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Safety assessment and risk management of biosimilars, knowledge gaps of physicians and patients

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Safety assessment and risk management of biosimilars
Knowledge gaps of patients and physicians

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Safety of biologicals: a classification

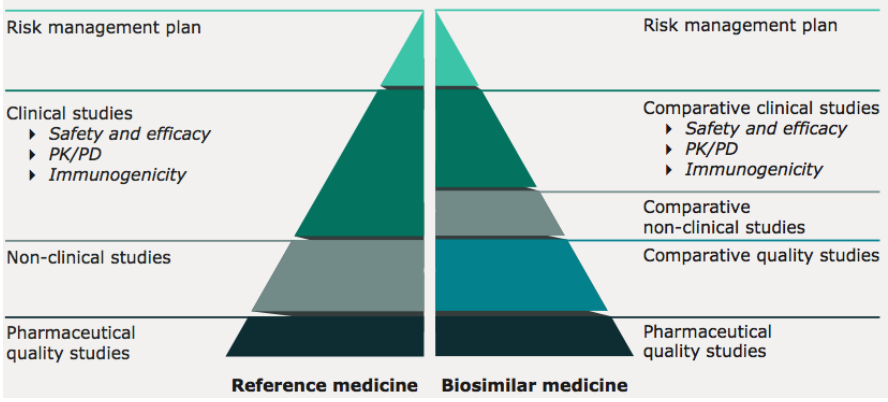
- **Exaggerated pharmacology*:***
  - TB with TNF-alfa inhibitors
  - PML with natalizumab
  - Thromboembolic events with epoetines

- **Immunological reactions:**
  - Neutralizing antibodies
  - Hypersensitivity reactions
  - Anaphylactic reactions

Safety assessment and risk management

- Safety data collected throughout complete clinical trial programme

- Adverse events (AEs) related to exaggerated pharmacology:
  - Safety data comparable
  - Differences might preclude approval as biosimilar
  - Safety data of reference product is the basis
  - Compare AEs in terms of nature, frequency and severity



Exaggerated pharmacology: an example

- Higher incidence of serious infections in pivotal clinical trial biosimilar infliximab

- Difference assessed as chance finding:
  - No adequate diagnosis and/or had pre-existing lesions in 4 cases
  - Total rate of infections was similar
  - No mechanistic explanation

Immunogenicity

- Starts during quality assessment
- Studied in a comparable manner in sensitive population
- Number of data based on experience with reference product and/or product class
- Duration of immunogenicity study should be justified
- Assessed in relation to clinical efficacy and safety

Immunogenicity

- Lower immunogenicity for biosimilar might be acceptable
  - Could erroneously suggest more efficacy for biosimilar
  - Subgroup analysis is advised to preclude higher efficacy

Extrapolation of immunogenicity data

Extrapolation of immunogenicity data is not automatic, as it always requires justification. This is because immunogenicity is determined by more than product-related characteristics.

Pharmacovigilance

Same rules apply to biosimilars as to all biologicals and new chemical entities

- Biosimilar companies should:
  - Submit a risk management plan as part of the marketing application → based on RMP of reference product
  - Collect spontaneously reported adverse events
  - Submit Periodic Safety Update Reports

Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilar medicines and their reference medicines.

Pharmacovigilance plan of a biosimilar

Post-marketing studies not only to compare safety profile but also to learn from rare adverse events

- Participate in already existing studies, e.g. rheumatology registries
- Initiate studies at companies own discretion

Study
Study CT-P13 1.2: A randomized, double-blind, parallel-group, Phase 1 study to evaluate the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Philippines)
Study CT-P13 1.3: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 in patients with ankylosing spondylitis who were treated with Infliximab (Remicade or CT-P13) in Study CT-P13 1.1 (Global)

Risk minimisation for biosimilar

Risk minimisation activities in place for the reference product also applies to the biosimilar

