Monoclonal antibody biosimilars in the treatment of solid tumours: Perspectives for pharmacists

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How similar is a biosimilar? Comparability, interchangeability and extrapolation

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What is the consensus on MAb biosimilar use among the oncology community?

Biosimilars are advocated by many professional health organizations around the world

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Biosimilars will play an important role in the future care of patients with cancer and will improve access to valuable medicines.[1]

World Health Organization

The availability of biosimilars has decreased prices, making even innovative treatments more affordable and hopefully available to more people.[2]

Dr Mariângela Simão, WHO Assistant Director General for Medicines and Health Products.

eahp
european association of hospital pharmacists

EAHP supports the view that a reference product and its biosimilar(s) are interchangeable and therefore can be switched.[3]

Health Canada

Health Canada authorizes biosimilars for sale using the same rigorous regulatory standards for quality, efficacy and safety as for all other biologic drugs.[4]

efpia
European Federation of Pharmaceutical Industries and Associations

All biologics, whether originators or biosimilars, approved by the Japanese regulatory authorities are safe, effective and of high quality.[5]

EFPIA Japan Biologics Committee (2017).

ASCO, American Society of Clinical Oncology; EAHP, European Association of Hospital Pharmacists; EFPIA, European Federation of Pharmaceutical Industries and Associations; ESMO, European Society for Medical Oncology; WHO, World Health Organization.

1. Lyman GH, et al. *J Clin Oncol.* 2018;36:1260–5; 2. WHO. Available at: www.who.int/news/item/18-12-2019-who-prequalifies-first-biosimilar-medicine-to-increase-worldwide-access-to-life-saving-breast-cancer-treatment (accessed 29 January 2021); 3. EAHP. Available at: www.eahp.eu/practice-and-policy/biosimilar (accessed 29 January 2021); 4. Health Canada. Available at: https://biosimilarscanada.ca/#:~:text=Health%20Canada%20authorizes%20biosimilars%20for,the%20original%20brand%20biologic%20medicine (accessed 29 January 2021); 5. EFPIA Japan Biologics Committee. Available at: http://efpia.jp/link/Final_EFPIA_J_Biosimilar_Statement-revised_v6_ENG.pdf (accessed 29 January 2021).

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The benefit of biosimilars for patients may vary by country

In countries with:	Potential benefits of biosimilar access
Full access to biosimilars	• Constraints on the **drug budget will decline**[1] • Headroom for **innovation** may be created[1]
Partial access or access with co-payment	• **Reimbursement** may become **feasible**[2] • **Direct costs** for patients **may go down**[1]
No access/biologics in general unaffordable	• Patients may get **access to life-saving medicines** with biosimilars[3]

Every health system can benefit from biosimilars

1. Simoens S, Vulto AG. *Expert Opin Biol Ther.* 2021;21:9–17; 2. Smeeding JP, et al. *P T.* 2019;44:54–63; 3. Kang HN, Knezevic I. *Bull World Health Organ.* 2018;96:281–5.

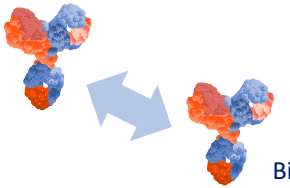
What is a MAb biosimilar and how does it differ from its reference product?

How similar is ‘similar enough’?

What practical targets will a hospital pharmacist set for biosimilars?

