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Health Products Regulatory Authority

Welcome to the HPRA Biosimilar Information Evening for Healthcare Professionals

HPRA Offices

18 October 2017

Overview

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Speaker	Title	Topic
Una Moore	Pharmaceutical Assessment Manager	Overview of biological and biosimilar medicines
Maeve Lally	Senior Pharmaceutical Assessor (Biologics)	Quality and non-clinical data requirements
Sandra Bright	Clinical Assessor	Clinical data requirements
Emma Lawless	Vigilance Assessor	Pharmacovigilance
Joan O'Callaghan	Researcher	Interchangeability and international trends
Anthony O'Connor	Consultant Gastroenterologist and Honorary Senior Lecture, TCD	A biosimilar switch – real world experience

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Overview of biological and biosimilar medicines

Una Moore
Pharmaceutical Assessment Manager, HPRA

Biological Products - what are they?

– A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

→ Directive 2001/83/EC

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→ Directive 2001/83/EC

Annex II GMP Guide:
Can be defined largely by reference to their method of manufacture

Manufacture of recombinant proteins

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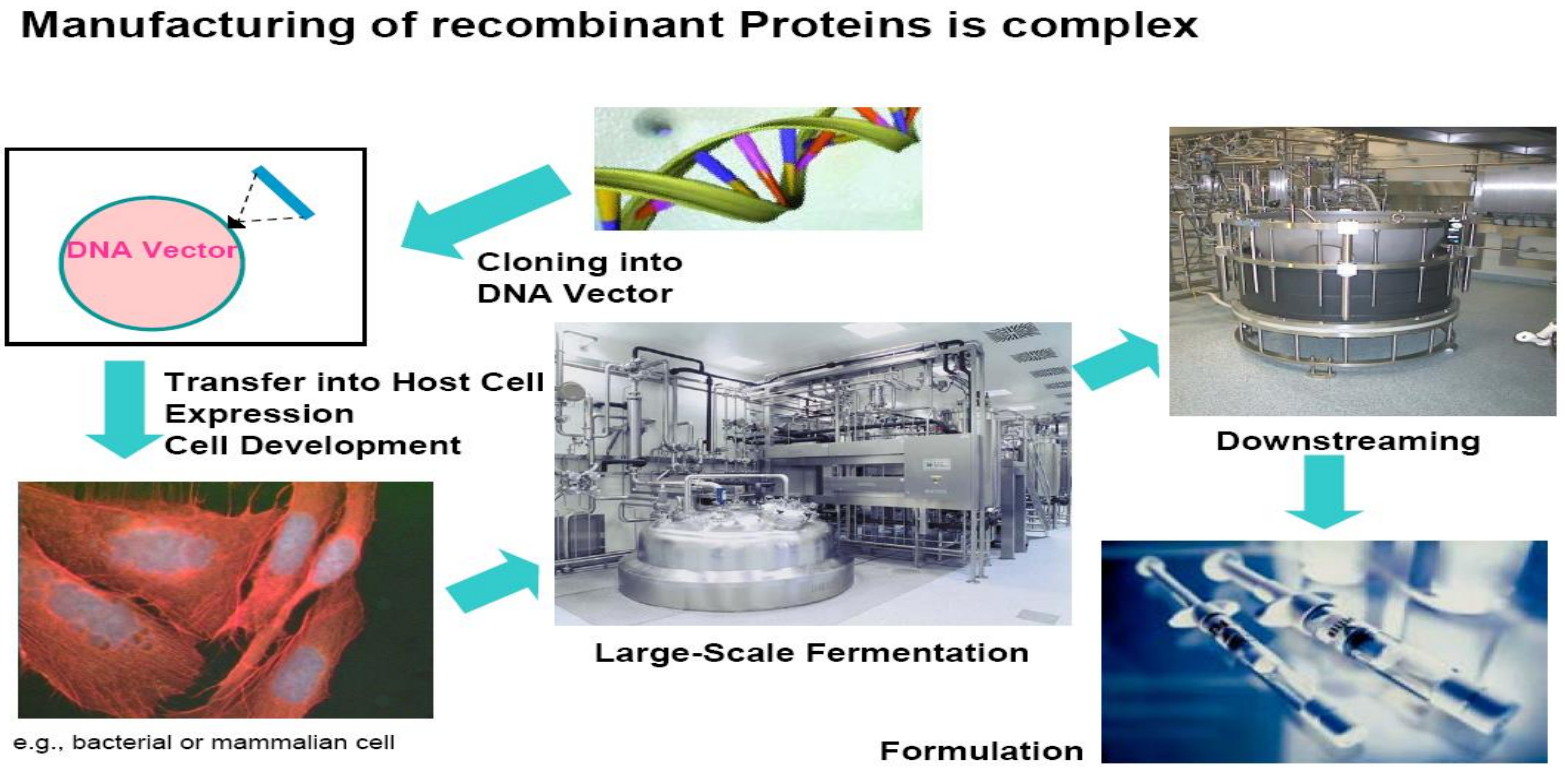
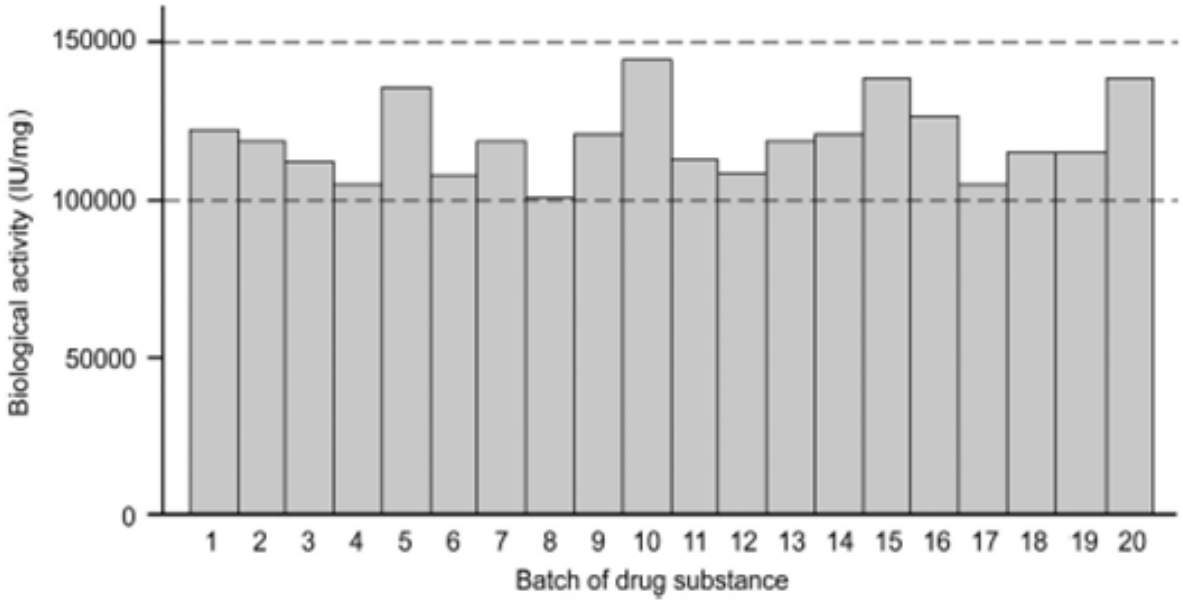


Production process and control are considered part of the biological product -

Source: Slide by Nanna Aaby Kruse, Mediacademy, Oct 2011

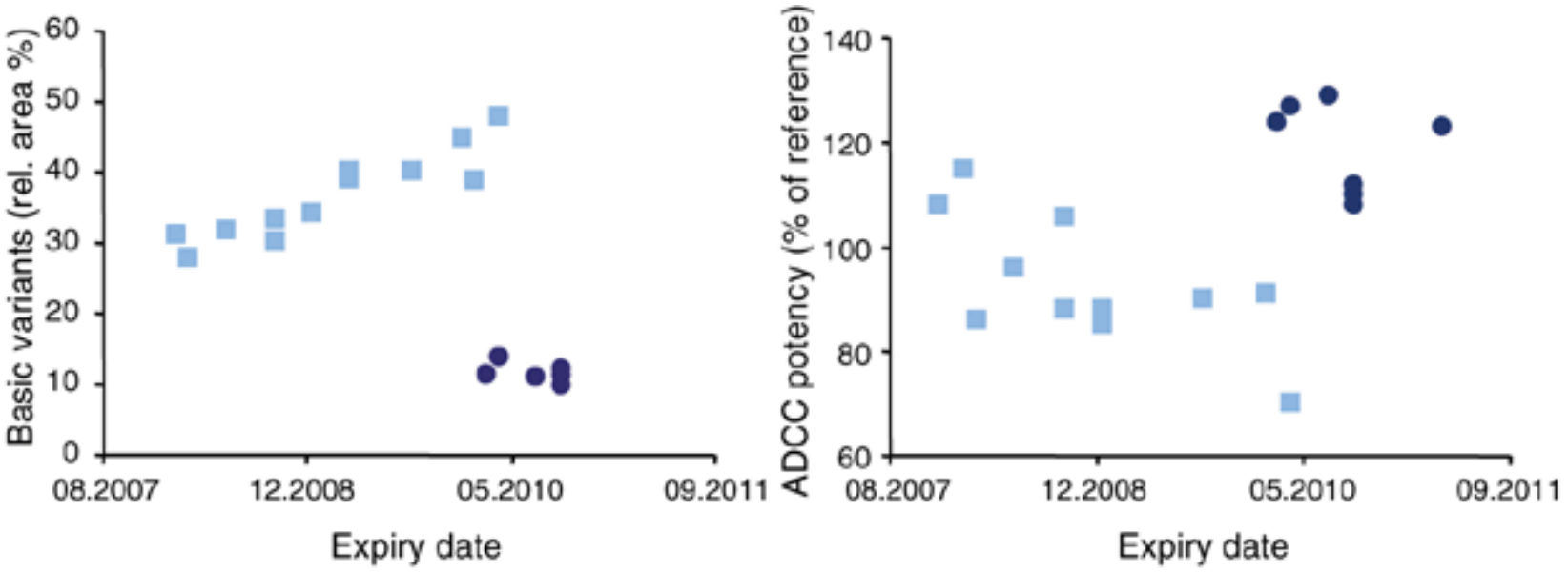
Heterogeneity of biological products

Batch to batch heterogeneity is seen with biological products. Successive batches are not truly identical due to the use of variable biological materials, processes used in their manufacture and their complexity.



Batch to Batch Consistency?

Difference in quality profile of Mabthera following manufacturing change



Nature Biotechnology 29, 310–312 (2011)

What's a Biosimilar?

- A *close* copy of an authorised biological product – any biological product.

Oh a generic!!! Not entirely!

Biosimilar idea has evolved from generics – so the concept is the same!

- Generics have the same qualitative and quantitative composition in active substance
- Biosimilars are essentially the same as the approved product but with minor differences to the active substance

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What's a Biosimilar?

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised biological medicine product (reference) in the EEA.