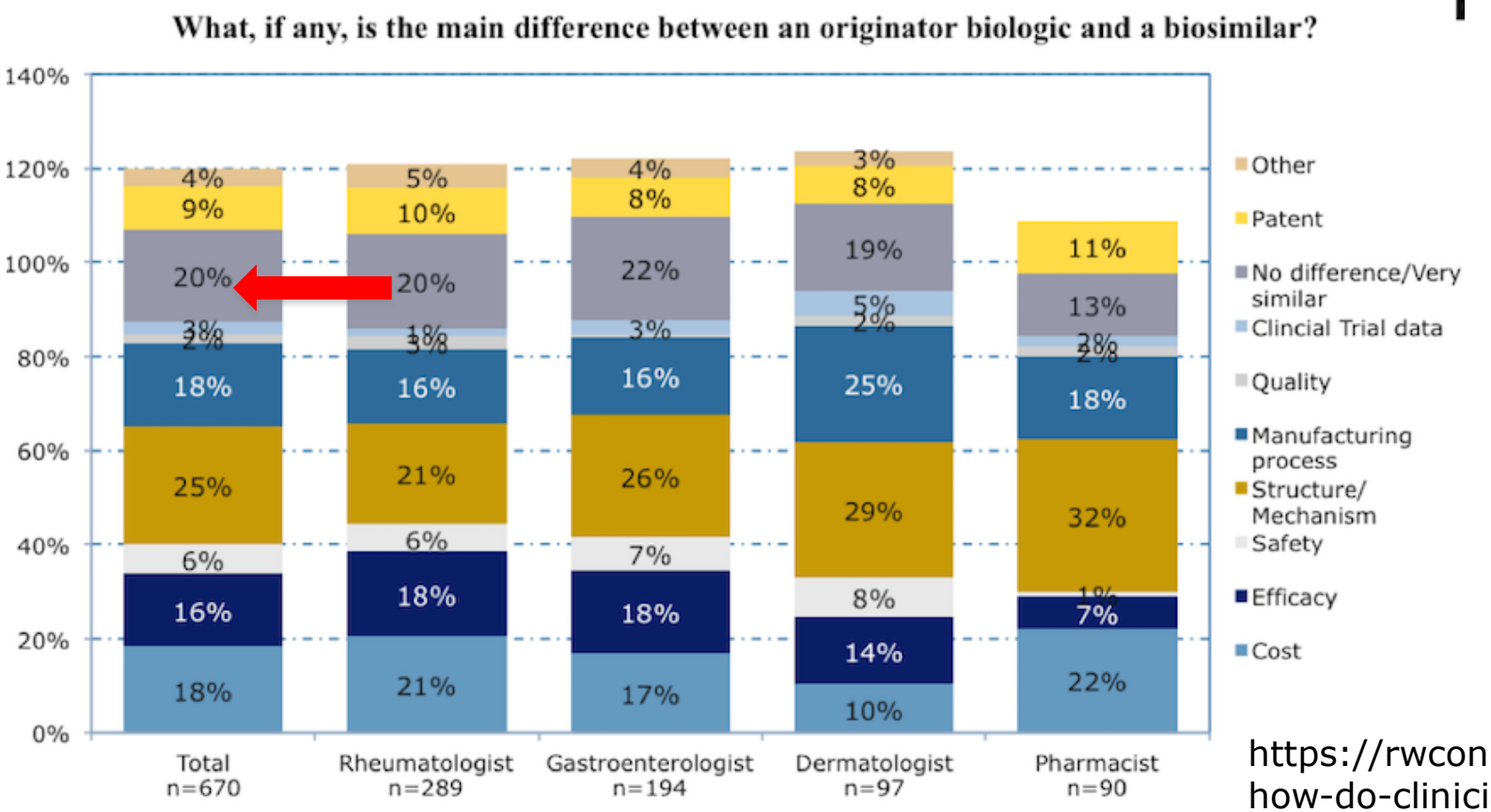
Unless:

Risk minimisation activity is related to the device by which the reference product/biosimilar is administered

Safety concern	Proposed risk minimisation activities (routine and additional)
Important Identified risks	
HBV reactivation	Routine: Labelling Additional: -Patient Alert Card -Educational material for HCPs.
Opportunistic infections	Routine: Labelling Additional:

