Lessons learnt from the European Experience Regarding Biosimilars and Immunogenicity

European Immunogenicity Platform
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NDA Advisory Board

Purpose of this presentation

1. What products have been approved / not approved?
2. Weight of evidence for immunogenicity-related risks?
3. What lessons have been learnt?
4. How has this influenced the EU regulatory approach?

Chamberlain PD. Multidisciplinary approach to evaluating immunogenicity of biosimilars: lessons learnt and open questions based on 10 years' experience of the European Union regulatory pathway. *Biosimilars* 2014, 4, 23-43

Guidance for immunogenicity evaluation of biosimilars

EU

- Main biosimilars guidelines:
  - **Principles**: CHMP/437/04 Rev 1, Oct 2014;
  - **Non-clin & Clin**: EMEA/CHMP/BMWP/42832/2005 Rev1, Dec 2014
  - **Quality**: EMA/CHMP/BWP/247713/2012, May 2014
- Product-specific biosimilars guidelines
- Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006***) under revision***
- Guideline on Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010)

Biosimilar applications reviewed in EU

Status at 18th Feb 2015

Approved:

14 distinct products / 7 different molecules

- 2 x somatropin
- 2 x epoetin
- 5 x filgrastim
- 1 x infliximab
- 2 x follitropin
- 1 x insulin glargine
- 1 x etanercept

Date	Product
04/2006	Omnitope®
04/2006	Valtropin®
08/2007	Binocrit®
12/2007	Silapo®
09/2008	Ratiograstim®
02/2009	Zarzio®
06/2010	Nivestim®
09/2013	Remsima®
09/2013	Ovaleap®
10/2013	Grastofil®
03/2014	Bemfola®
09/2014	Abasaglar®
09/2014	Accofil®
01/2016	Benepali®

Negative Opinions:

- Alpheon®
- Solumarv®

Applications withdrawn:

- Epostim®
- Solumarv®/Isomarv®/ Combimarv®

No ***approved*** biosimilar products withdrawn due to safety or immunogenicity issues

Biosimilar applications currently under review

Source: EMA web site, 18th February 2016

Product	No. of Applications
Enoxaparin sodium	2
Infliximab	1
Rituximab	1
Etanercept	1
Pegfilgrastim	3
Adalimumab	2
Insulin glargine	1

Impact of product quality risk factors for immunogenicity of candidate biosimilars identified in ***pre***-authorisation phase

Detected difference	Impact
HMW variants associated tungsten residue (Binocrit®) Seidl et al 2012	Possible association with induction of 2 cases of nAbs; 1 confirmed case of PRCA (CKD SC route only)
E.coli HCP impurity (early version of somatropin) EPAR for Omnitrop®	Treatment-emergent antibodies to HCP + reported enhancement of ADA reactive with somatropin (?)
Higher level of Neu5Gc EPAR for Ovaleap®	None
Different product-related impurity profile Refusal AR for Alpheon®	No apparent difference in immunogenicity; analytical & clinical comparability not demonstrated

All these risks were effectively identified & mitigated by prevailing regulatory controls

Main evidence of comparative immunogenicity obtained in same study used to demonstrate therapeutic equivalence (*exception: filgrastim*)

Zarzio®

4 x PK/PD studies in HV (n=146 total)
IV and SC; 4 dose levels (dose-response)
+ uncontrolled safety / immunogenicity in breast cancer (n=153)

Controlled, comparative PK/PD

Silapo®

2 x comparative PK cross-over studies in HV

3 x Therapeutic equivalence (Ph3) studies:

- Correction in H/D CKD via IV admin (n=609)
- Maintenance in CKD via IV admin (n=313)
- Maintenance in CKD via SC admin (n=462)

Safety in chemotherapy-related anemia (n=208)

Subjects enrolled into open-label extensions to enable longer-term monitoring of immunogenicity