Legal basis: Directive 2001/83/EC

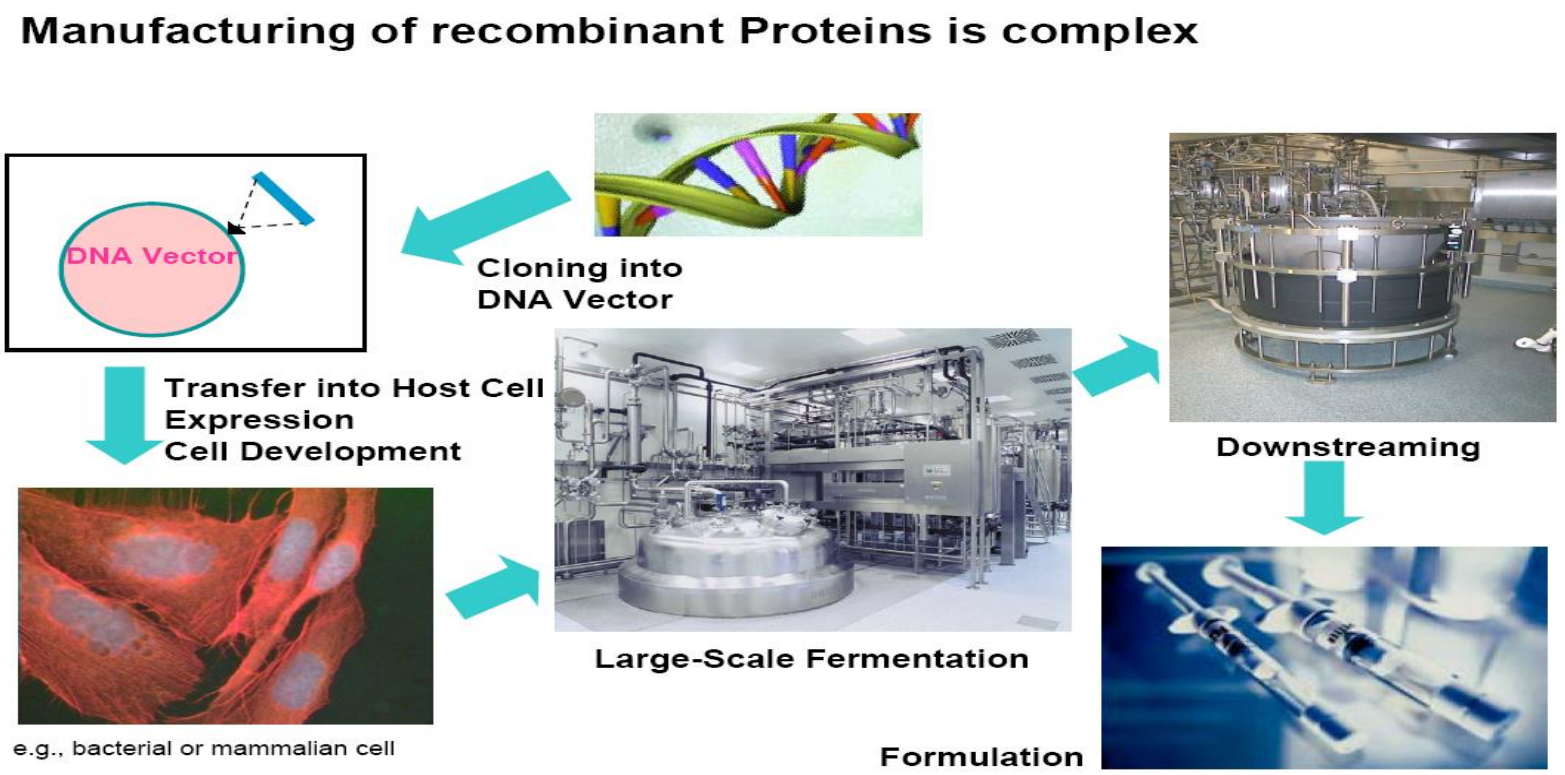
Article 10(1) allows for the authorisation of generics

Article 10(4) - Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines……

Annex I -The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a **case by case basis** in accordance with relevant scientific guidelines

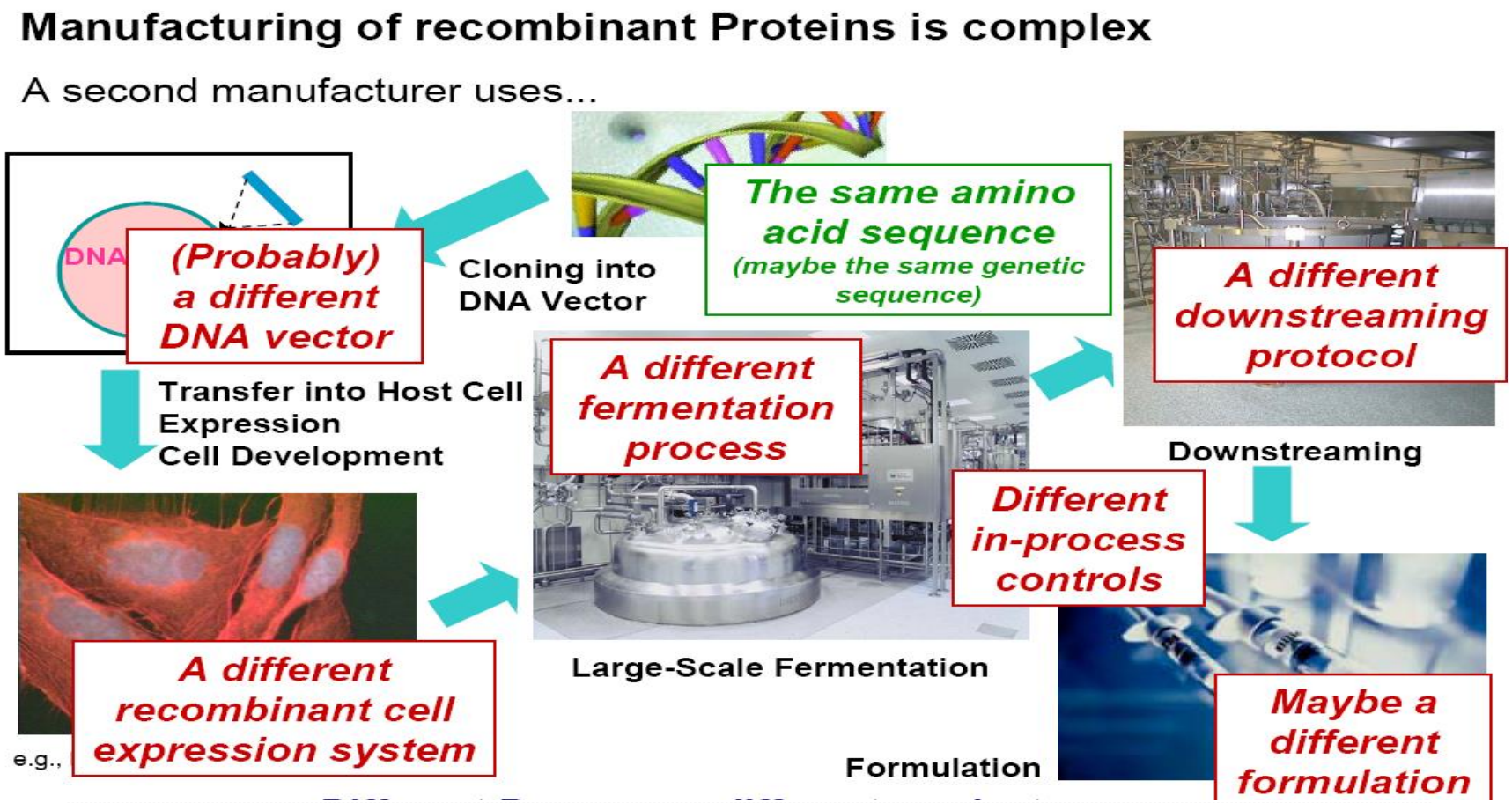
Manufacture of recombinant proteins



Production process and control are considered part of the biological product

Source: Slide by Nanna Aaby Kruse, Mediacademy, Oct 2011

Difficulties with manufacturing exact copies of reference product



Source: Slide by Nanna Aaby Kruse, Mediacademy, Oct 2011

Biosimilar approval process

- Manufacturers must demonstrate that biosimilars are similar to the reference product in terms of quality, safety and efficacy and there are no clinically meaningful differences between the two
- Tailored approach which involves a comparability exercise against the reference product
  - First step: quality comparability
  - Second step: non-clinical comparability
  - Third step: clinical comparability
- Only comes on market after patent of reference product has expired
- Encourages competition which can lead to price reductions and improve patient access to high cost medicines

Marketing Authorisation Applications (MAAs) submitted to EMA (Oct 2017)

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41 MAAs reviewed

2 refused

Interferon alfa (1)
Insulin human (1)

36 positive

Enoxaparin sodium (2)
Somatropin (1)
Epoetin (5)
Etanercept (2)
Filgrastim (7)
Follitropin (2)
Infliximab (3)
Insulin glargine (2)
Insulin Lispro (1)
Teriparatide (2)
Adalimumab (3)
Rituxumab (6)

3 Withdrawn post-authorisation

Filgrastim (2)
Somatropin (1)

Information obtained from the EMA Website

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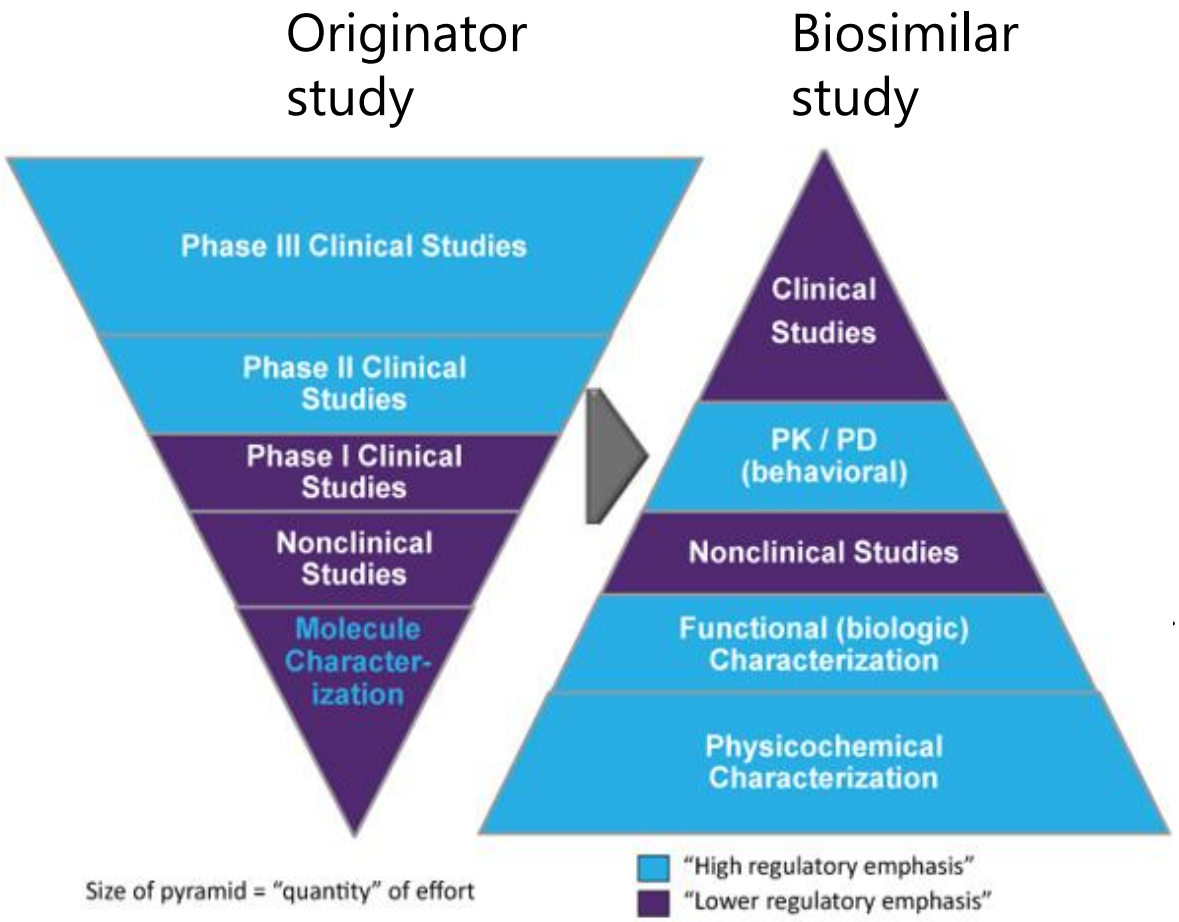
Quality and non-clinical data requirements

Maeve Lally
Senior Pharmaceutical Assessor (Biologics)

Biosimilarity is based on the "totality of evidence"

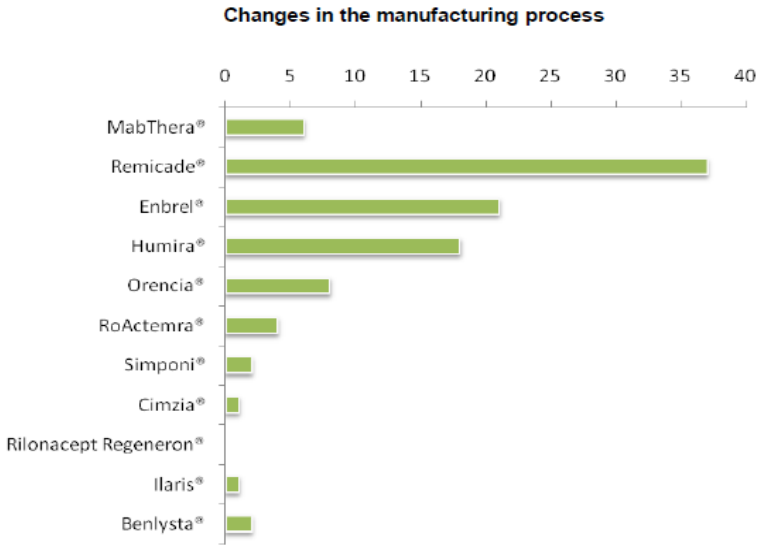


Physiochemical and functional assays are the most sensitive to reveal subtle differences

Source: Cleveland clinic website

Biosimilarity – a new concept?