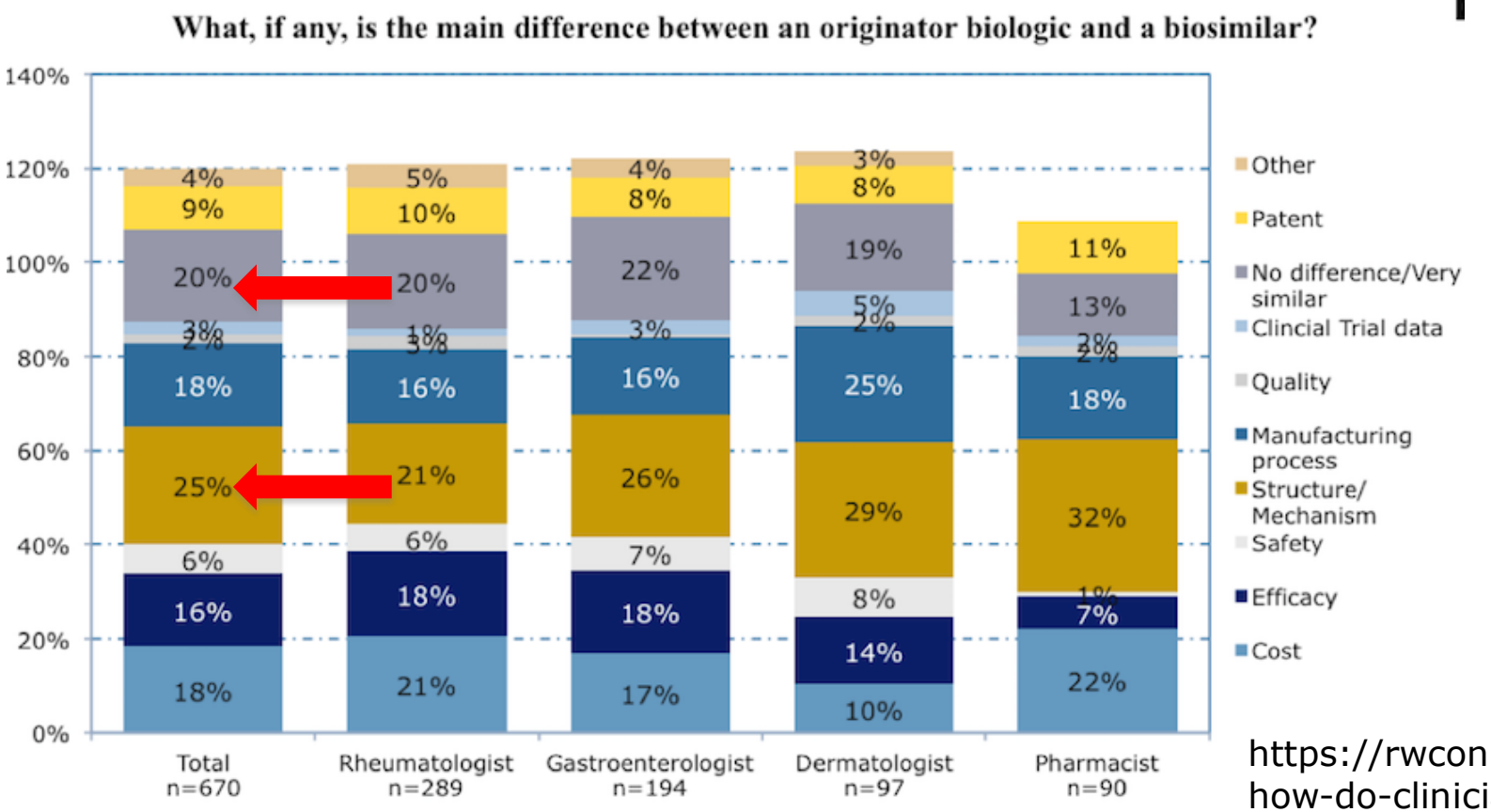
Knowledge gaps of patients and clinicians

Clinicians views against biosimilars



https://rwconnect.esomar.org/how-do-clinicians-in-the-japac-region-view-biosimilars/