12-month immunogenicity data on n=585 subjects to support authorisation

No pre-defined acceptable difference in ADA incidence/titer

- Arbiter is clinical impact, not relative ADA signal
- Assay-specific nature of ADA signal
- If assay differs from originator, not possible to extrapolate data on clinically impactful threshold
- Need to consider dynamics of ADA formation relative to clinical endpoints
- Depends on risks identified for reference product and extent of differences for biosimilar at product quality level

Biosimilar could have ***lower*** immunogenicity if a significant and clinically relevant increase in efficacy can be excluded

Defining risks for reference product

Product	Clinical impact of immunogenicity / ADA
epoetin-alfa	Cross-reactive neutralizing ADAs causing amPRCA
cetuximab	Severe allergic reactions in pre-sensitised subjects
infliximab	Immune complex-related hypersensitivity & loss of efficacy
adalimumab	Loss of efficacy & increased incidence of injection site reactions
rituximab	Loss of efficacy in patients with severe pemphigus & rare cases of hypersensitivity reactions
somatropin	Possible reduction in PK / PD / efficacy in rare cases
insulin	Possible reduction in PK / PD / efficacy in rare cases
follitropin-alfa	Negative impact not identified
bevacizumab	Negative impact not identified
trastuzumab	Negative impact not identified
etanercept	Negative impact not identified
(peg)filgrastim	Negative impact not identified

Formulation differences

Ref: EPAR's

Qualitative and quantitative differences in formulation of the drug product are allowed, and have been approved for biosimilars in EU:

- Omnitrop®, Silapo®, Ratiograstim®, Zarzio®, Ovaleap®, & Benepali®

Implies increased weight of evidence for comparable stability & PK & safety of the drug product formulation-primary container combination ***to be commercialized***:

- Real-time stability
- Accelerated degradation / stress
- In-use stability
- Comparative PK & ADA
- Safety signals, including infusion / injection reactions, hypersensitivity etc.

Pivotal clinical data should be generated with drug product intended for commercialization

Assays for comparative immunogenicity

Draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006 Rev. 1, 24 Sep 2015

ADA testing recommendations:

- ***Same*** assay and sampling schedule
  - Use biosimilar as target antigen
- Operator-blinded testing
- Validate assay to demonstrate detection of antibodies against both reference and biosimilar products
- Incidence, titer and neutralizing activity
  - Also cross-reactivity and target epitopes

Testing comparative ADA formation

Comparative PK studies can be informative for relative anti-drug antibody response for products for which there is a measurable signal for the originator

Adalimumab: 3-arm, single 40-mg SC dose, parallel group study in healthy subjects

Kaur *P et al* Ann Rheum Dis 2014, 73, Suppl2
http://www.abstracts2view.com/eular/view.php?nu=EULAR14L_FRI0264

Product	Number treated	ADA positive N (%)	neutralising ADA N (%)	AUC inf ng.h/ml
Humira (EU)	67	45 (67%)	14 (21%)	2047
ABP 501	67	36 (54%)	12 (18%)	2137

Allows most sensitive comparison of ADA formation on PK

Despite complexity, biosimilar mAbs had comparable magnitude of ADA formation *vs*. reference products…

Source: EPAR

Phase 3
RA study
EOS sample

nAb titer category	CT-P13 3 mg/kg (N=302)	REMICADE® 3 mg/kg (N = 300)
Negative	113 (37.4%)	121 (40.3%)
Low	39 (12.9%)	44 (14.7%)
Medium	49 (16.2%)	38 (12.7%)
High	69 (22.8%)	66 (22.0%)