- For regulators, is comparing two proteins to show they are similar a new concept?
- **No** – we have been doing this for decades when companies change the manufacturing process of biological products

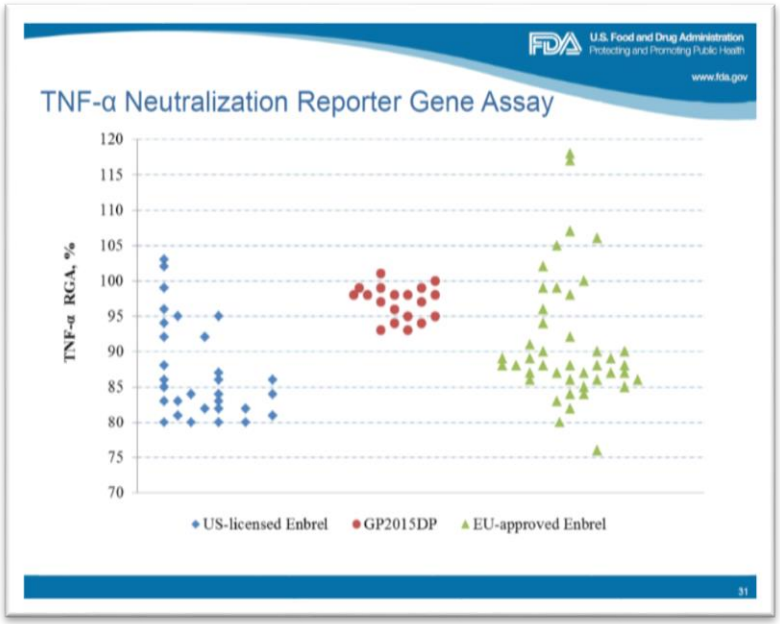


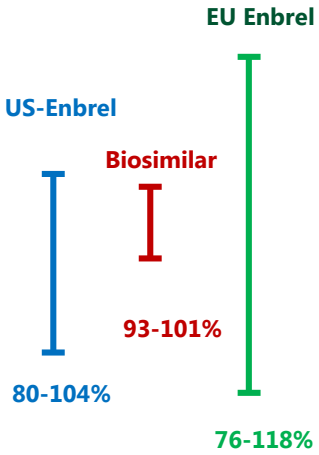
- Batches of the pre- and post-change product are compared using physiochemical and biological assays
- In the majority of cases these assays are sufficient but in some cases additional clinical studies are necessary

Schneider. Ann Rheum Dis. 2013, 72: 315-318

Variability in biological medicines

- Since they are made using living organisms, variability in biological products is the norm! Each new batch is never truly "identical" to the previous ones
- Likewise a biosimilar will never be “identical” to the reference product





Source: FDA Advisory Committee Meeting 13 July 2016

"Similar but not identical"

- Not a new concept for biological medicines
- Stepwise head to head comparison is needed to demonstrate that the biosimilar and reference product have **highly similar profiles** in terms of quality, safety and efficacy
- There should be no **clinically meaningful differences** between the two products

Development pathway for biosimilar

- Tailoring

  Analysis of several batches of the reference product for key characteristics. Range of variation defines the target ranges for the biosimilar product (QTPP)

- Fitting

  The manufacturing process is adjusted to produce a protein that fits into the desired target ranges

- Comparison

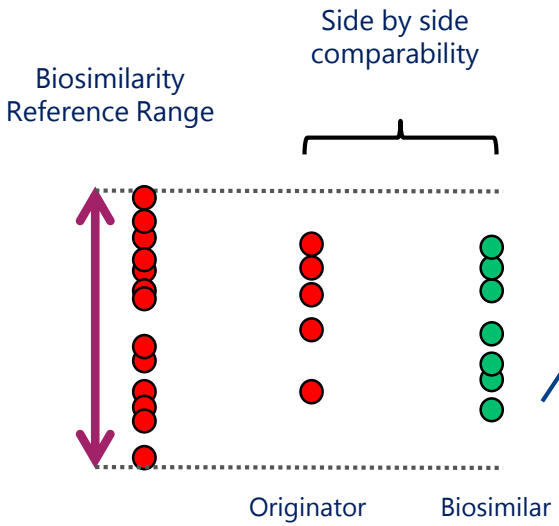
  Extensive head-to-head comparison to the reference product by physicochemical and *in vitro* biological tests

- Confirmation
  - Comparable pharmacokinetics
  - Comparable safety and efficacy

Demonstration of biosimilarity

- Batches of reference product (RMP) are tested throughout development in order to establish the Quality Target Product Profile (QTPP)

- This represents the variability of the reference product which the biosimilar should aim to be within and is used to set the **reference range**



Side by side analysis of representative number of RMP and biosimilar batches is also carried out on the same day with the same equipment etc. (reduces variability due to methods)

!! If any biosimilar batches fall outside the reference range, must be justified to not impact safety or efficacy

Typical quality attributes and characteristics to be considered in the similarity assessment of a mAb

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PRIMARY STRUCTURE
- Amino acid analysis
- Peptide map
- Intact mass
- Disulfide map
- Free sulfhdryl

SECONDARY/TERTIARY STRUCTURE
- FTIR
- Near/Far UV CD
- DSC
- NMR
- Fluorescence spectroscopy

CHARGE
- CEX-HPLC
- IE-HPLC
- IEF
- cIEF

GLYCOSYLATION
- N-linked glycans
- Oligosaccharide profile
- Monosaccharides
- Sialic acid analysis

BIOLOGICAL ACTIVITY
- Cell-based assay
- Target binding (e.g. SPR, FRET)
- FcγR binding
- FcRn binding
- ADCC
- CDC

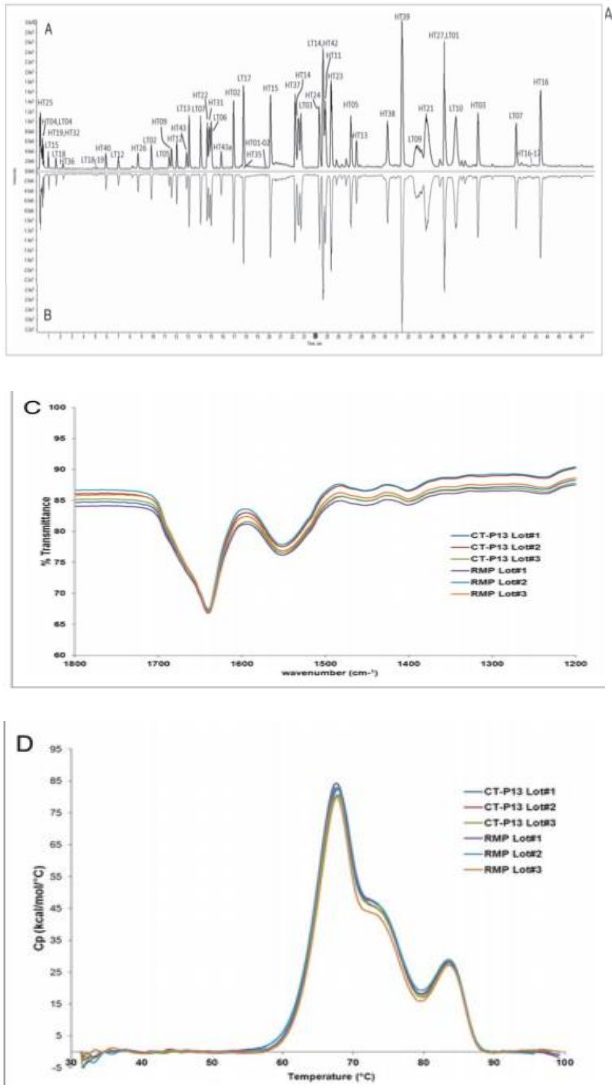
PURITY
- SE-HPLC
- CE-SDS
- SDS-PAGE
- AUC
- MALS
- FFF

PROTEIN MODIFICATIONS
- Deamidation
- Oxidation
- Glycation
- N-term Pyro-Glu
- C-term Lys

Physiochemical and biological properties

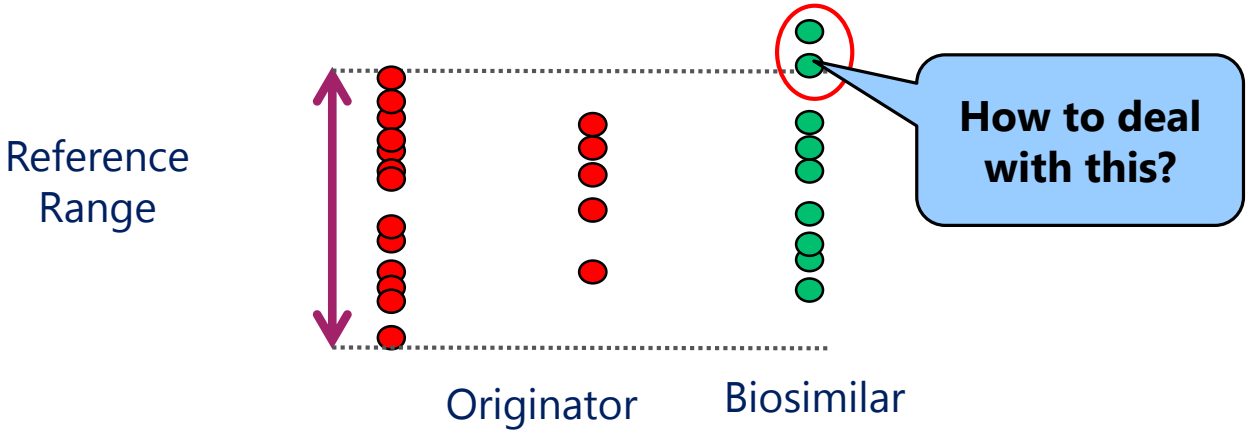
- The amino acid sequence must be the same and purity must be similar
- Potency and effector function are closely scrutinised
- Small differences in microheterogeneity pattern of the molecule may be acceptable
- The manufacturing process must comply with all current quality requirements and must be state of the art i.e. a biosimilar is of equal quality to the reference product.

There should be no **clinically meaningful differences** in terms of quality safety and efficacy based on a comprehensive comparability exercise.



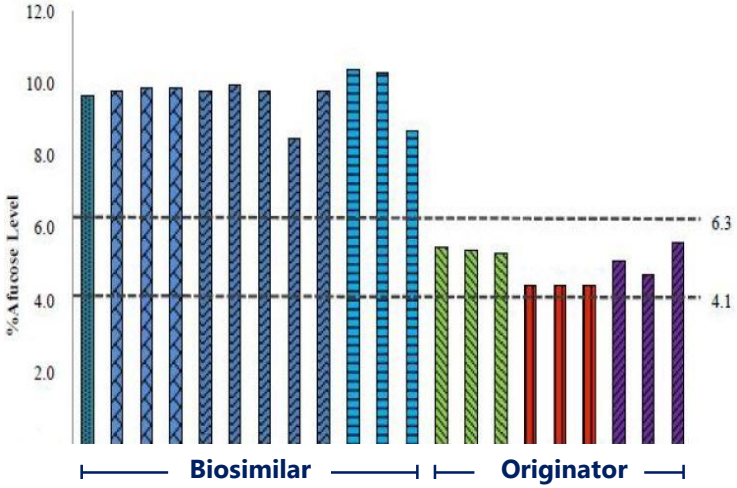
mAbs. 2014 6(5): 1163-1176

What to do when there are differences at the quality level?



- The biosimilar is not expected to be analytically identical to the reference product
- Depends on the quality attribute
- **Residual uncertainty** can be addressed with additional functional data or clinical/non-clinical data
- Any differences detected in quality attributes must be justified in relation to safety and efficacy
- Clinical data cannot be used to justify substantial differences in quality attributes

What to do when the biosimilar falls outside the reference range?