Quality, safety and efficacy

Comparable QSE

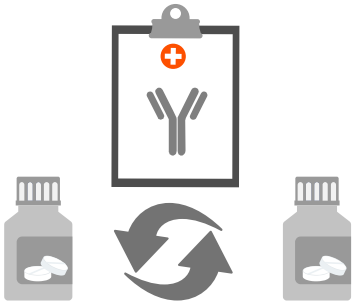


Biosimilars must be ‘similar enough’ to show **no clinically meaningful differences** from the reference biologic

Switching

No significant difference in immunogenicity –

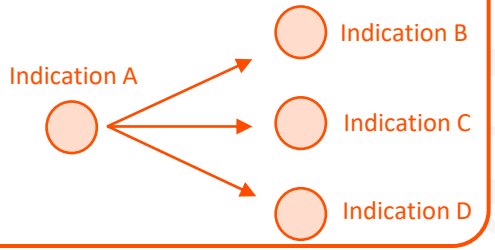
enabling brand switching with each new drug tender cycle



Extrapolation

Must match the potency of the reference biologic in all modes of action –

enabling pharmacies to potentially stock only one brand for all approved indications



QSE, quality, safety and efficacy.

Figure adapted from McCamish M, et al. *Mabs.* 2011;3:209–17.

Cornes P, McBride A. *Fast Facts: Biosimilars in Hematology and Oncology*. 1st ed. Oxford, UK: Karger Publishers Limited, 2020.

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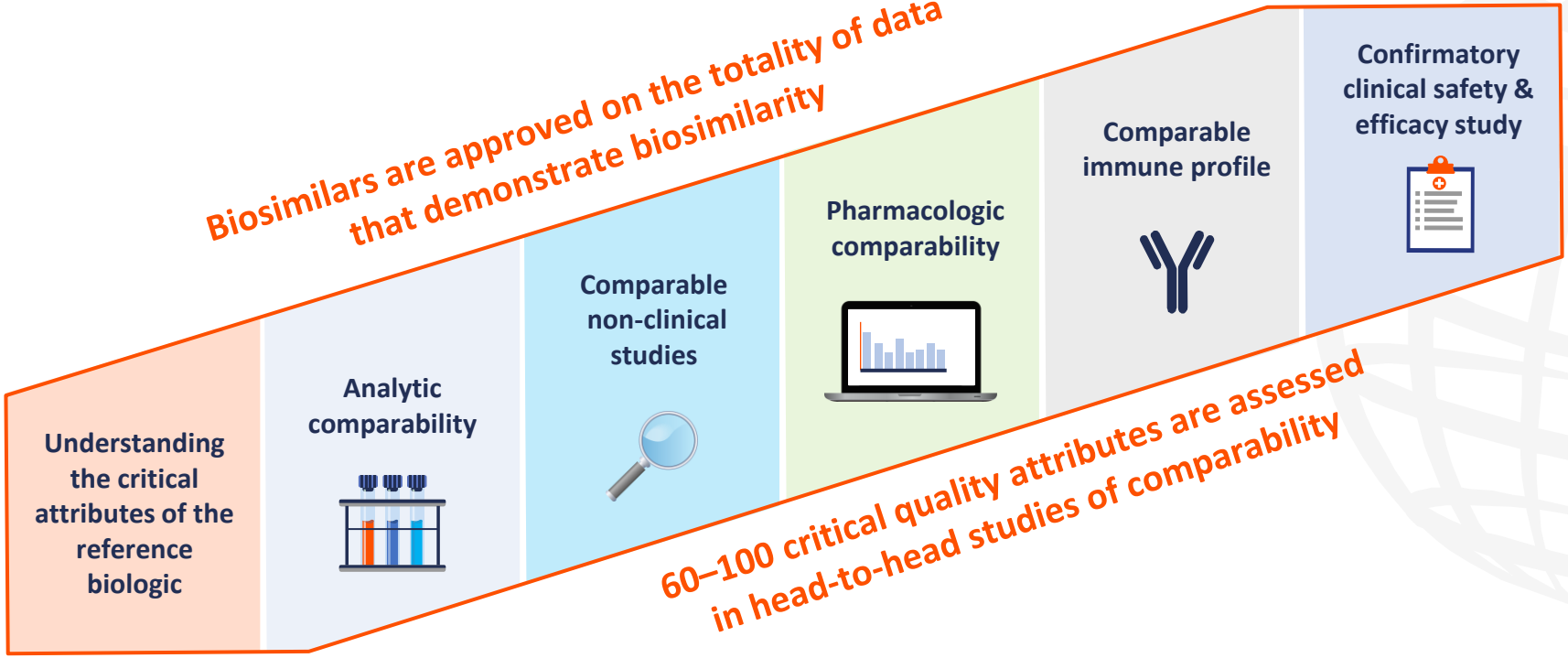
What is the regulatory approval pathway for MAb biosimilars?