Clinicians views against biosimilars



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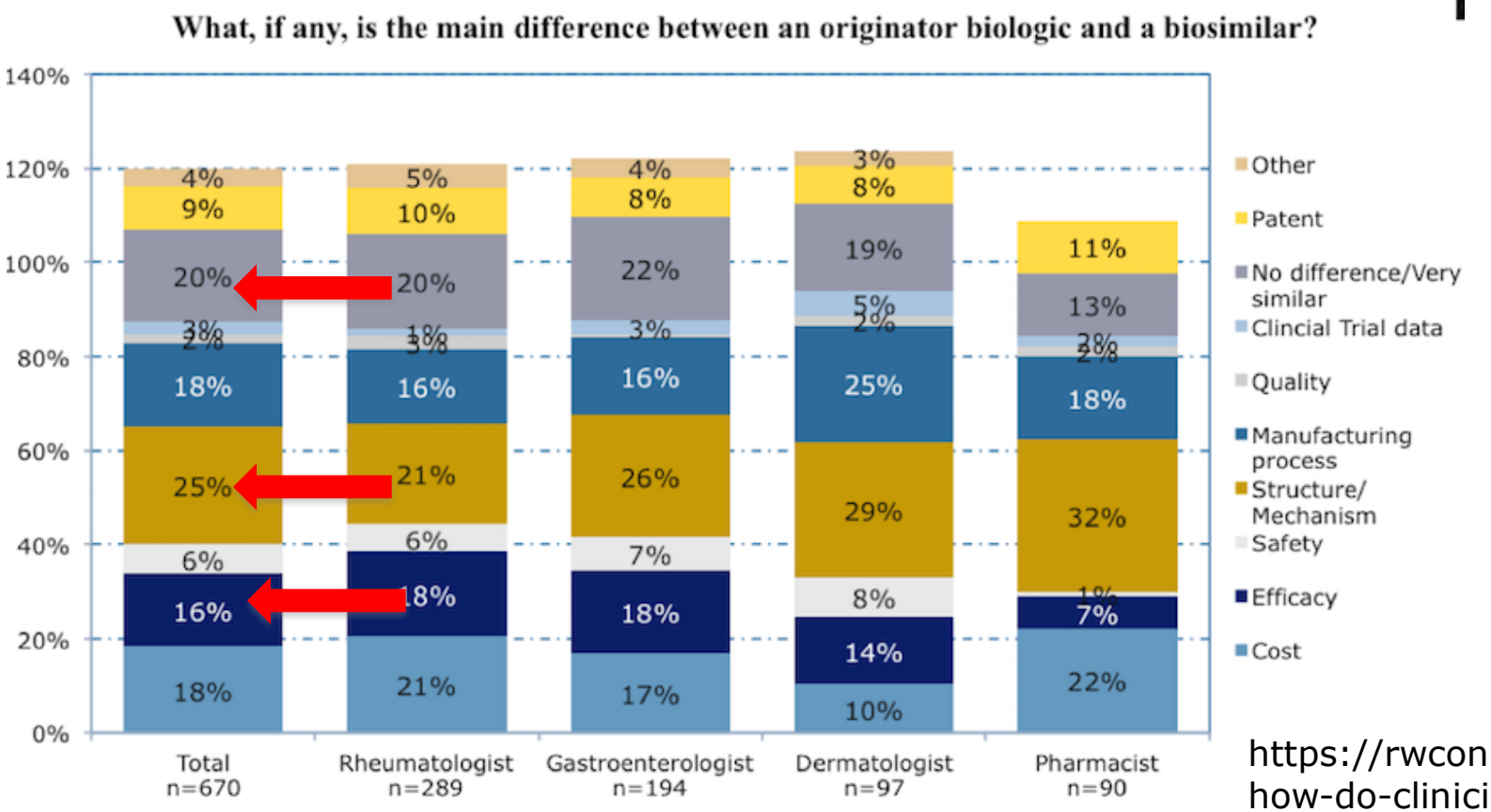