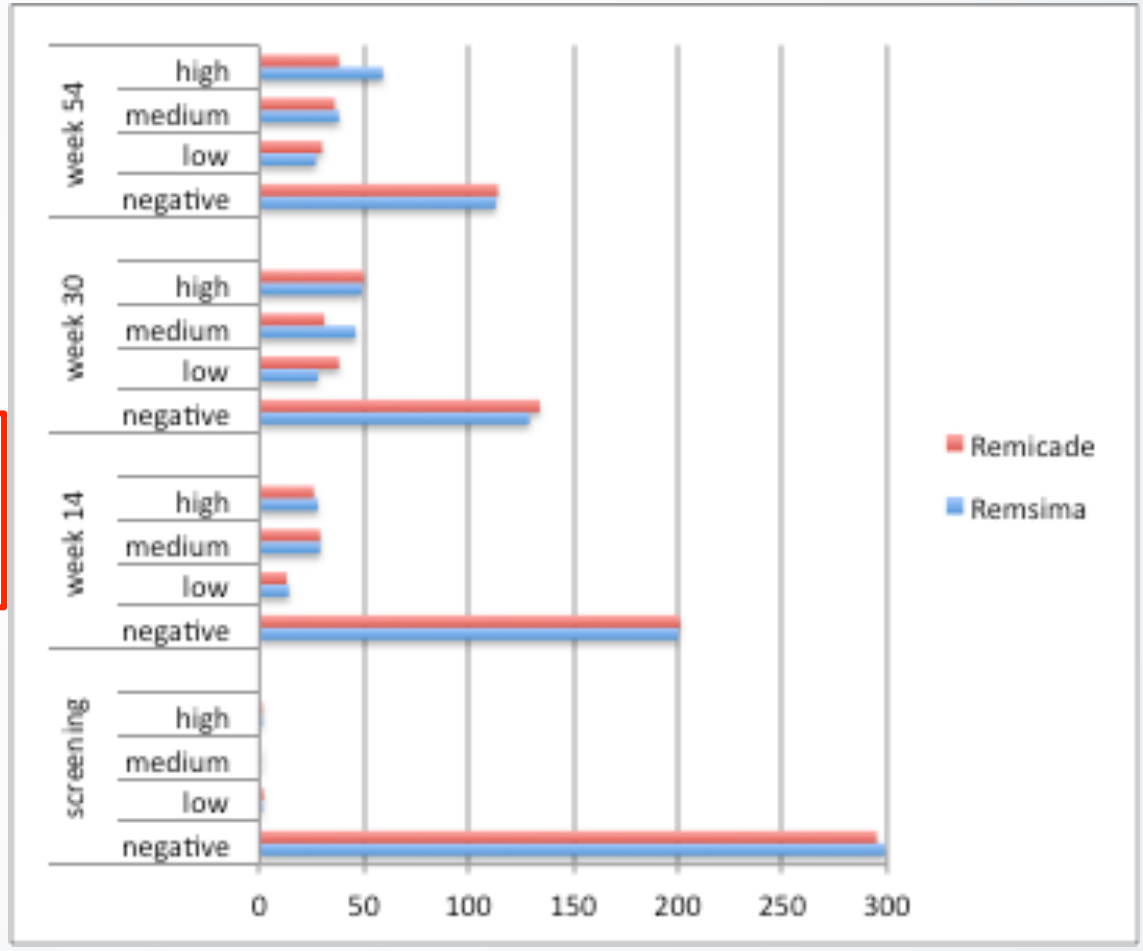
…& comparable incidence of infusion-related reactions for ADA +ve / -ve subpopulations

ADA status	Treatment	At Week 54		Up to Week 54
		ASAS20 Phase 1 study n/N (%)	ACR20 Phase 3 study n/N (%)	Hypersensitivity/Infusion-related reactions in Phase 1 & 3 Safety pop n/N (%)
POSITIVE	CT-P13	14/29 (48.3)	82/167 (49.1)	23/212 (10.8)
	REMICADE®	21/32 (65.6)	73/164 (44.5)	34/202 (16.8)
NEGATIVE	CT-P13	57/77 (74.0)	90/135 (66.7)	4/218 (1.8)
	REMICADE®	54/76 (71.1)	85/139 (61.2)	8/219 (3.7)