Biosimilars undergo stepwise development and regulation[1,2]



1. European Medicines Agency. Biosimilars in the EU. Available at: www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed 29 January 2021); 2. Cornes P, McBride A. *Fast Facts: Biosimilars in Hematology and Oncology*. 1st ed. Oxford, UK: Karger Publishers Limited, 2020.

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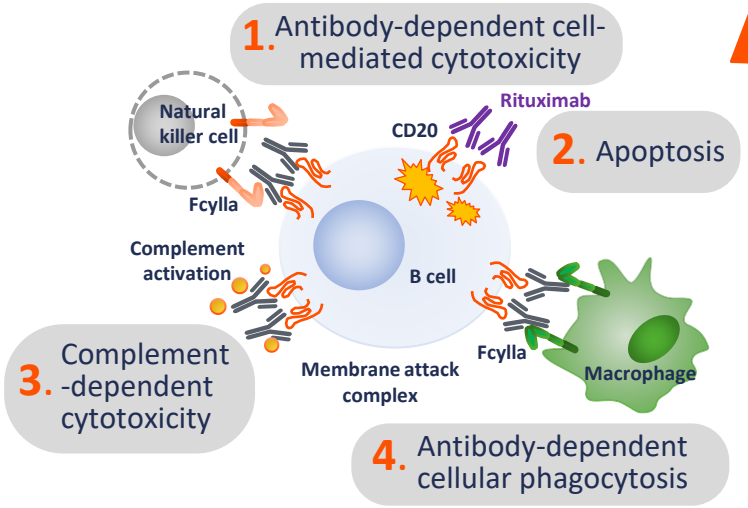
Biosimilar development and regulation start with a deep understanding of the original reference product

For example, rituximab has 4 mechanisms of B-cell mediated cell death:



These mechanisms are examples of **critical quality attributes** of the rituximab reference product

A rituximab biosimilar needs to show **comparable receptor binding and biopotency in all 4 mechanisms** to ensure no clinically meaningful differences from the reference product

A typical biologic will have **60–100 critical quality attributes** that a biosimilar will need to match, in order to predict similar clinical performance

Illustration adapted from Food and Drug Administration Briefing Information for the October 10, 2018 Meeting of the Oncologic Drugs Advisory Committee. Available at: www.fda.gov/advisory-committees/advisory-committee-calendar/meeting-oncologic-drugs-advisory-committee-10102018-10102018 (accessed 29 January 2021).

Cornes P, McBride A. *Fast Facts: Biosimilars in Hematology and Oncology*. 1st ed. Oxford, UK: Karger Publishers Limited, 2020.

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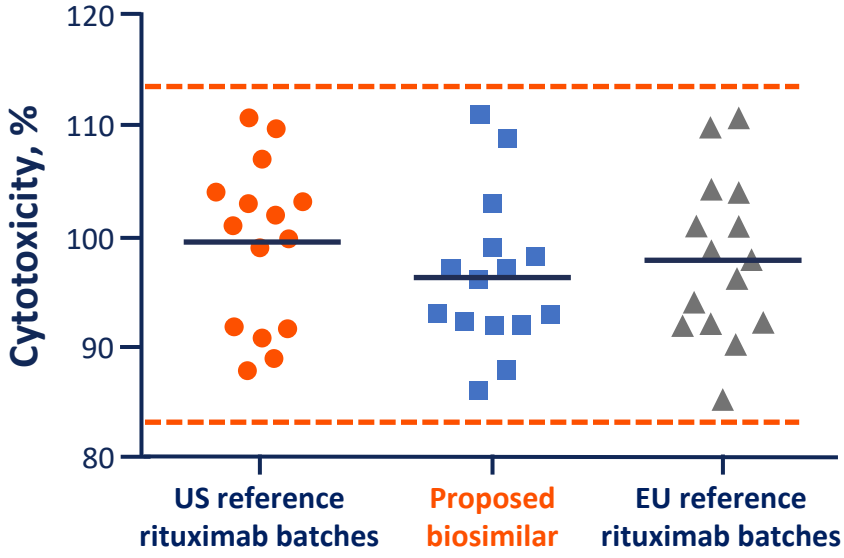
Matching critical quality attributes

