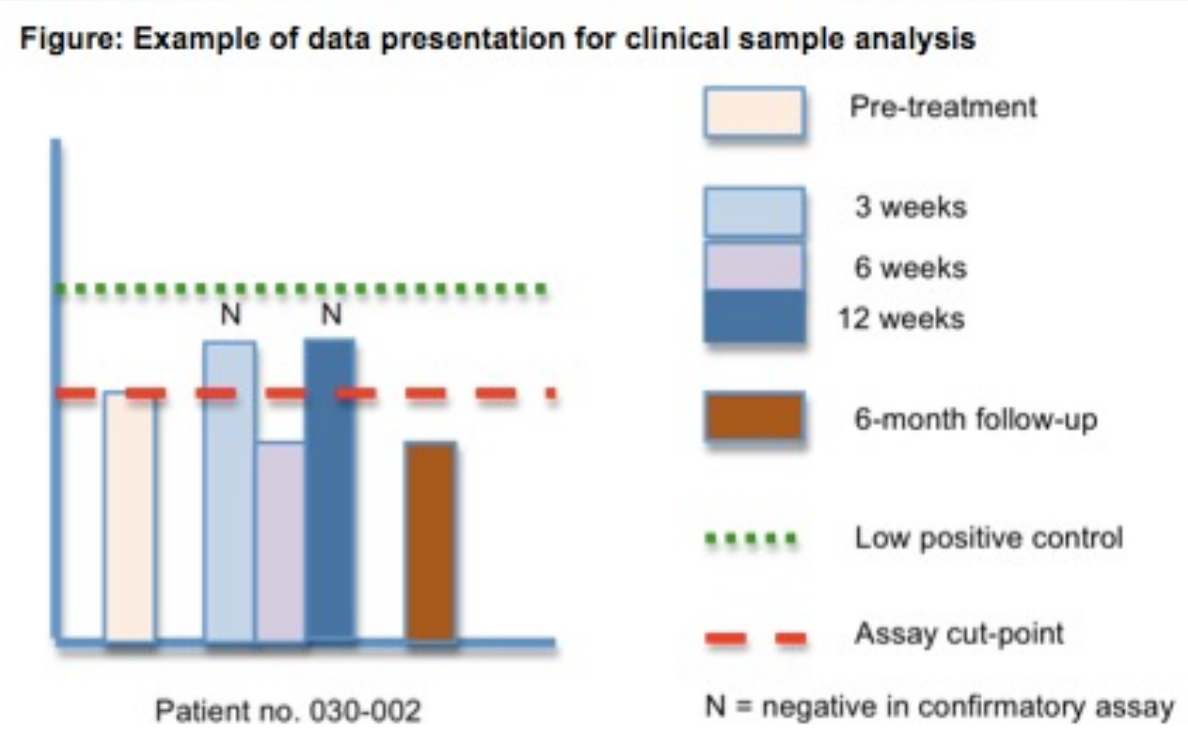
Assessing potential cross-reactivity of human endogenous matrix metalloproteinases (MMPs) with collagenase Clostridium histolyticum (CCH) antibodies in human serum for patients with Dupuytren's Contracture