ADA response dynamics: Infliximab

EPAR for REMSIMA™
Study CT-P13 3.1
Rheumatoid Arthritis

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



Biosimilar etanercept (Benepali®)

Sustained ADA considered more important for safety and efficacy

Table S4. Incidence of ADA by Visit and Treatment Group

	SB4 (N=299)		ETN (N=297)	
Timepoint	n/n'	(%)	n/n'	(%)
Week 0	0/299	(0.0)	0/297	(0.0)
Week 2	0/298	(0.0)	1/295	(0.3)
Week 4	1/299	(0.3)	32/291	(11.0)
Week 8	1/298	(0.3)	6/288	(2.1)
Week 12	0/294	(0.0)	1/280	(0.4)
Week 16	0/290	(0.0)	0/277	(0.0)
Week 24	0/288	(0.0)	0/272	(0.0)
Week 24 overall	2/299	(0.7)	39/297	(13.1)

ADA, anti-drug antibody
n': number of patients with available overall 24-week ADA assessment results. Percentages were based on n'.
Overall 24-week ADA result was defined as positive for patients with at least one ADA positive result up to Week 24 after Week 0

Emery P, Vencovský J, Sylwestrzak A, et al. Ann Rheum Dis
Published Online First July 6 2015 doi:10.1136/annrheumdis-2015-207588

Differences in Neu5Gc *not* relevant for follitropin

Potential impact of detected product quality differences on immunogenicity-related risk was taken into account as part of "totality of evidence" of biosimilarity

Ref: EPAR for Ovaleap® – follitropin

Biosimilar follitropin expressed in CHO cells contained slightly higher levels of Neu5Gc compared to reference product

Humans have pre-existing antibodies that react with Neu5Gc
Question: Potential for enhanced clearance leading to reduced efficacy?

Risk mitigated by:

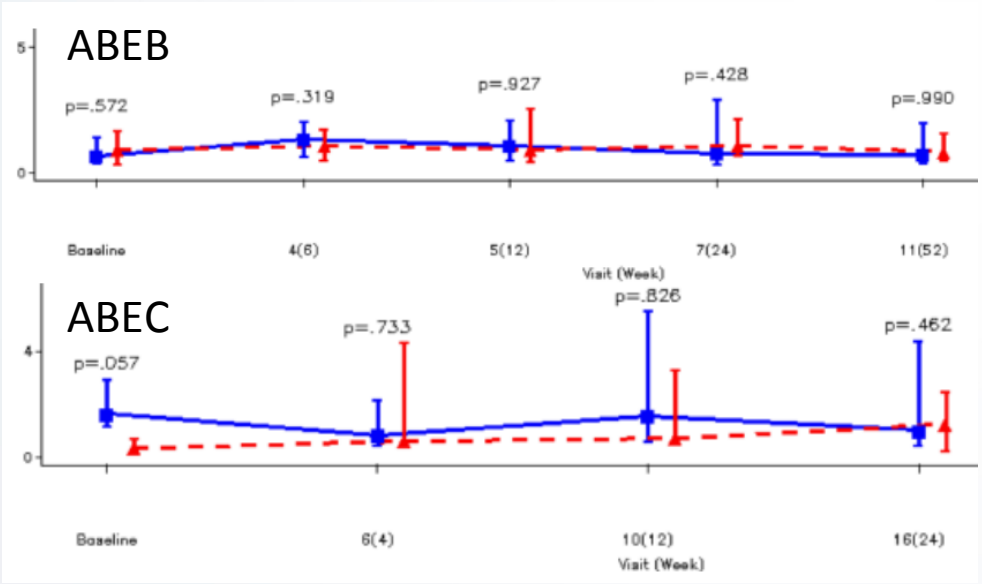
- Quantitative analysis of Neu5Gc by HPAEC-PAD
- Measurement of pre-existing Neu5Gc-reactive antibodies in subjects
- Demonstration that baseline status for Neu5Gc-reactive antibodies did not impact treatment outcomes