- Previous knowledge might be sufficient for justifying differences in **low criticality attributes**
- For **medium to high criticality attributes** the impact of the difference need to be addressed, primarily using suitable *in vitro* functional assays

Anti-TNF mAb example

- ✓ Apoptosis - outside-in signalling
- ✓ Cytokine release assays
- ✓ Regulatory macrophages
- ✓ Intestinal epithelial cell assays
- ✓ Adhesion molecule expression
- ✓ Use of patient cells

In vitro assays can be more sensitive to detect differences than clinical studies

Remsima: additional assays

Test Method	Key Findings
Binding to Fcγ receptors: Ex vivo assay with NK cells	• Isolated NK cells - healthy donors & Crohn's disease (CD) - differences • Presence of diluted CD patient serum – no difference
Reverse signalling	• Reverse signalling induced apoptosis – comparable • Blockade of pro-inflammatory cytokine production – comparable
Cytokine secretion	Suppression of pro-inflammatory cytokine secretion from co-stimulated epithelial cell line – comparable
Apoptosis	Suppression of epithelial cell line apoptosis – comparable
Suppression of T cell proliferation by regulatory macrophages in MLR assay	• Inhibition of T cell proliferation of PBMCs - comparable • Induction of regulatory macrophages using PBMCs - comparable • *In vitro* wound healing of colorectal epithelial cells - comparable
ADCC - tmTNFα transfected Jurkat target cells	<u>Effector cells:</u> • NK cells from CD patients (V/V & V/F) – differences • Healthy PBMCs – no difference • PBMCs from CD patients (V/F or F/F genotype) – no difference • Whole blood from (healthy donor & CD) – no difference
ADCC - LPS-stimulated monocytes target cells	No ADCC activity was seen with Remsima and Remicade when PBMCs from a healthy donor (V/F) or a CD patient (V/F) were used as effector cells

Source: Remsima EPAR

The most important take home message from this example is that the **most sensitive** assays should be used to look for differences and the real world **clinical relevance** of the data must be considered

Non-clinical data requirements

- Requirement for *in vitro* tests but the need for animal studies is limited
- Animal PK data are not particularly informative for biotherapeutics and are superseded by human data
- *In vitro* cell-based assays are more sensitive than *in vivo* models
- Animal models are poor predictors of immunogenicity
- There is often a lack of relevant animal models

Link between quality and clinical data

- Where significant differences are seen at the level of quality, this cannot be overcome by showing equivalence in clinical trials
- Clinical trials can not be used to justify substantial differences in quality attributes
- Trials should be used to **confirm** the biosimilarity already shown at the quality level

Quality and non-clinical data requirements: Summary

- The criteria for assessment of biosimilars is well developed in the EU
- Relies on a solid foundation of quality comparability, *in* vitro tests and confirmatory clinical trials
- The combination of physiochemical and functional assays should allow for a clear decision on biosimilarity
- Where uncertainty still exists, additional data should be requested
- If biosimilarity has not been shown at the quality level this cannot be overcome by clinical trials.

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Clinical data requirements

Sandra Bright, PhD
BMWP
Clinical Assessor

Clinical studies

- The aim of a biosimilar development programme is **not** to establish patient benefit *per se (this has already been done for the reference product)*
  - The trial design and endpoints may differ from the normal guideline principles

- Clinical studies use a homogeneous "model" (as opposed to a clinically challenging one)
  - The clinical study should use the most sensitive model to detect differences

- Comparability margins:
  - Represent the largest difference in efficacy that would not matter in clinical practice
  - Should be pre-specified and justified

Clinical studies

The type and extent of clinical data needed will vary and depend on:

- The complexity of the active substance
- How well it can be characterised (at quality level)
- Availability of surrogate end points
- If any safety concerns are associated with the reference product or product class

Clinical Studies Required – Stepwise development

1. Phase I Comparative Pharmacokinetics (PK) / Pharmacodynamics (PD) data
2. Phase III Safety + Efficacy trials

Pharmacokinetics (PK) studies

- Phase I clinical trial comparing biosimilar to reference product
- A single dose cross-over study in healthy volunteers preferable
- Primary end-points:
  - Cmax: Maximum concentration in the blood
  - $AUC_{0-\infty}$: Area under the curve
- Secondary end-points
  - Tmax, $t_{1/2}$, AUC_{0-last}
- Safety data
- Immunogenicity data

Pharmacodynamics (PD) studies

- Should be incorporated into PK studies where feasible
- Not all products will have suitable PD targets
- If suitable PD targets, should be validated surrogate markers
- PD end-point = co-primary with PK end-points, study should be powered accordingly

Biosimilar	Validated PD end-point
Filgrastim	Absolute neutrophil count (ANC)
Heparin	AUC of anti-Xa, anti-IIa, TFPI
Insulin	Euglycaemic clamp test
Teriparatide	Serum calcium concentration

Efficacy studies

- Phase III clinical trial in patient population comparing biosimilar to reference product
- Adequately powered, randomised, parallel group comparative clinical trial(s), double-blind
- Equivalence design preferable
- Primary end-points: Efficacy – depends on the indication
- Secondary end-points: Efficacy – depends on the indication
- Safety data
- Immunogenicity data
- PK/PD data in patients (particularly important if main PK study performed in healthy volunteers)

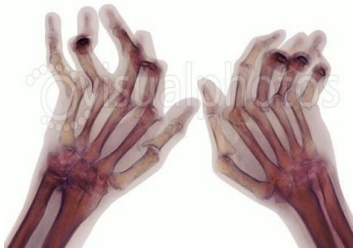
Safety Data

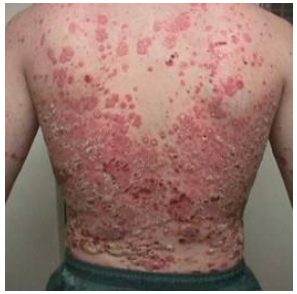
- Captured during PK/PD studies and pivotal efficacy studies
- Overall should have the same safety profile as reference product
  - Similar frequency, severity, type of adverse reactions
- Risk minimisation procedures in place during clinical studies
- Safety data up to 1 year in order to identify any differences between the biosimilar and reference
  - Includes immunogenicity testing
- Pharmacovigilance and risk management activities necessary during the post-authorisation phase
- Over 10 years experience with biosimilars

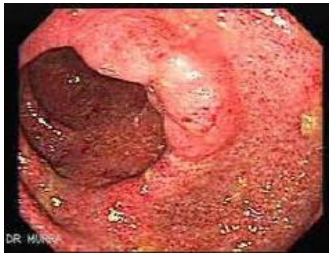
Immunogenicity Data

- Incidence of anti-drug antibodies (ADA) and neutralising antibodies (Nabs) must be investigated
- Captured during PK/PD studies and pivotal efficacy studies
- Different biological actives will have different incidences of ADAs
- Usually one year follow-up required pre-licensing for long term treatment

Indication extrapolation







Once biosimilarity has been established in one or more indications, a biosimilar may be approved for additional or all other indications for which the originator has been approved without the need for additional clinical trials

If there is:

1) A convincing demonstration of biosimilarity based on totality of the evidence obtained through a comprehensive comparability exercise
2) Demonstration of comparable clinical efficacy and safety in a sensitive patient population
3) Similarity of mechanism of action across indications

Indication extrapolation not automatic but it may not be necessary to repeat the entire clinical development programme of the reference product

Extrapolation

Not unique to biosimilars - has been used for many years in originator products which have undergone a manufacturing change

Aranesp (darbepoetin alfa) line extension for new master cell bank and new manufacturing technology

- ✓ Head to head trial in patients with chronic kidney disease using pre- and post-change batches - extrapolation to anaemia indication accepted

Herceptin (Trastuzumab) new s.c formulation with hyaluronidase

✓ Clinical study in neoadjuvant setting - extrapolation to metastatic setting based on totality of evidence, *"population was considered more homogenous with fewer confounding factors than patients with MBC"* Herceptin EPAR, 2013

Rituximab Biosimilar - Truxima

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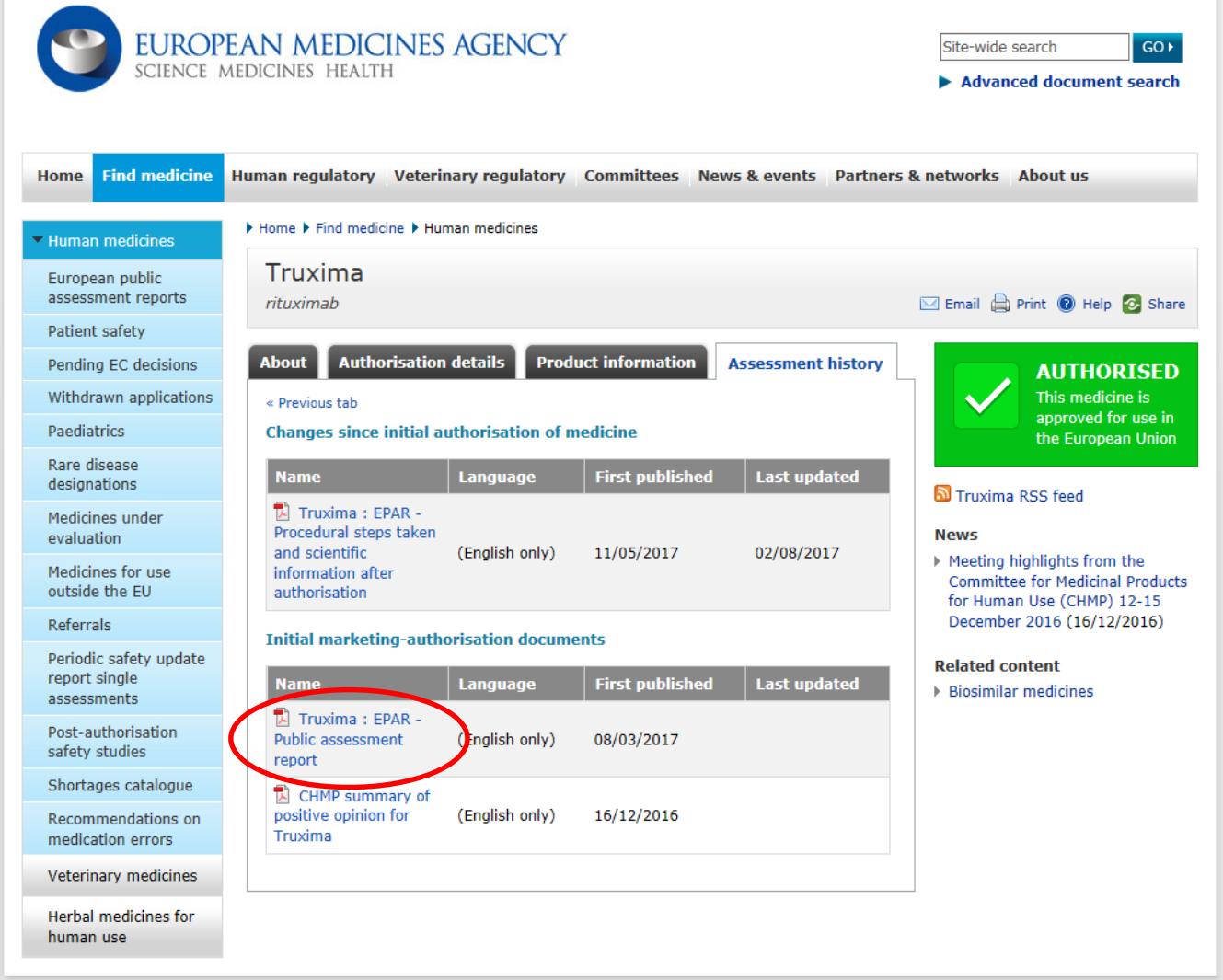

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Truxima
rituximab

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Changes since initial authorisation of medicine

Name	Language	First published	Last updated
Truxima : EPAR - Procedural steps taken and scientific information after authorisation	(English only)	11/05/2017	02/08/2017

Initial marketing-authorisation documents

Name	Language	First published	Last updated
Truxima : EPAR - Public assessment report	(English only)	08/03/2017	
CHMP summary of positive opinion for Truxima	(English only)	16/12/2016	

AUTHORISED
This medicine is approved for use in the European Union

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Rituximab Biosimilar - Truxima