Edkins TJ *et al*; Clin Vaccine Immunol 2012, Feb 22



Data Presentation

Clear presentation of individual subject profiles is extremely helpful

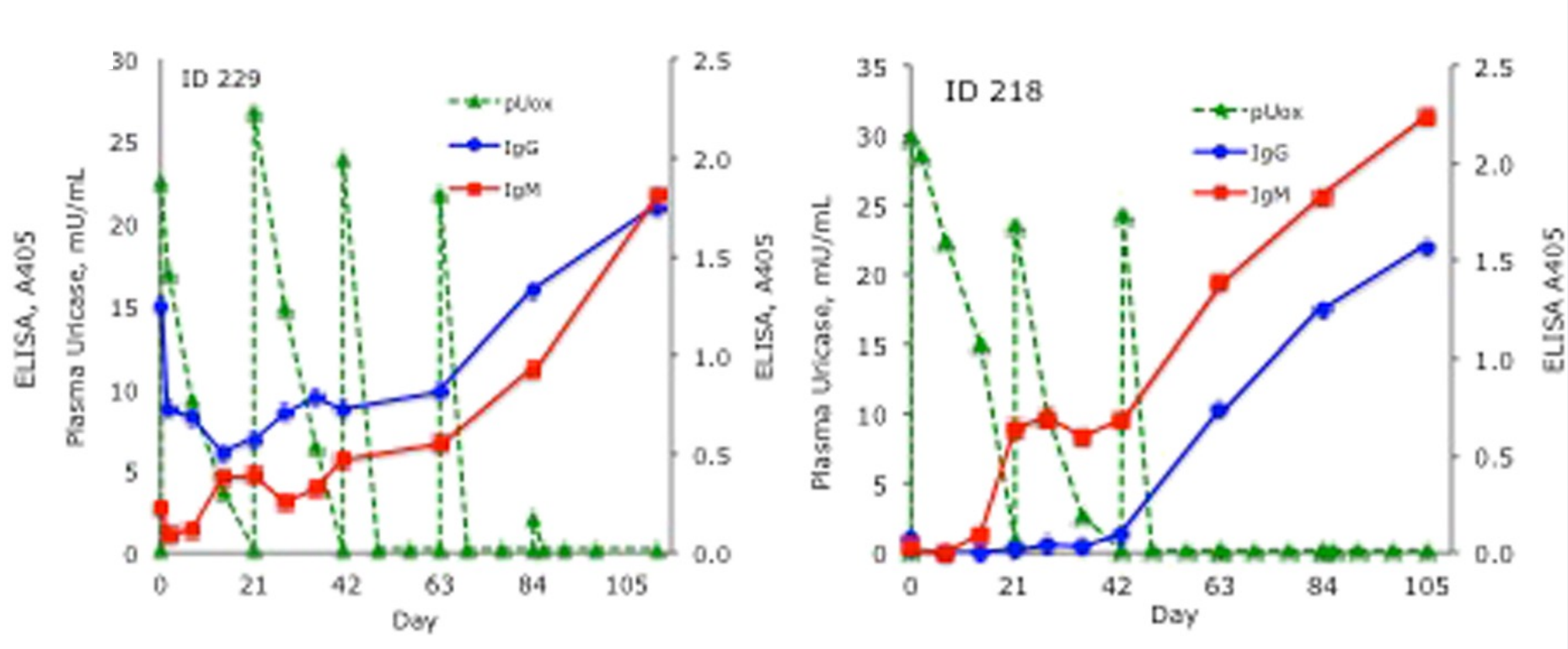


Include as Annex to Integrated Summary of Immunogenicity or in individual Clinical Study Reports

Can be particularly helpful to illustrate magnitude of signals relative to cut-point

Individual subject profiles

Illustrate temporal relationships of ADA response to drug exposure



Hershfield et al. Arthritis Research & Therapy 2014, 16:R63

SECTION 4 = CONCLUSIONS

Conclusions	• Impact on overall clinical benefit & risk • Linkage to Risk Management Plan	*Effective risk mitigation?*

Overall conclusions

- Impact of immunogenicity on overall clinical benefit and risk for claimed therapeutic indications, taking into account:
  - Methodological limitations?
  - ADA response profiles in different clinical populations?
  - Relationship of ADA response to clinical parameters
    - Drug exposure
    - PD markers
    - Efficacy
    - Immune-mediated AE's?
- Inferences for Risk Management?

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SECTION 5: RISK MITIGATION

Risk Mitigation

The final section of the ISI provides an opportunity to justify the proposed risk mitigation plan, including:

- Prescribing information that helps clinicians to:
  - Understand probability, severity of consequences and reversibility of undesirable immunogenicity during treatment
  - Recognise and manage any adverse effects
  - Identify patient sub-populations who might be at higher risk
- Scale of uncertainty relative to weight of evidence available at time of registration
- Longer-term follow-up monitoring of patients treated during controlled clinical studies
- Any proposed prospective observational cohort studies and/or Patient Registries
- Adequacy of routine pharmacovigilance to mitigate identified and potential risks

The aim if this section is to assure the regulator that risk associated with uncertainty about the scale of potential impact of undesirable immunogenicity on clinical benefit-risk will be adequately mitigated by ongoing monitoring / follow-up measures