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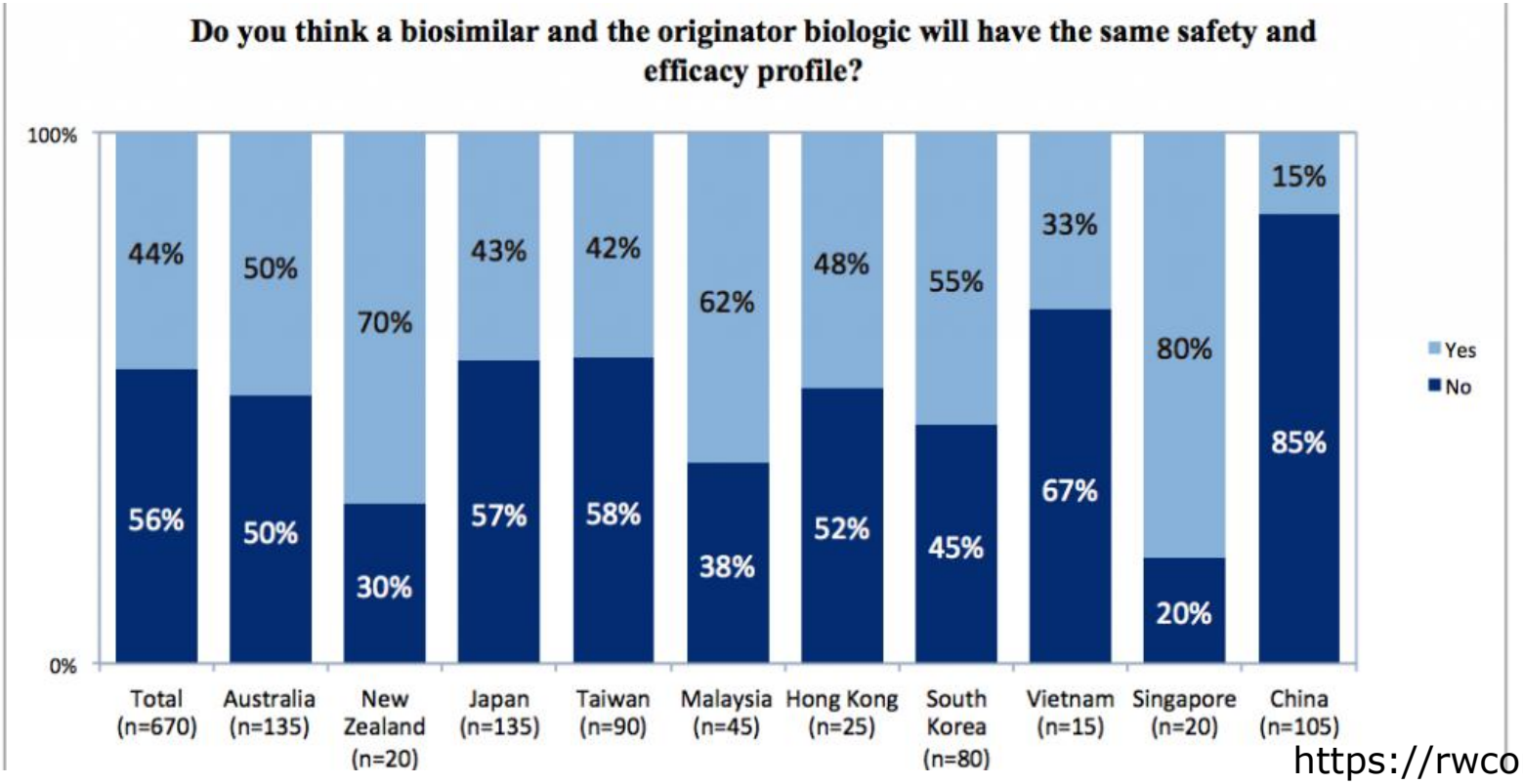

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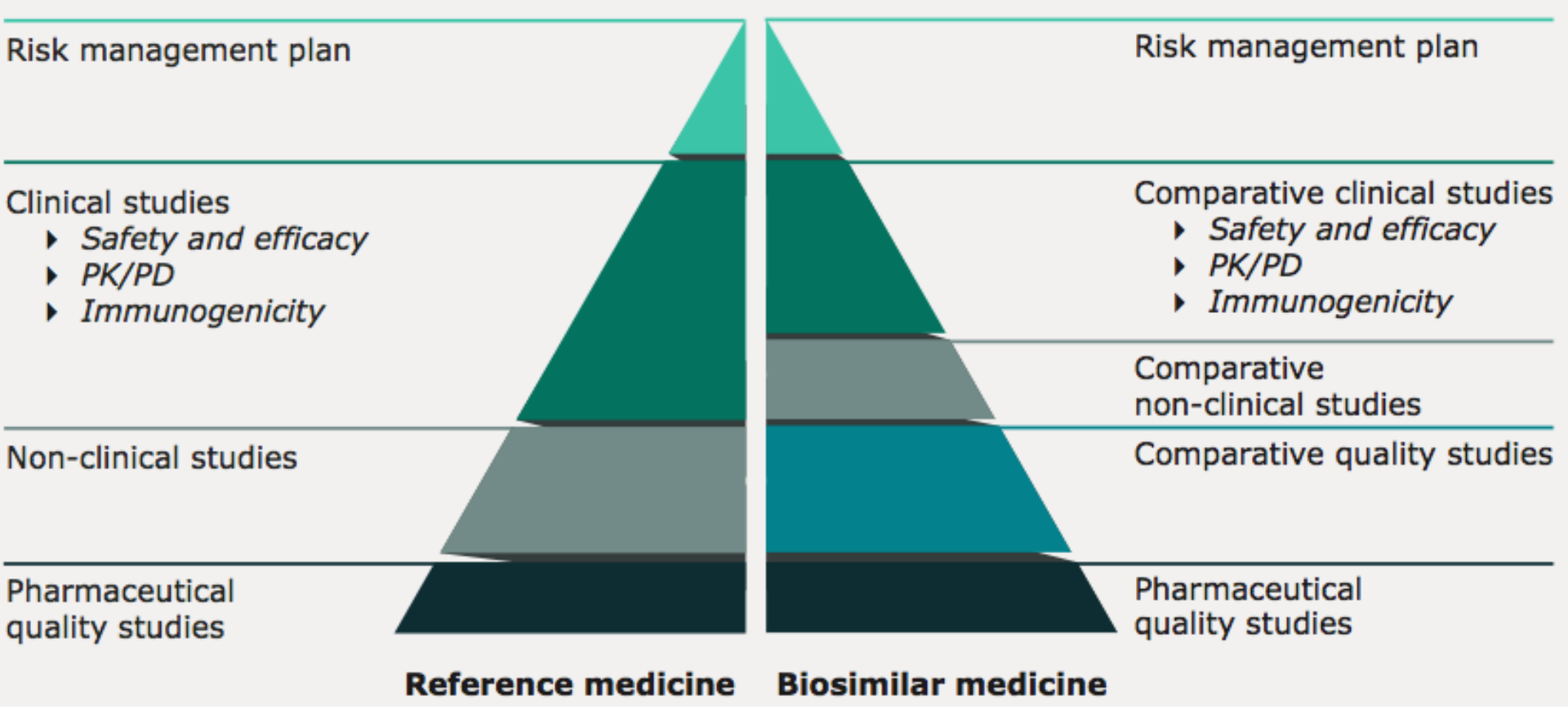
Principles of biosimilar development not well understood