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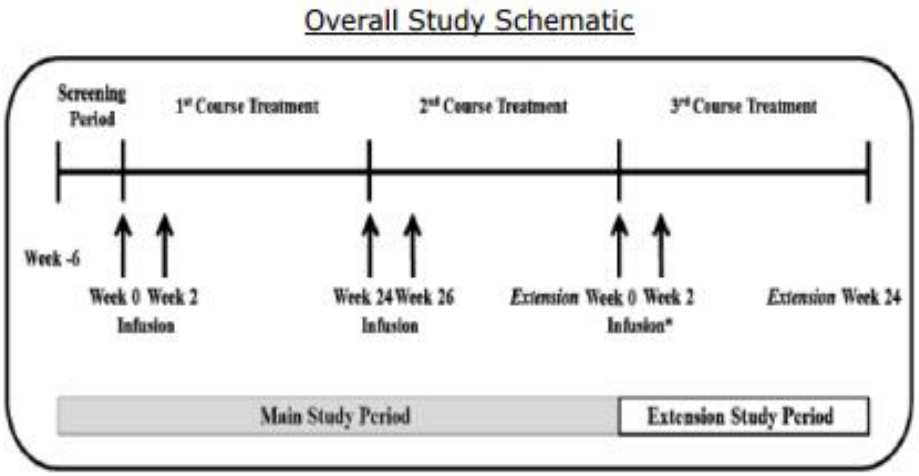
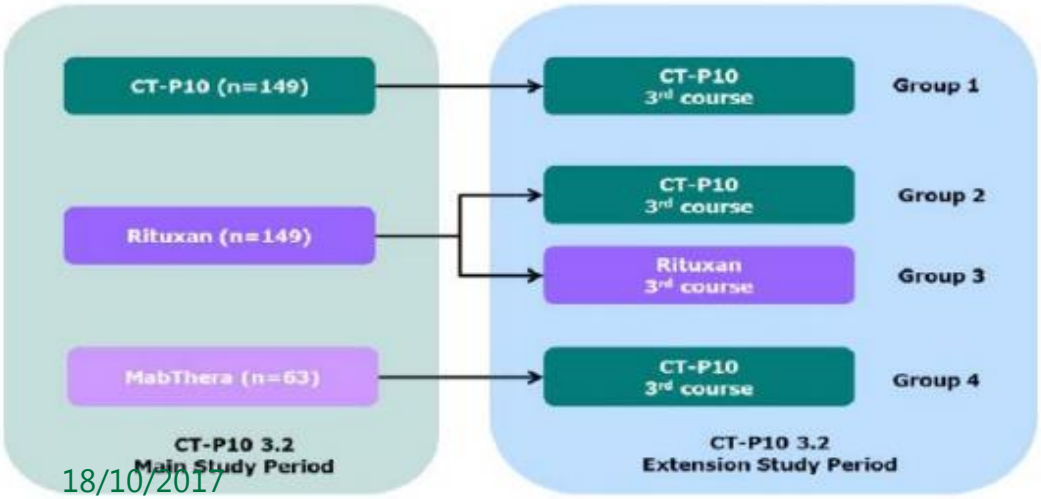


* The third treatment course was initiated between Week 48 and Week 52 of the entire study period based on the results assessed within 8 weeks from Extension Week 0.

Figure 9–3 Patient Assignment for the Extension Study Period



- CT-P10: Biosimilar
- MabThera: EU reference
- Rituxan: US reference

Truxima in Rheumatoid Arthritis

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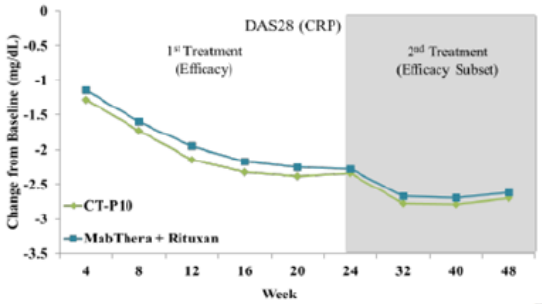
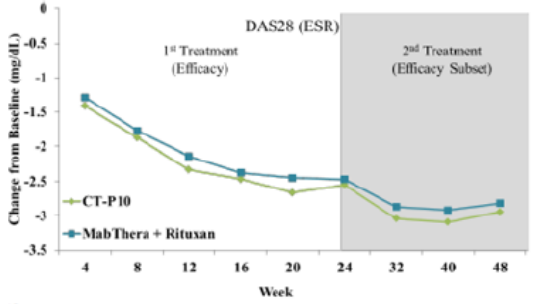
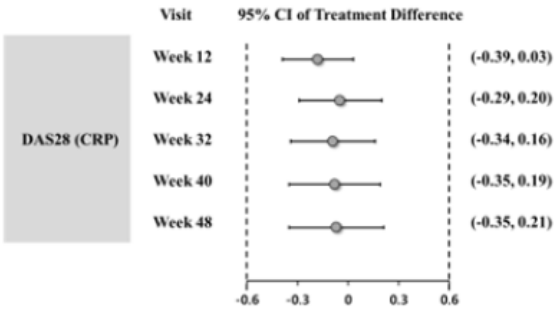
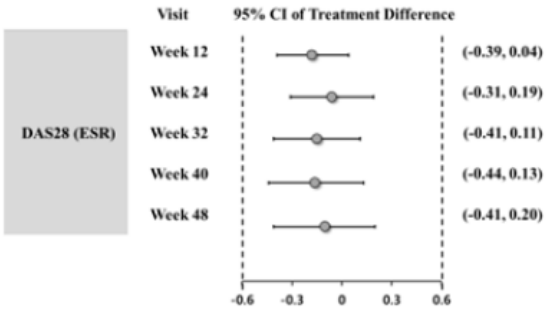


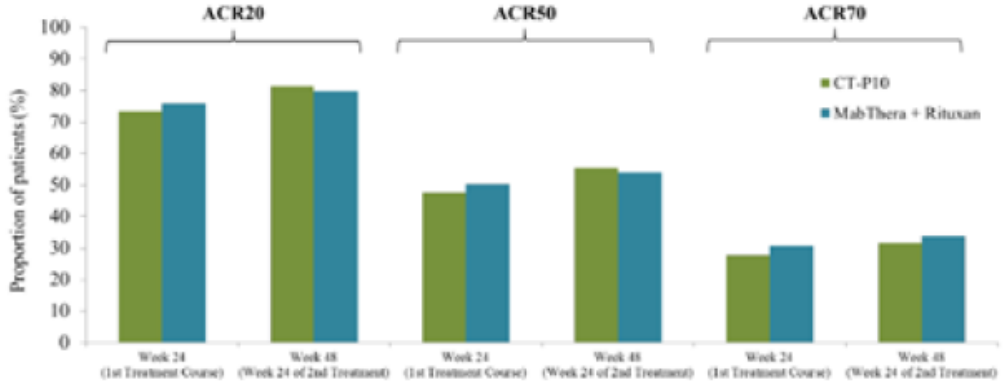


Efficacy Population





Efficacy population



Efficacy Population

Truxima in advanced follicular lymphoma

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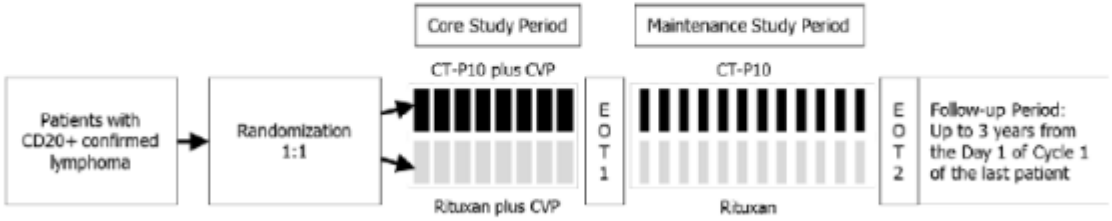
STUDY CT-P10 3.3

This study was a Phase 1/3, randomised, parallel-group, active-controlled, double-blind study to demonstrate equivalence of pharmacokinetics and non-inferiority of efficacy for CT-P10 in comparison with Rituxan, each administered in combination with cyclophosphamide, vincristine and prednisone (CVP) in patients with Advanced Follicular Lymphoma (AFL).



Abbreviations: CD20+, cluster of differentiation 20 positive; CVP, cyclophosphamide, vincristine, and prednisone; EOT1, first end-of-treatment visit; EOT2, second end-of-treatment visit.

Table 22: Proportion of Patients Achieving ORR (CR + CRu + PR) over Cycle 8 (Week 24) of Core Study Period According to the 1999 IWG Criteria in Study CT-P10 3.3: PP population - Central Review

Number of patients (%)	CT-P10 (N=66)	Rituxan® (N=68)	Difference[1]
ORR (CR + CRu + PR)	64 (97.0)	63 (92.6)	(4.3)
CR	20 (30.3)	15 (22.1)	-
CRu	6 (9.1)	8 (11.8)	-
PR	38 (57.6)	40 (58.8)	-

[1] Difference was calculated using percentages not the round off values.
ORR: Overall response rate, CR: Complete response, CRu: Unconfirmed complete response, PR: Partial response

Clinical data - Summary

- Comparability exercise ensures the new biosimilar has the same safety and efficacy in all indications as the reference product
- Clinical data is confirmatory
- The assessment of biosimilars is well developed in the EU with a good safety record over 10 years
- Clinical trial data is required for all biosimilar licence approvals
  - Phase I PK data / PD data (if suitable marker available)
  - Phase III efficacy study (if suitable PD marker not available)
  - Safety and immunogenicity data
- Extrapolation from one indication to another is common
  - If similar mechanism of action
  - Thoroughly and scientific justified
- Biosimilarity is based on the **totality of evidence**, not just the clinical evidence

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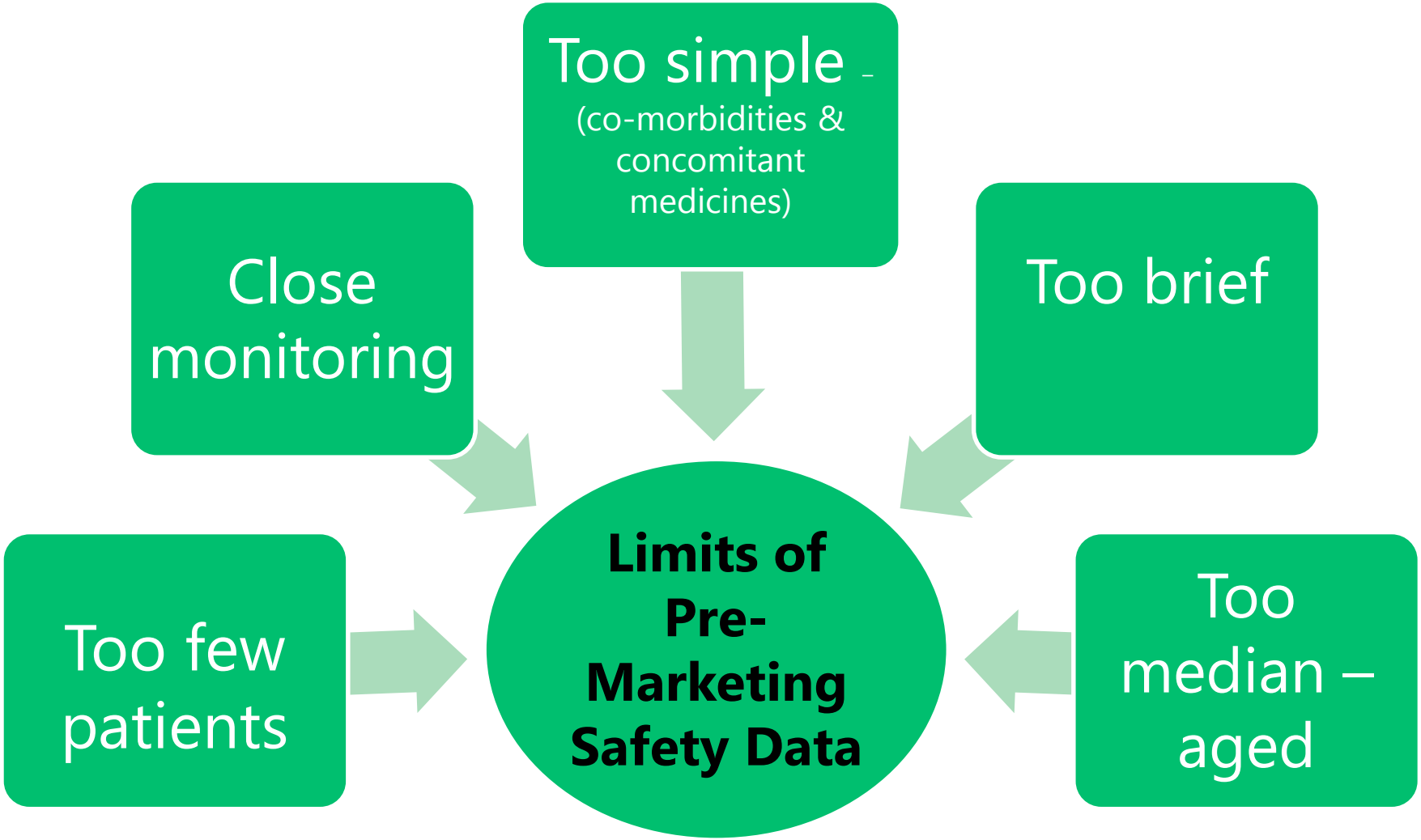
Pharmacovigilance considerations for biological medicines