Biologic drugs, such as rituximab, are made in living cells and show inherent variation in structure and function

Variation in the biopotency of rituximab[a]



No batches of the reference biologic are identical, but they are **highly similar**

That variation sets the **acceptable range of variation** for a proposed biosimilar

[a]Example of inherent variation in antibody-dependent cellular cytotoxicity of 30 different batches of originator reference rituximab.
Illustration adapted from Food and Drug Administration Briefing Information for the October 10, 2018 Meeting of the Oncologic Drugs Advisory Committee. Available at: www.fda.gov/advisory-committees/advisory-committee-calendar/meeting-oncologic-drugs-advisory-committee-10102018-10102018 (accessed 29 January 2021).

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How similar are biosimilars and their reference products in biochemical structure?

Characteristic	Similarity of biosimilar to its reference product
Amino acid sequence Primary sequence	**Identical**
Folding Secondary, tertiary, quaternary structure	**Indistinguishable**
Glycosylation and related substances	**Identical structures in comparable amounts** Differences are only acceptable if they are clinically not relevant
Biological functions	**Comparable**

Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Available at: www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product (accessed 29 January 2021).

What can we learn from real-world data on MAb biosimilar use?

Real-world data support biosimilar use in clinical practice

No clinically significant differences shown between biosimilars and their reference biologic in clinical practice

Quality, safety and efficacy

>14 years of use in Europe[1]

>70 biosimilars approved and marketed[2]

>2 billion documented patient days exposure[3]

Switching

No evidence of enhanced immunogenicity of biosimilars in Europe[4]

European regulators have **approved brand switching**[4]

Interchangeability of biosimilars supported by **178** clinical studies of brand switching (March 2020)[5]

Extrapolation

Extrapolation is assessed after biosimilarity is confirmed[6]

Regulatory process requires equivalence in biopotency in all MOAs to allow biosimilar use within all approved indications[7]

Biosimilar use outnumbers originator brand prescriptions each year in many European nations[8]

MOA, mechanism of action.

1. Medicines for Europe. Biosimilars. Available at: www.medicinesforeurope.com/wp-content/uploads/2016/03/infographic-biosimilars.pdf (accessed 29 January 2021); 2. Gheghescu I, Delgado-Charro MB. *Pharmaceutics.* 2021;13:48. 3. Medicines for Europe, MIDAS MAT Q2 2020 data, presented at Global Biosimilars Week, Nov 2020. Available at: www.medicinesforeurope.com/wp-content/uploads/2020/12/BIOS5.pdf (accessed 5 February 2021); 4. Kurki P, et al. *BioDrugs.* 2017;31:83–91; 5. Barbier L, et al. *Clin Pharmacol Ther.* 2020;108:734–55; 6. European Medicines Agency. Biosimilars in the EU. Available at: www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed 29 January 2021); 7. Food and Drug Administration Briefing Information for the October 10, 2018 Meeting of the Oncologic Drugs Advisory Committee. Available at: www.fda.gov/advisory-committees/advisory-committee-calendar/meeting-oncologic-drugs-advisory-committee-10102018-10102018 (accessed 29 January 2021). 8. Personal communication from Dr Paul Cornes.