ECCO view against biosimilars in 2013

- A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective.
- Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis

Journal of Crohn's and Colitis **2013,** 7, 586-89

Divergent regulatory positions: Infliximab

- Phase 3 clinical trial performed in RA
- Small difference at physicochemical level → potential impact on efficacy and safety in IBD

Based on the totality of the evidence regulatory authorities had a divergent view:

European Medicines Agency	***YES***
Health Canada	***NO***

Between 2013 and 2016

- Multiple studies of infliximab in IBD has been performed → generally no differences between biosimilar and reference product
- US FDA approved biosimilar including all indications (April 2016)
- Health Canada approves IBD indications (June 2016)

ECCO position 2016

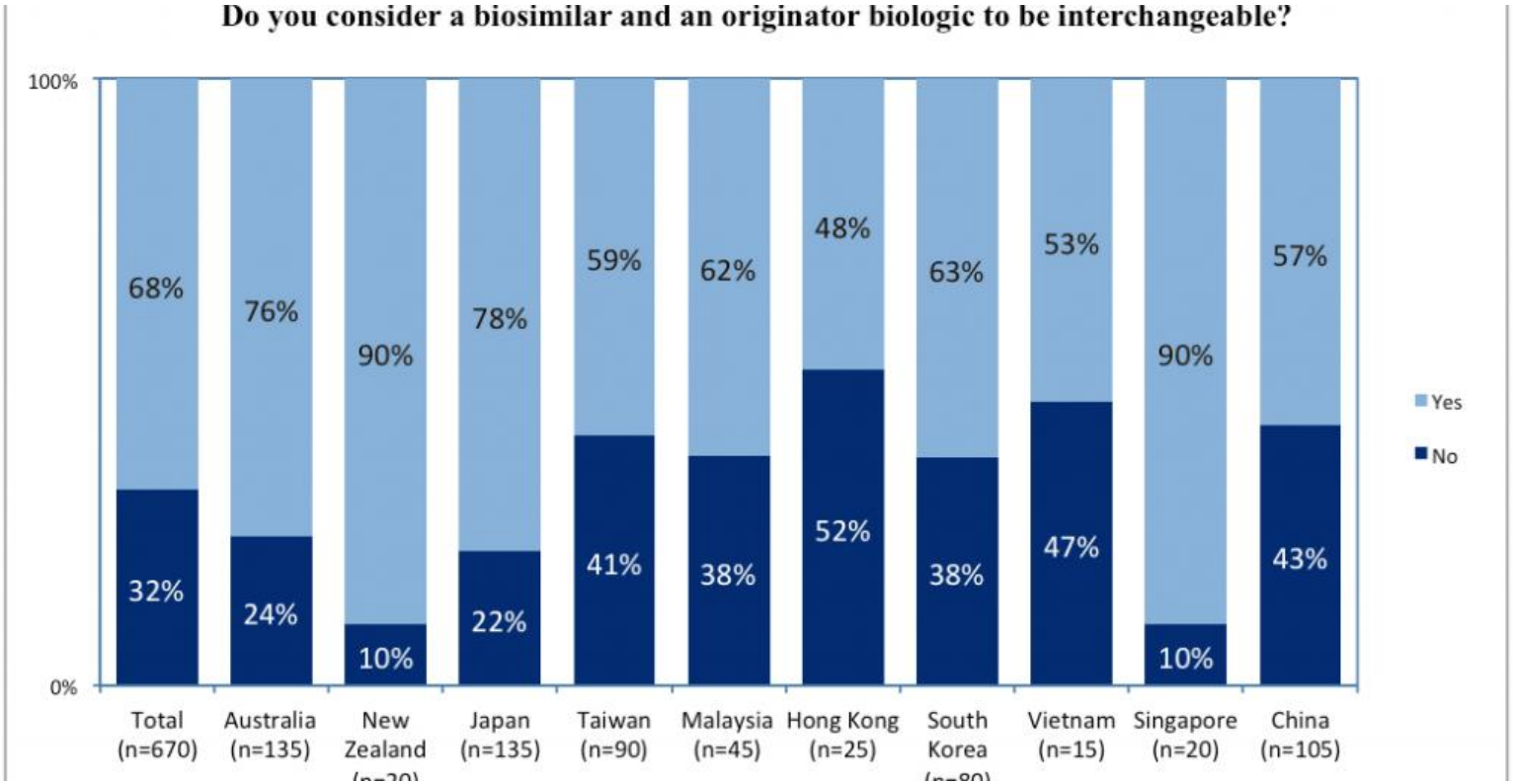
2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.
3. When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics.