Emma Lawless
Vigilance Assessor

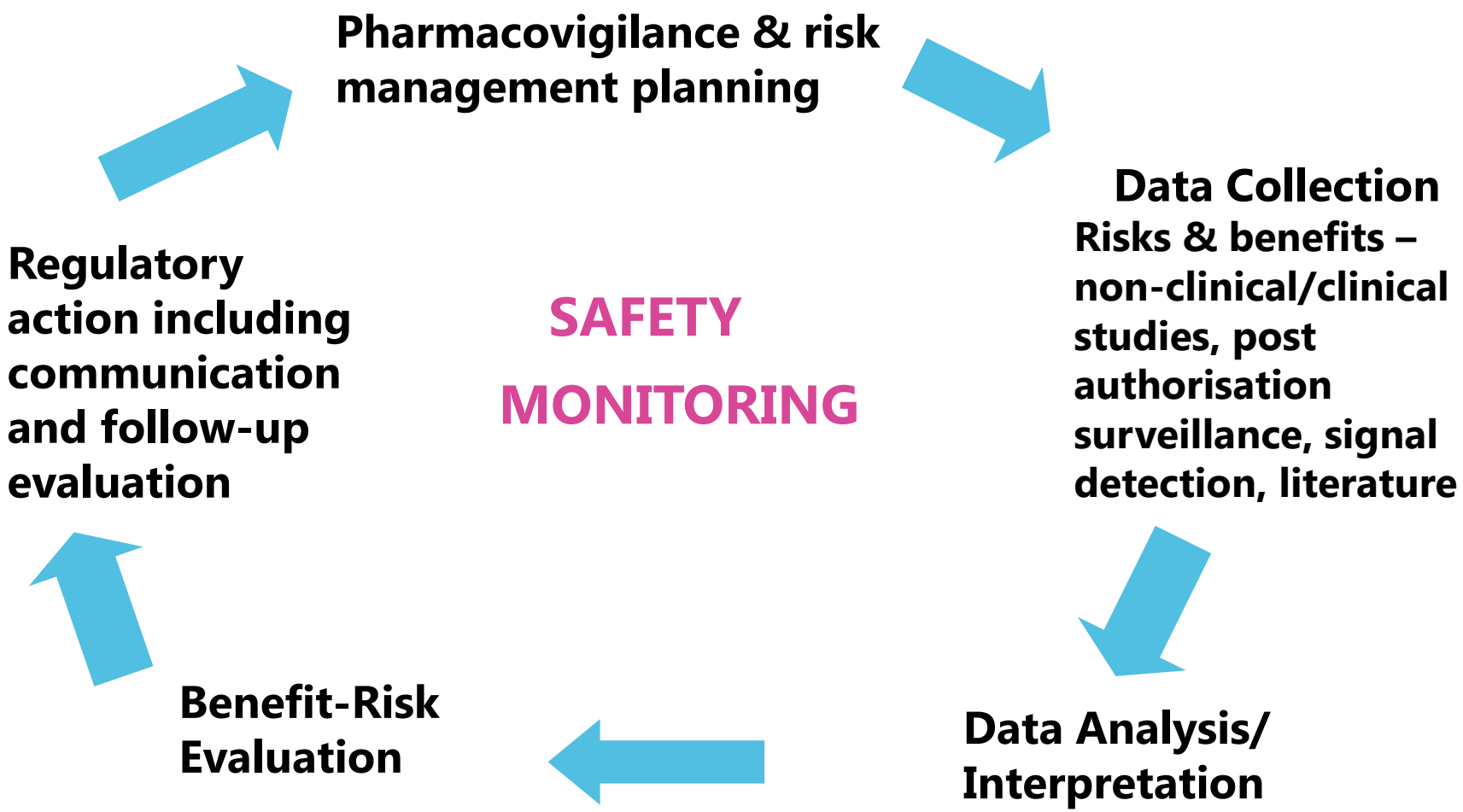
Pharmacovigilance

- Detection/identification of adverse reactions/risks
- Characterization of risks
  - Frequency
  - Reversibility
  - Severity
  - Risk Factors
- Risk management
- Pharmacovigilance planning
- Benefit-risk assessment

Pharmacovigilance – why?



Proactive Pharmacovigilance



Specific challenges in risk management of biologicals

- Limited predictability of pre-clinical to clinical data
- Often indicated for rare diseases and often as second and third line therapy
- Nature of safety issues (often severe e.g. PML, other immune/infection responses, malignancies)
- Impact of production/manufacturing on safety and quality attributes
- Changes in safety profile may emerge- product and batch specific
- Traceability (particularly in the context of immunogenicity, product switching)

Risk Management Plan (RMP)

An RMP includes information on a medicines safety profile and plans for pharmacovigilance activities designed to gain greater knowledge. They also explain how risks will be minimised in patients and how these efforts will be measured.

Important risks and/or unique challenges for biologicals factored into the development of RMPs to ensure these are tailored to specific products:

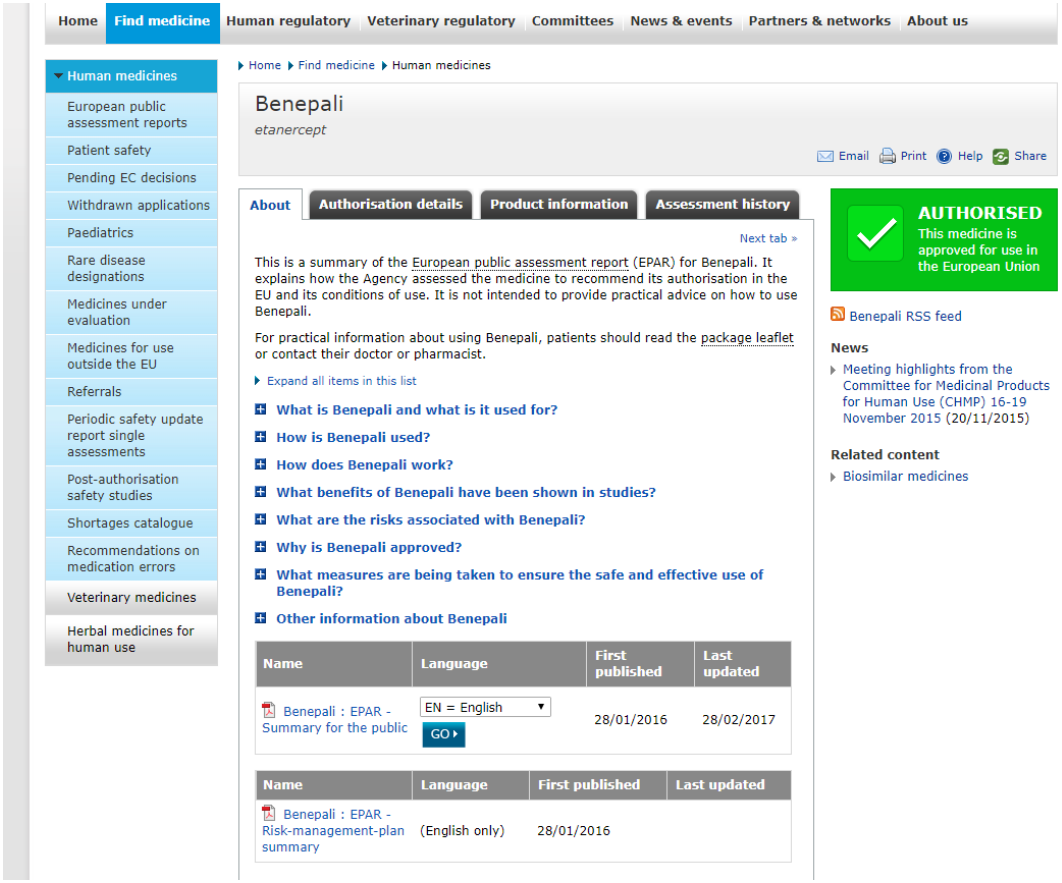
- potential immunogenicity
- potential for changes in safety profile over time
- exposure data and brand and batch tracking/ traceability
- safety differences between biosimilars

RMP for biological product may include additional pharmacovigilance activities e.g. registry study, immunogenicity study

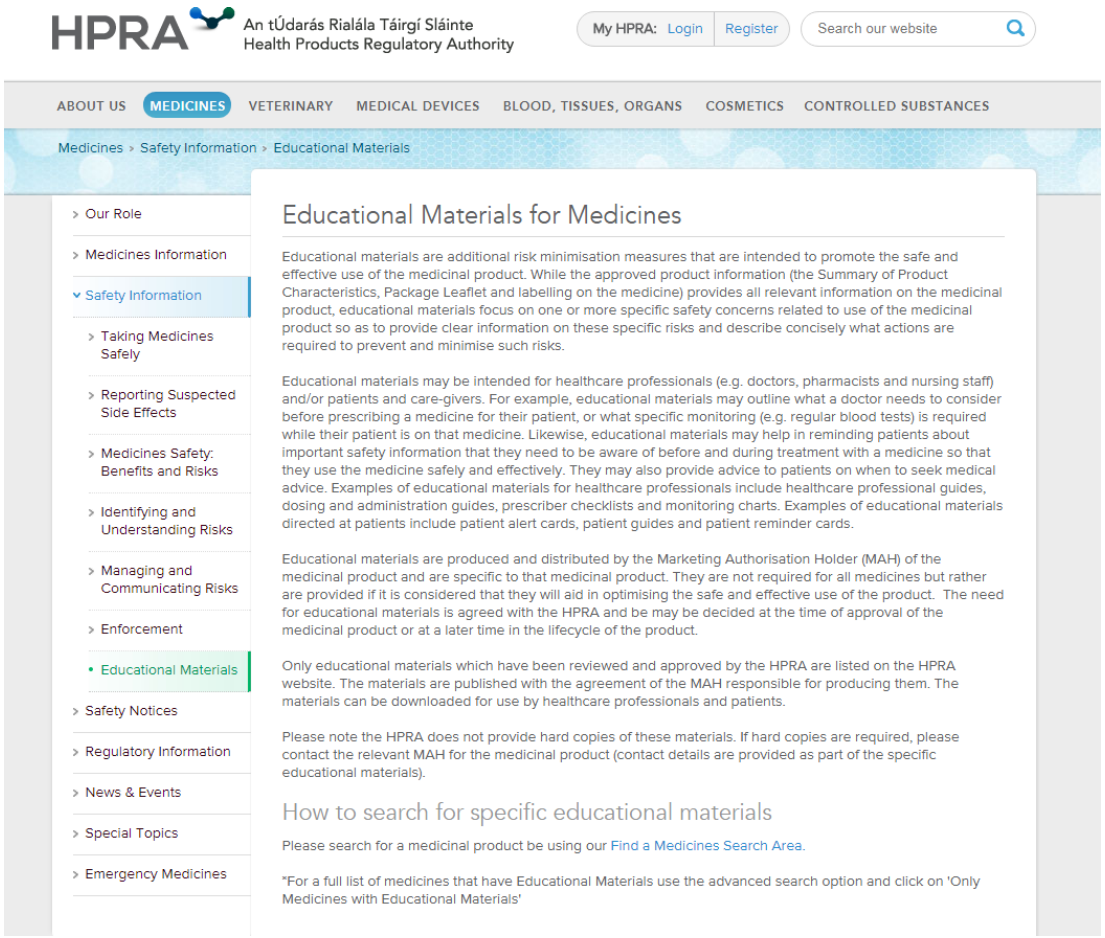
Additional risk minimisation measures may be in place e.g. education materials for HCPs and/or patient

Public summary of RMP

Published on EMA website since 2014- information behind the decision making process



Education materials on HPRA website



Identification and traceability of biological products –requirements for ADR reporting

Member States shall:

- 'ensure, through the **methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number'**

Article 102 (e)

AUGUST 2017

HPRA DRUG SAFETY
NEWSLETTER

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Biological traceability

The legislation also requires clear identification of any biological medicinal product which is the subject of a suspected adverse reaction report, indicating that the brand name and batch number of the product should be specified for adverse reaction reports. In accordance with this strengthened requirement, all adverse reaction reports associated with vaccines and other biological products will be followed up by the HPRA / Marketing Authorisation Holder to obtain this information if missing.