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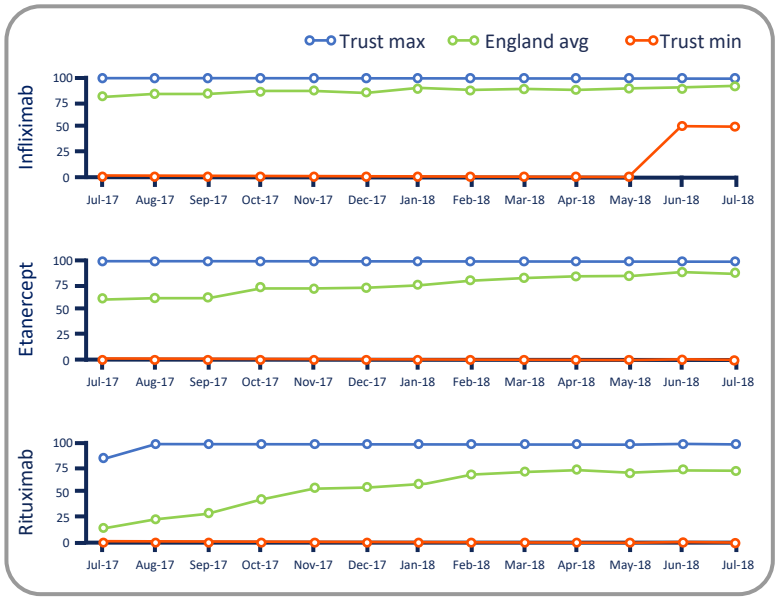
What can we learn from real-world experience of switching to biosimilars?

Evidence of real-world experience of switching to biosimilars

NHS England: Biosimilar uptake driven by a specific education and information strategy ‘Cancer Vanguard’[1]



70–95% uptake of 3 MAb biosimilars by July 2018[2]

With each new launch, NHS England gets better at assessing the savings from biosimilars [1,2]

Launch sequence

Drug	Time to 50% market share (months)	Biosimilar use by May 2018 (% of treatments)
Infliximab	17	91%
Etanercept	13	82%
Rituximab	5	73%

MAb, monoclonal antibody.

1. The Cancer Vanguard. NHS. Available at: http://cancervanguard.nhs.uk/biosimilars-getting-it-right-first-time/ (accessed 29 January 2021); 2. Data provided by courtesy of Dr Paul Cornes from the 2018 NHS Business Services Authority Medicines Optimization Dashboard (authorized access only).

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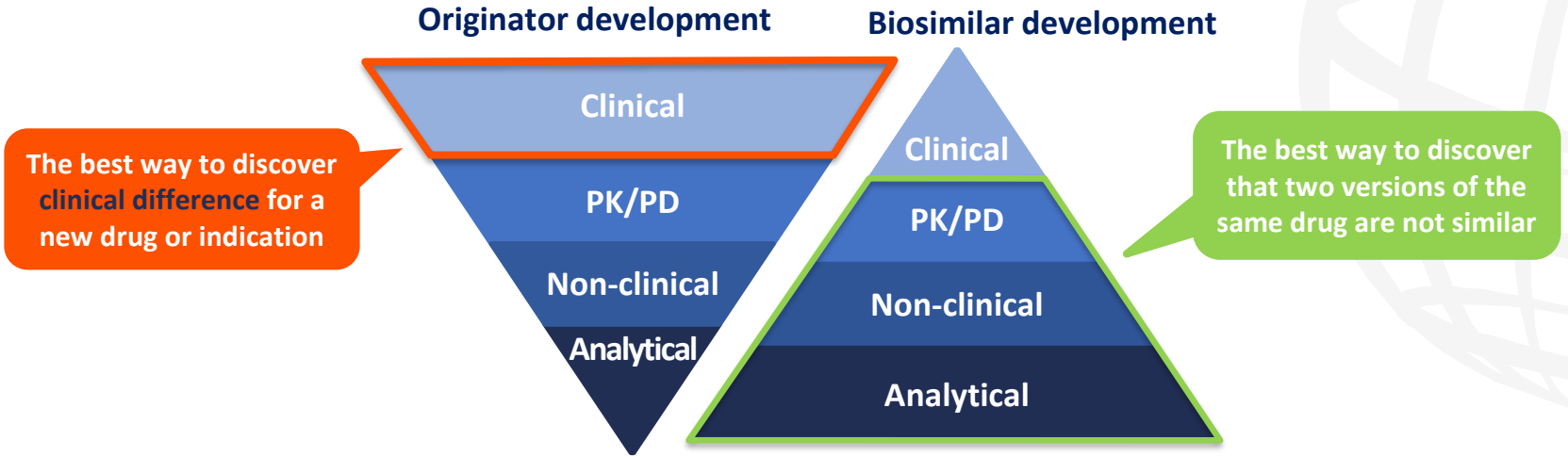
Why are pharmacists so important?