Manner of analysing / presenting ADA results is important

Ref: EPAR for Abasria ® – insulin glargine

2 x Ph3 clinical studies performed: T1DM (ABEB study) & T2DM (ABEC) patients:

- No difference in incidence or magnitude of ADA response in T1DM
- Marginally higher incidence of ADA detected in T2DM



Learning points:

- Dynamics & magnitude of ADA formation more important than incidence
- Magnitude of ADA for most-sensitive population (T1DM) given higher weight
- Measurement of cross-reactive potential was instructive

Extrapolation of indications

Additional ***pre***-authorization clinical immunogenicity evaluation required for higher risk populations

All indications granted for:

- Growth Hormone
- Filgrastim
- Infliximab
- Follitropin
- Insulin
- Etanercept

↓

Authorization linked to risk minimisation provisions in RMP

Additional immunogenicity data required for:

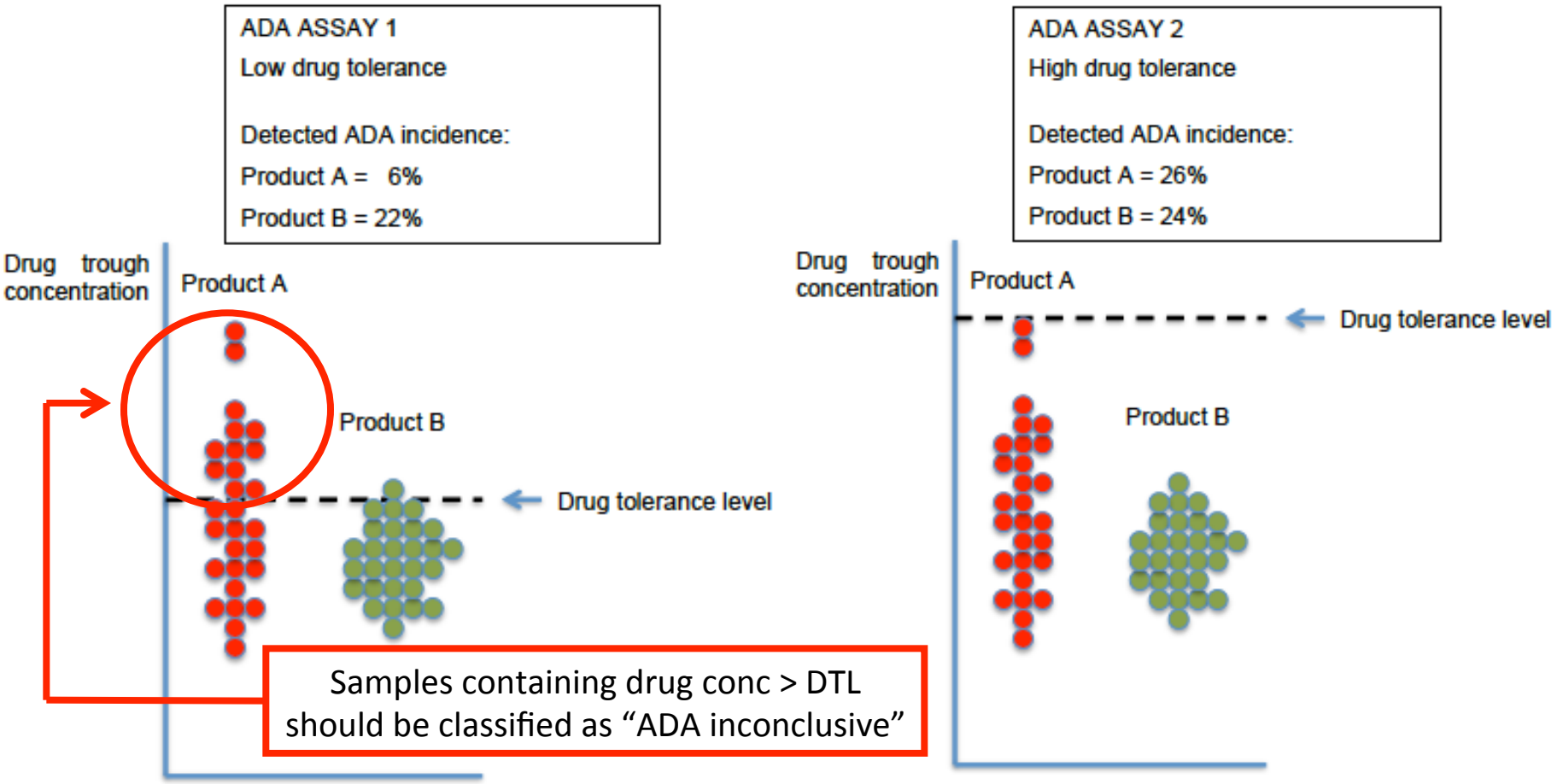
- Erythropoietin
  - *from* CKD / IV *to* CKD / SC
  - *from* CKD / IV *to* SC / Oncology