Key Message: Please include the brand name, batch number and expiry date (where available) when reporting a suspected adverse reaction to a biological medicinal product.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

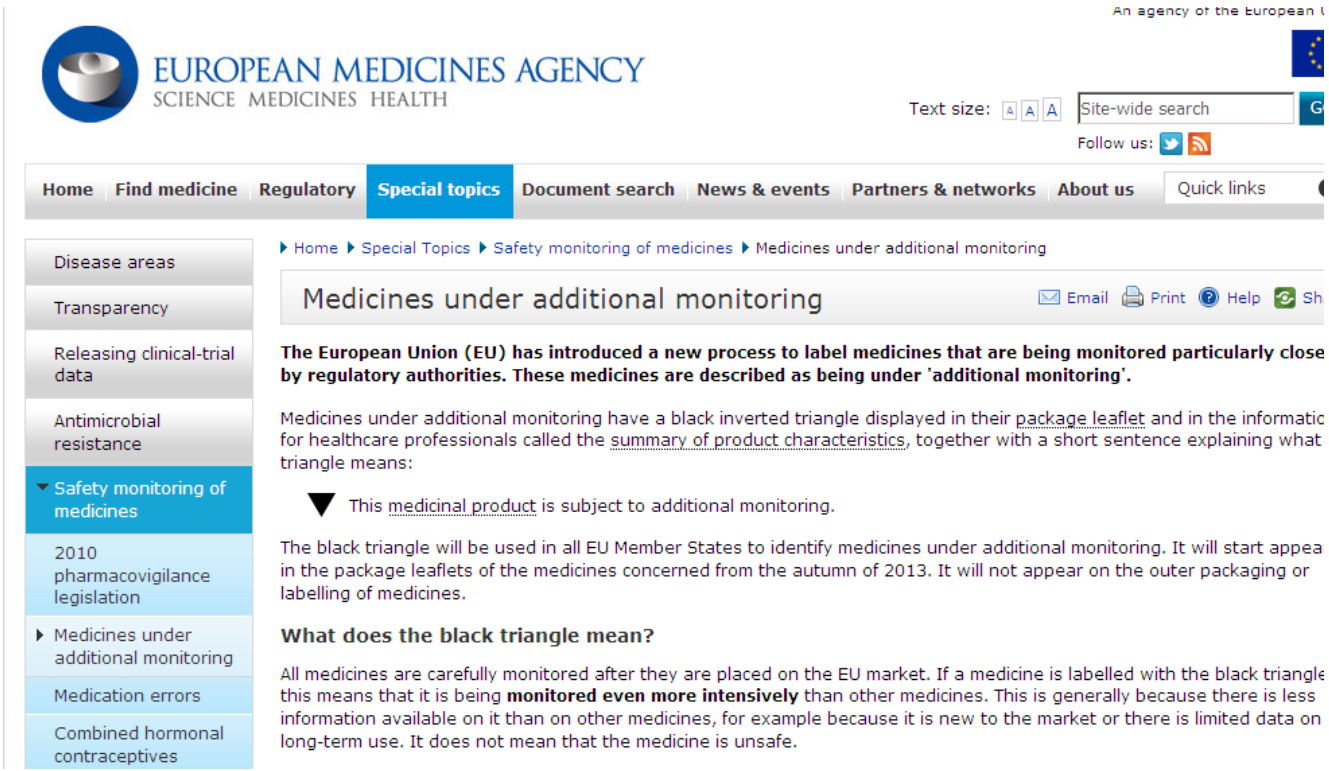
1. NAME OF THE MEDICINAL PRODUCT

Remsima 100 mg powder for concentrate for solution for infusion

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Additional monitoring list



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  - 2010 pharmacovigilance legislation
  - Medicines under additional monitoring
  - Medication errors
  - Combined hormonal contraceptives

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Medicines under additional monitoring

Email Print Help Sh

The European Union (EU) has introduced a new process to label medicines that are being monitored particularly close by regulatory authorities. These medicines are described as being under 'additional monitoring'.

Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and in the informatic for healthcare professionals called the summary of product characteristics, together with a short sentence explaining what triangle means:

▼ This medicinal product is subject to additional monitoring.

The black triangle will be used in all EU Member States to identify medicines under additional monitoring. It will start appea in the package leaflets of the medicines concerned from the autumn of 2013. It will not appear on the outer packaging or labelling of medicines.

What does the black triangle mean?

All medicines are carefully monitored after they are placed on the EU market. If a medicine is labelled with the black triangle this means that it is being **monitored even more intensively** than other medicines. This is generally because there is less information available on it than on other medicines, for example because it is new to the market or there is limited data on long-term use. It does not mean that the medicine is unsafe.

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Interchangeability

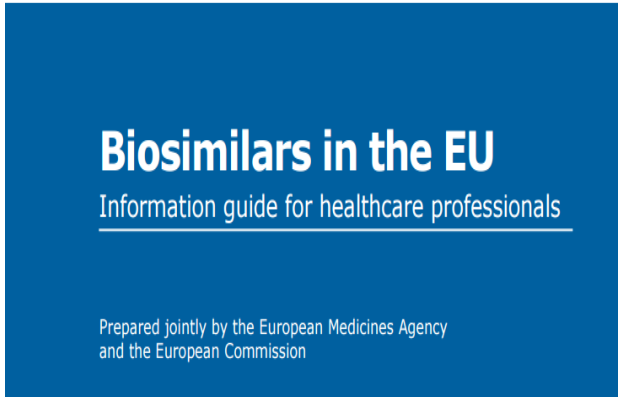
Joan O'Callaghan
Regulatory Science Ireland Biosimilar Research Project

Interchangeability, switching and substitution

Interchangeability: refers to possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect

Switching: when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent

Substitution: practice of dispensing one medicine instead of another equivalent medicine at pharmacy level without consulting the prescriber



Interchangeability

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EMA does not make recommendations on interchangeability

HPRA recommends treating physician should be involved in any decision regarding switching

Substitution of biological medicines currently not possible under Irish legislation

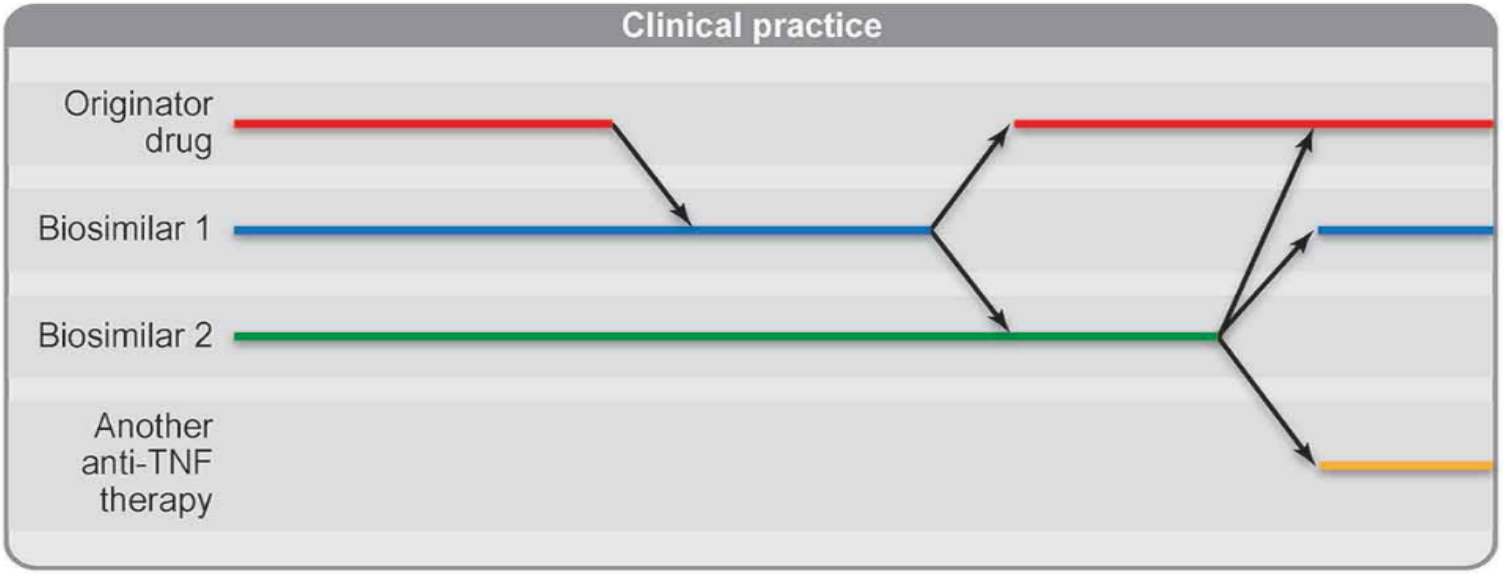
HPRA position on interchangeability

If it is planned to change the medicine a patient receives from a reference to a biosimilar, or vice versa, the treating physician should be involved; this should involve discussion between the prescriber/patient and prescriber/dispensing pharmacist

- It is not recommended that patients switch back and forth between a biosimilar and reference medicine, as the current time the availability of data on the impact of this is limited

Switching studies

- Clinical trials for MA applications often incorporate a single switch
- Real-world experience indicates that switching has no impact on safety, immunogenicity and efficacy*



Source: Faccin, F, *et al.* (2016) *Expert Opin Biol Ther*, 16(12), 1445-1453.

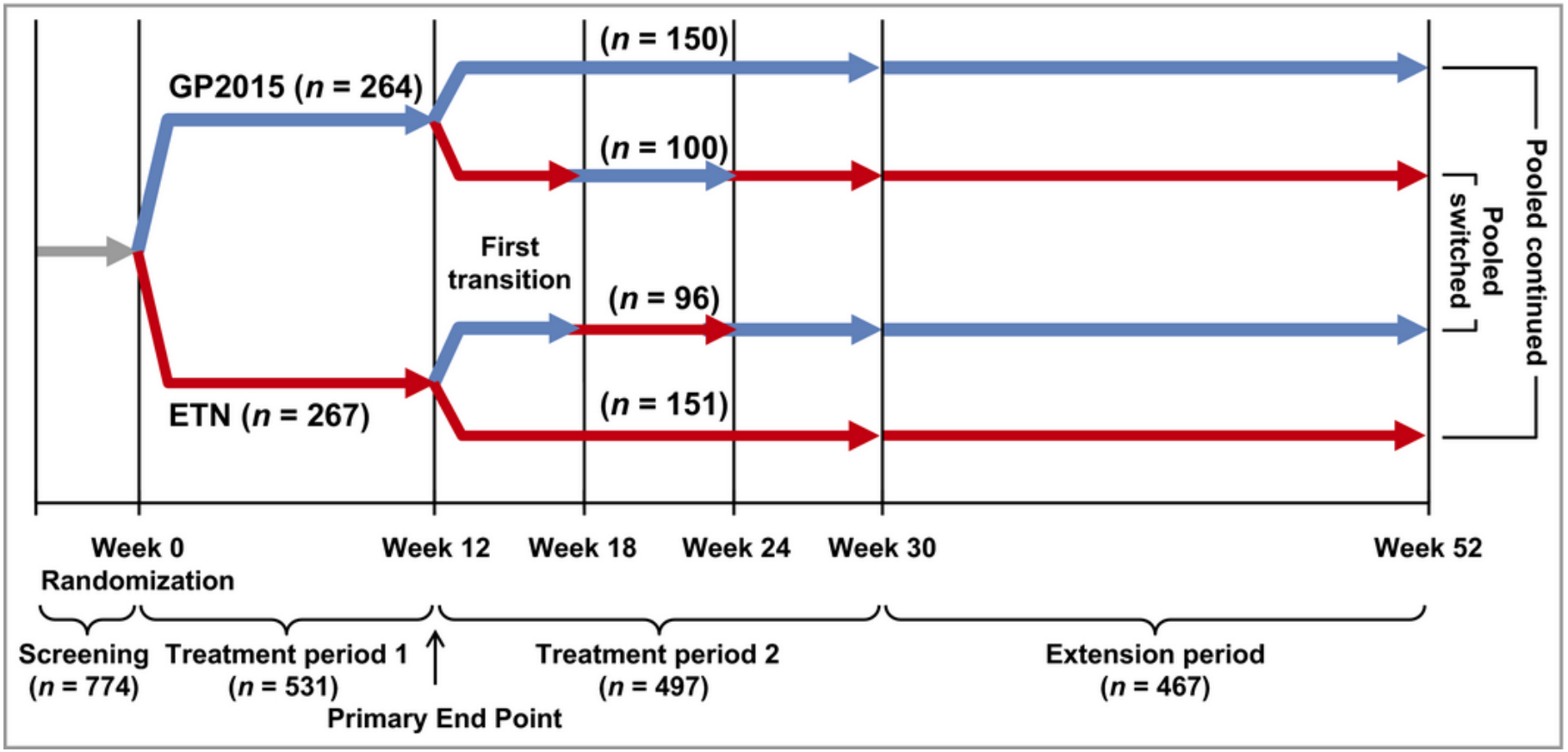
*Inotai *et al.*, Expert Opin Biol Ther, 17(8), 915-926.