Ongoing education is key as more oncology biosimilars are being approved worldwide

While regulators decide what constitutes a biosimilar based on analytical and non-clinical testing, and clinical trials together (the totality of evidence), clinicians focus on clinical testing[1]

Original reference products need to show a clinical difference to be approved[3]

Biosimilars need to show similarity across 60–100 tests of equivalence[3]



PK/PD, pharmacokinetics/pharmacodynamics.

1. Generics and Biosimilars Initiative. Clinicians and regulators need to talk. Available at: www.gabionline.net/Biosimilars/Research/Biosimilars-clinicians-and-regulators-need-to-talk (accessed January 2021); 2. Cornes P, McBride A. *Fast Facts: Biosimilars in Hematology and Oncology*. 1st ed. Oxford, UK: Karger Publishers Limited, 2020.

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Managing the differences in biosimilar formulations: What are the practical considerations?

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Why are MAb biosimilars not considered generic medicines, if both aim to replicate an originator product?

Comparison of generic and biosimilar products

Generics

- **Small molecules** with standard production methods and well-defined structures
- **Structurally identical** to originator
- **Bioequivalent** or **therapeutically equivalent**
- **All indications** approved for reference medicine can be granted based on bioequivalence, **without need for further data**

Similarities

Follow-on versions of branded originator whose patent has expired

More affordable treatment option

Approved via abbreviated pathways that avoid full clinical trials

Biosimilars

- **Large, complex proteins** made using living cells
- Have same amino acid sequence but may **differ slightly from reference**
- Development based on **biosimilarity** using **comparability studies**
- Demonstrate **high similarity in structure, function, efficacy, safety and immunogenicity** to reference
- **Extrapolation of data** to other indications is possible

Biosimilars require more studies for regulatory approval vs generics to ensure that minor differences do not affect safety or efficacy

European Medicines Agency. Biosimilars in the EU. Available at: www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed 29 January 2021).

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What are the similarities and differences in formulation between MAb biosimilars and reference products?

There are no clinically meaningful differences between a biosimilar and its reference medicine

SIMILARITIES[1]

- **Same, biologically** (e.g. same amino acid sequence for the protein)
- **Same dose and route of administration**

DIFFERENCES[1]

Some differences are allowed if no effect on efficacy or safety:

- **Formulation** (excipients)
- **Presentation** (e.g. powder for reconstitution vs solution ready for injection)
- **Administration device** (type of delivery pen)

Excipients are added to biologics for stability, preservation, and facilitation of drug delivery[2]

1. European Medicines Agency. Biosimilars in the EU. Available at: www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed 29 January 2021); 2. Ionova Y and Wilson L. *PLoS One.* 2020;15:e0235076.