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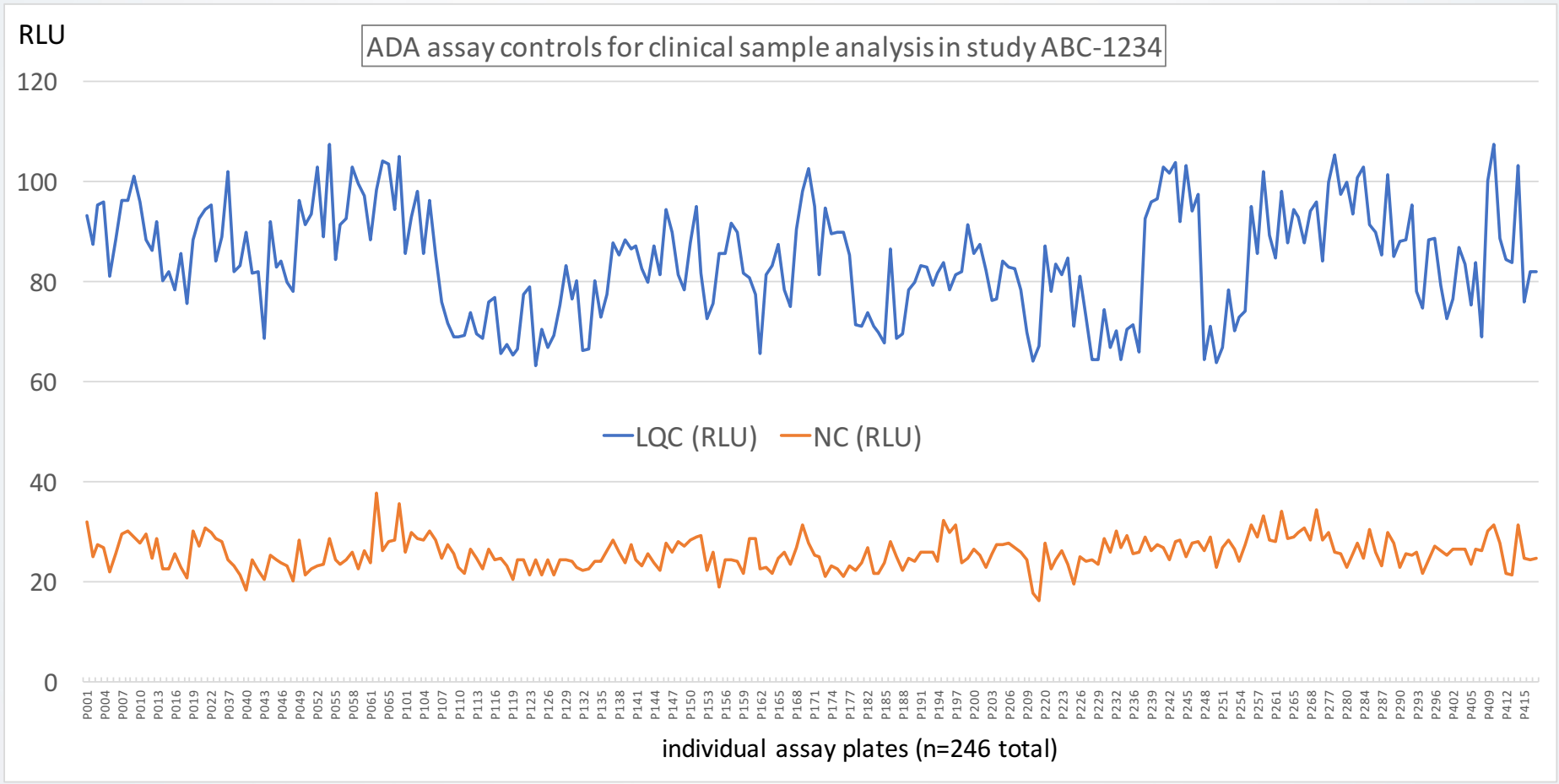
Question-based approach to RMP

Table 6. Risk management plan	
Questions	
1.	Are there potential patient sub-populations to whom this product should not be administered?
2.	Under which circumstances might it be necessary to modify or stop treatment?
3.	What monitoring methods should be applied to investigate suspected host immune responses to the product?
4.	Is it necessary to collect additional data, eg from a patient registry, to monitor long-term risks in a wider population?
5.	What are the risks associated with off-label use?

Chamberlain P. Addressing immunogenicity-related risks in an integrated manner. *Regulatory Affairs Pharma*, Jan 2011, 10-15

SECTION 6: APPENDICES

Quality Control Charts



PROCESS

When?

Basis for Introductory section of ISI is the evolving Immunogenicity risk assessment document, which is then supplemented by additional sections

PROCESS

- Initiate “ISI Work-stream” 18 months ahead of submission date
- Drafting of outline ISI format
- Bioanalytical methods review
- Alignment of Statistical Analysis Plan / data management activities to ISI
- Define CMC items to include
- Prepare Mock ISI
- Consolidation of Phase 3 data into ISI → Multi-disciplinary peer-review
- Check consistency with results presented in CSR’s
- Preparation of summary text for Module 2 summaries

NDA

THANK YOU FOR
YOUR LİSTENİNG

DO YOU HAVE
ANY QUESTİONS?