Switching studies: Examples

- **Infliximab in RA and AS:** PLANTERA[1] and PLANETAS[2] – open label single switch - extension study from reference to infliximab biosimilar (n=144 and n=86)
- **Somatropin[3]:** paediatric patients switched from reference to biosimilar: single centre study (n=98)
- **Etanercept[4]** - chronic plaque type psoriasis. EGALITY study – 3 treatment switches between reference and biosimilar etanercept between week 12 to week 30 (switch groups: n =100 + n= 96)

[1]Yoo et al (2017), *Annals of the Rheumatic Diseases*, 76(2), 355.
[2]Park et al (2017), *Annals of the Rheumatic Diseases*, 76(2), 346
[3]Flodmark (2013), *Biologics in Therapy*, 3(1), 35-43
[4]Griffiths (2017), *Br J Dermatol*, 176(4), 928-938.

The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis



British Journal of Dermatology
Volume 176, Issue 4, pages 928-938, 1 MAR 2017 DOI: 10.1111/bjd.15152
http://onlinelibrary.wiley.com/doi/10.1111/bjd.15152/full#bjd15152-fig-0001

Nor-switch

- A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with maintained treatment with innovator infliximab
- 481 patients across all indications
- Primary endpoint: disease worsening (week 52)
- Non-inferiority margin: 15%
- Disease worsening in 26.2% of reference and 29.6% of biosimilar arm
- Frequency of adverse events similar between two groups
- Switching was not inferior to continued treatment with infliximab originator

Jorgensen *et al.* (2017) 'Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial', *Lancet*, 389(10086), 2304-2316.

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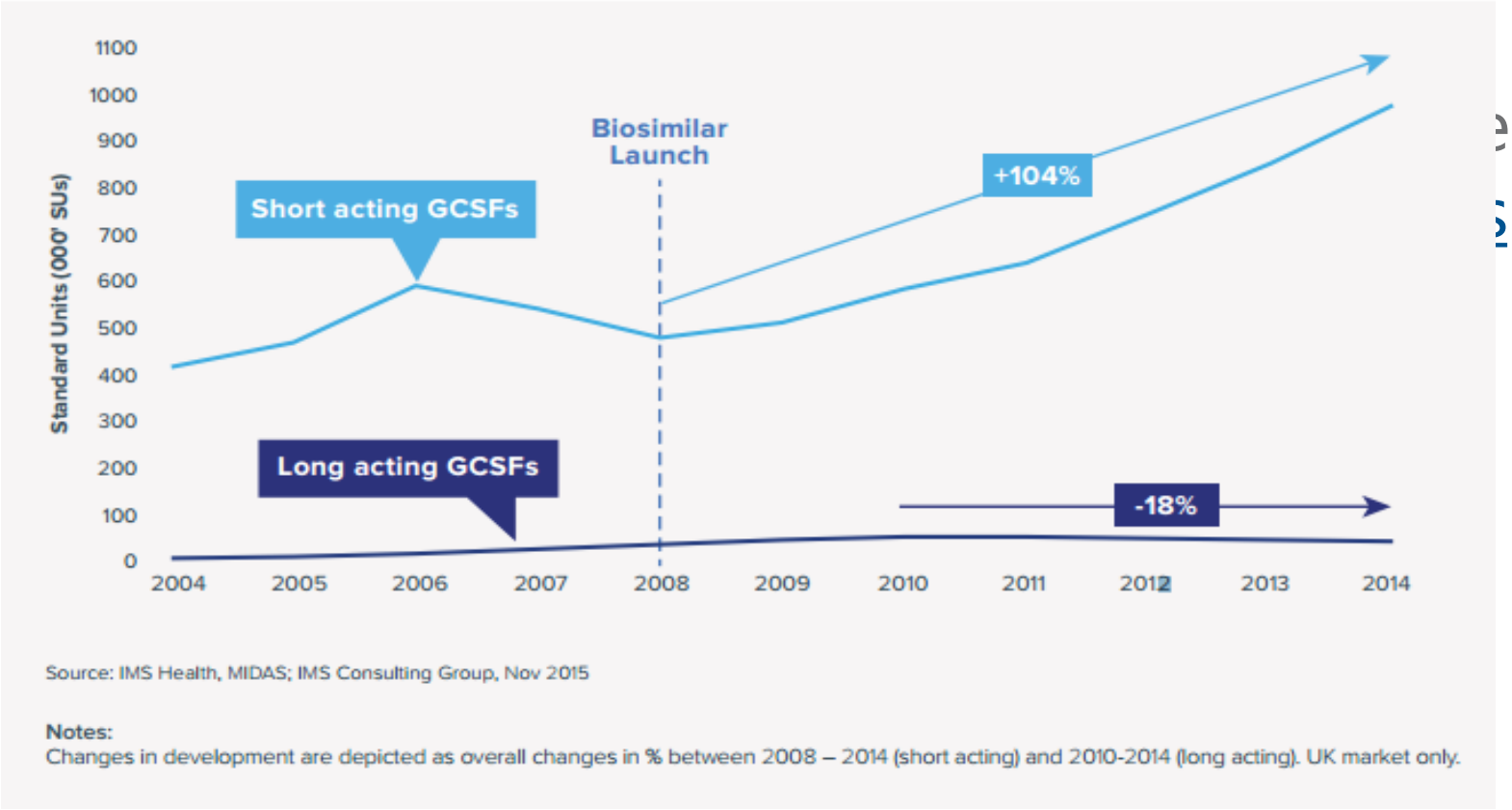
International trends

Joan O'Callaghan
Regulatory Science Ireland
Biosimilar Research Project

IMS Report: The impact of biosimilar competition

- Describes effect of biosimilar competition on price, volume and market share
- Competition drives down price
- Contributes to increased patient access

G-CSF in UK: increased access after introduction of biosimilar



Source: IMS Health, MIDAS; IMS Consulting Group, Nov 2015

Notes:
Changes in development are depicted as overall changes in % between 2008 – 2014 (short acting) and 2010-2014 (long acting). UK market only.

Source: IMS Report – delivering on the potential of biosimilar medicines

IMS Report: The impact of biosimilar competition – Market share in Ireland

	Biosimilar v's Reference Product	Biosimilar v's Total Market
Epoetin	91%	3%
G-CSF	23%	3%
Anti-TNF (Infliximab and Etanercept)	5%	3%

Source: 2017 IMS Biosimilar report – The Impact of Biosimilar Competition in Europe
http://ec.europa.eu/DocsRoom/documents/23102

Examples of policies

Supply side

- Price linkage
- Price re-evaluation
- Tendering

Demand side

- Information and education
- Prescription quotas
- Guidelines
- Financial incentives
- Co-payments
- Substitution policies

Remuzat *et al.* (2017) 'Supply-side and demand-side policies for biosimilars: an overview in 10 European member states', *J Mark Access Health Policy*, 5(1), 1307315.

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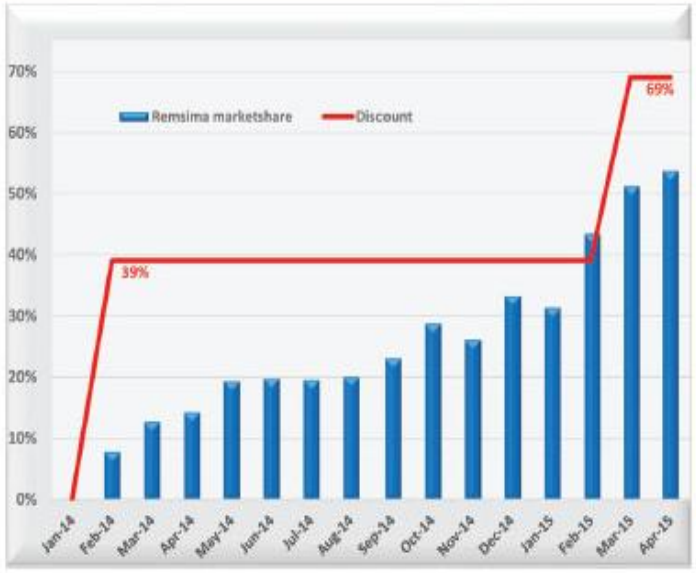
Tendering

- Hospital tendering processes in Norway and Denmark have resulted in high uptake
- Large scale switching
- Norwegian Health Authorities sponsored 'Nor-Switch' in order to increase confidence in biosimilars
- DK- increased focus in agency on monitoring ADRs associated with switching

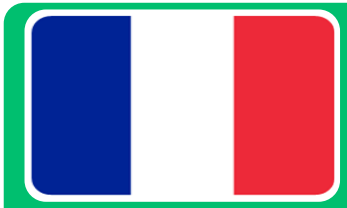
Figure 3: Biosimilar performance since launch



Bars show Remsima market share in volume. The line shows the Remsima discount compared with the Remicade tender price.
Source: Farmastat (database with only Norway market data)

Norway: http://gabi-journal.net/norway-biosimilars-in-different-funding-systems-what-works.html
Denmark: http://gabi-journal.net/pharmacovigilance-on-biologicals-and-biosimilars-a-danish-perspective.html

Examples of substitution policies



Pharmacist substitution on treatment initiation

- Substitution policy under restricted conditions which has been legally adopted but not implemented

Pharmacist substitution permitted

- Decision taken by Pharmaceutical Benefits and Advisory Committee
- Caveats apply

'Interchangeable' biological products

- Additional standards for 'interchangeability'
- Substitution possible if state legislation has been passed

France: http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility
Australia: http://www.pbs.gov.au/info/general/biosimilars
US:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/

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Summary

- Biologicals are heterogeneous and can vary batch to batch
- Changes in manufacturing processes (even for originator medicines) have resulted in different versions of the same medicine
- The concept of biosimilarity is based on the comparability exercise
- Stepwise exercise conducted at quality, non-clinical and clinical levels
- Physiochemical and functional assays are used to reveal subtle differences between a biosimilar and reference

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Summary

- Clinical data is confirmatory
- Extrapolation from one indication to another is common if there is a similar mechanism of action. Extrapolation must be thoroughly and scientifically justified
- There are specific challenges in the risk management of biologicals
- ADR reports for biologicals should contain brand name and batch number
- In Europe interchangeability is not assessed as part of the licencing procedure but real world evidence to support practice of switching is growing
- Policies around biosimilar medicines vary from country to country

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Useful links

- HPRA Guide to Biosimilars for Healthcare Professionals and Patients
- HPRA Q&A on biosimilar medicines for patients
- EMA and European Commission Information guide for healthcare professionals
- List of biosimilar medicines approved by the European Commission