Journal of Crohn's and Colitis **2017**, 26-34

Interchangeability

- **Interchangeability:** Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect:
  - **Switching**: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment
  - **Substitution**: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber

Clinicians views against interchangeability



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Switching induces immunogenicity

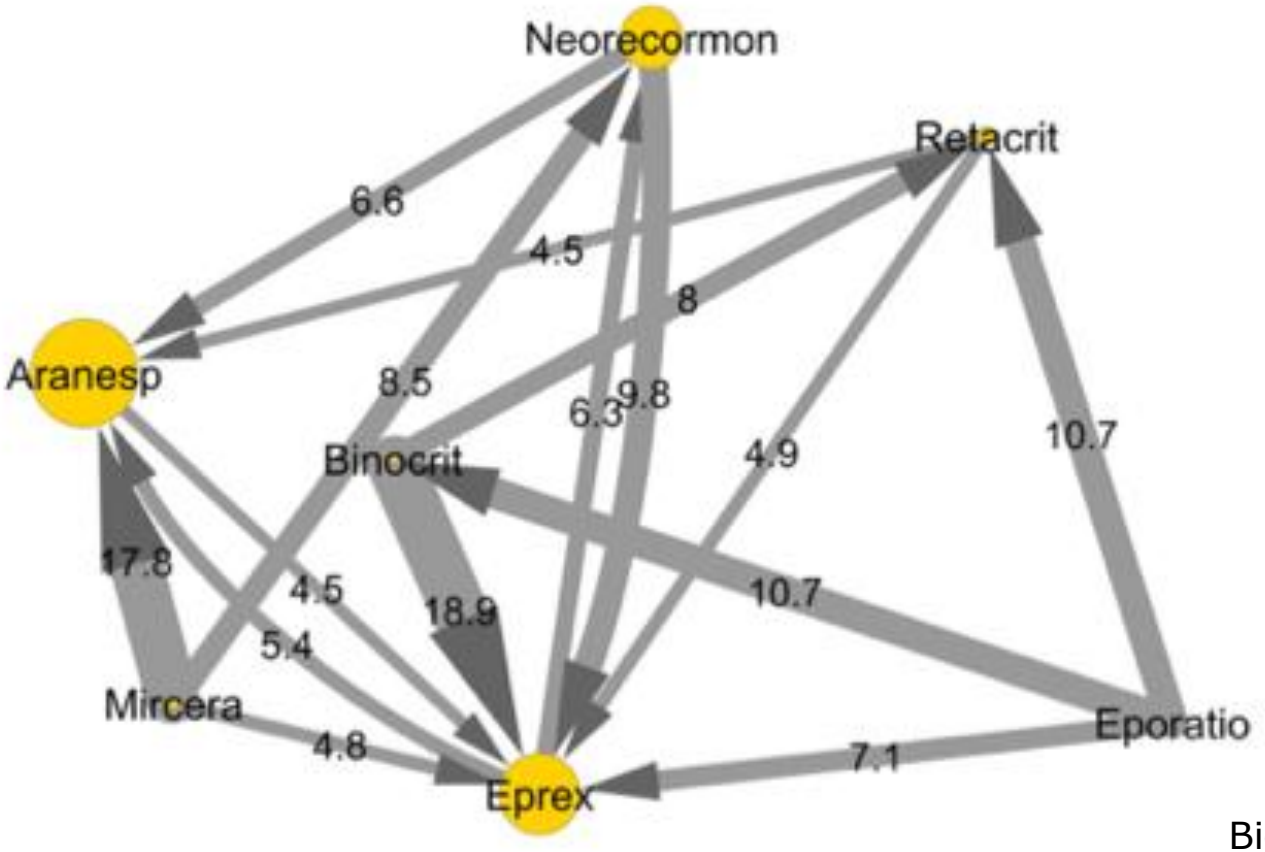
interchangeable. Switching between two similar biologic drugs increases the risk of anti-drug antibodies, which can lead to adverse immunologic reactions and decreased drug efficacy. Because the patient has received multiple drugs, the