Uncertain:

- Rituximab
  - Oncology to Rheumatology ?

PK and ADA are inter-dependent bioanalytical variables

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



Post-authorisation commitments: Immunogenicity

Additional ***post***-authorisation immunogenicity evaluation required only where there are identified risks / missing information

Ref: EPAR's

epoetin
somatropin
infliximab

Immunogenicity-related risks monitored within PASS's

Extent of interventional ADA monitoring not clear from EPAR's

filgrastim
follitropin
insulin

No additional monitoring required (SmPC warnings only)

Switching of infliximab

Rheumatoid Arthritis
PLANETRA extension

Yoo DH et al;
Arthritis Rheum 2013

Time-point	Maintained on CT-P13 (n=159)	Switched from Remicade to CT-P13 in extension phase (n=143)
	% ADA positive	
Week 54	49.1	49.3
Week 78	50.4	49.6
Week 102	46.4	49.6

Ankylosing Spondylitis
PLANETAS extension

Park W et al;
Arthritis Rheum 2013

Time-point	Maintained on CT-P13 (n=90)	Switched from Remicade to CT-P13 in extension phase (n=84)
	% ADA positive	
Week 54	22.2	26.2
Week 78	24.4	31.3
Week 102	25.0	30.7

Non-clinical data was *not* instructive for assessment of immunogenicity-related risk for approved biosimilars

Some differences in ADA incidence detected in directly comparative non-clinical studies of biosimilar *vs*. reference products:

SILAPO®

Source: EPAR

Rat	Comparative (*vs* ERYPO®), repeat-dose toxicology, 3 doses per week for 13-week duration, subcutaneous	No meaningful difference
Dog	Comparative (*vs* ERYPO®), repeat-dose toxicology, 13-week duration, intravenous	Higher incidence of non-neutralizing ADA's detected for SILAPO® (8/16 dogs) relative to ERYPO® (1/8); not considered instructive for clinical immunogenicity due to foreign nature / expected immunogenicity of human rhEPO

"In the development of similar biological medicinal products (biosimilars), the comparison of the anti- drug antibody response to the biosimilar and the reference product in an animal model is not recommended as part of the biosimilar comparability exercise, due to the low predictivity for the immunogenicity potential in humans. "

Draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006 Rev. 1, 24 Sep 2015

Summary

- 17 distinct MAA reviews completed + 11 MAA's under review
- Immunogenicity assessment highly product-dependent
- Issues identified in pre-authorisation phase:
  - Clinical impactful immunogenicity for one epoetin
  - ADA *vs.* HCP for early batch of somatropin
  - Additional data for glycosylation difference (follitropin)
  - ADA assay validation incomplete for interferon-alfa
- Extrapolation of indications permitted in most cases
- No post-authorisation immunogenicity-related issues to date
- *Impact of formulation differences?*