nal prescription. However, unlike small-molecule drugs, a biologic therapy that is repeatedly interchanged with a biosimilar agent might promote increased immunogenicity that could compromise the efficacy and safety of both medications.[29]

rules to prohibit the automatic substitution of biopharmaceuticals. Also, medical societies such as the French [33] and the Portuguese [34] Society of Nephrology have stated that there is no safe interchangeability of biopharmaceuticals. The main concern about switching from one biological medicine to another is the issue of immunogenicity.

qualified healthcare professional (8). As a consequence of their complexity, automatic substitution of biologics could give rise to different clinical consequences and should be ruled out for reasons of patient safety (9, 58).

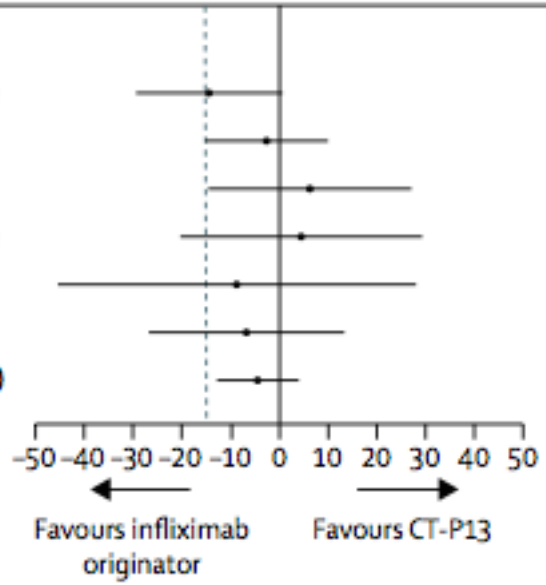
Switching in clinical practice



BioDrugs 2015; 29(4): 275-84

Data on switching will become available

	Infliximab originator n=202	CT-P13 n=206	Risk difference (95% CI)
Diagnosis			
Crohn's disease	14 (21·2%)	23 (36·5%)	−14·3% (−29·3 to 0·7)
Ulcerative colitis	3 (9·1%)	5 (11·9%)	−2·6% (−15·2 to 10·0)
Spondyloarthritis	17 (39·5%)	14 (33·3%)	6·3% (−14·5 to 27·2)
Rheumatoid arthritis	11 (36·7%)	9 (30·0%)	4·5% (−20·3 to 29·3)
Psoriatic arthritis	7 (53·8%)	8 (61·5%)	−8·7% (−45·4 to 28·1)
Psoriasis	1 (5·9%)	2 (12·5%)	−6·7% (−26·7 to 13·2)
Overall	**53 (26·2%)**	**61 (29·6%)**	**−4·4% (−12·7 to 13·2)**



www.thelancet.com Published online May 11, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30068-5

Building trust in biosimilars

Education, education, education

- Involve all stakeholders
- Take away misconceptions
- Building trust will help adoption of biosimilars in future

Concluding remarks

- Safety assessment is important and should be comparable
- Immunogenicity is of special importance
- Differences might question biosimilarity
- Physicians and patients should be educated to build trust
- Switching is safe

Biosimilars can safely be used in clinical practice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