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Excipients may affect the safety profile of biologic formulations

Safety assessment of excipients in biologic formulations

Excipient complexity quantified in N=230 formulations

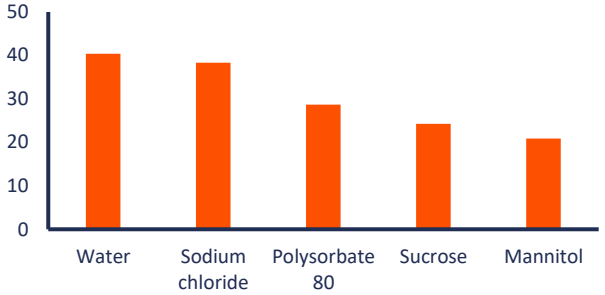
Excipient (surfactants, sugars and polyols, & preservatives)-related AEs identified through published case reports

Biologics contained **fewer excipients than** small molecule medicines

	Biologics	Small molecules
No of excipients (average)	**4.45**	**8.8**

There was a **high variability** in **excipient selection and concentration** in biological formulations

The most commonly occurring excipients in biological formulations (%)



- 17 case reports of adverse drug reactions to excipients in biologics included injection-site reactions, anaphylaxis, hyperglycaemia, and acute renal failure
- This review suggests that **excipients could affect the safety profile of a biologic** and may be the cause of certain AEs in some patients: **further analysis to include AEs beyond case reports is warranted**

AEs, adverse events.

Ionova Y and Wilson L. *PLoS One*. 2020;15:e0235076.

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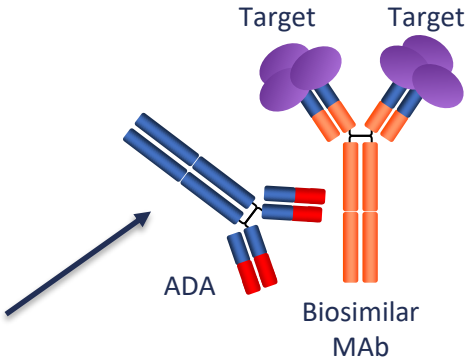
What is the potential for changes in immunogenicity when switching to a MAb biosimilar?

Immunogenicity is evaluated during the development of biosimilars, as per regulatory requirements

An increase in immunogenicity is one of the main voiced concerns when switching from a biologic reference medicine to a biosimilar[1]

Concerns that increased immunogenicity may occur due to **exposure to potentially different sets of epitopes** when switching between highly similar versions of a biologic medicine[1]

The **formation of ADAs** could lead to safety issues or a loss of efficacy of the treatment[1]



Immunogenicity data are required for regulatory approval of biosimilars and post-marketing monitoring is performed[2]

The biosimilars information guide for HCPs, prepared jointly by the EMA and the EC, indicates that:[2]

"there is no reason to believe that harmful immunogenicity should be expected after switching between highly similar biologic medicines"

ADA, antidrug antibody; EC, European Commission; EMA, European Medicines Agency; HCPs, health care professionals; MAb, monoclonal antibody.

1. Barbier L, et al. *Clin Pharmacol Ther.* 2020;108:734–55; 2. European Medicines Agency. Biosimilars in the EU. Available at: www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf (accessed 29 January 2021).

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The immunogenic potential of MAb biosimilars

Trastuzumab has low immunogenic potential, limiting the risk of immunogenicity-related AEs[1]

Trastuzumab biosimilar	ADA formation (Phase III safety study data)
ABP 980 Trastuzumab-anns (Kanjinti)	Two patients developed binding Abs. Neither tested positive for neutralizing Abs[a] One patient with binding, non-neutralizing ADA (switch group)[b]
CT-P6 Trastuzumab-pkrb (Herzuma)	NR[c] All post-infusion ADA tests were negative[d]
MYL 14010 Trastuzumab-dkst (Ogivri)	ADA similar between groups[c]
PF-05 Trastuzumab-gyyp (Trazimera)	One patient developed ADA (EU-RP)[c] No patients with ADA for PF-05 vs one patient for RP[d]
SB3 Trastuzumab-dttb (Ontruzant)	ADA 0.7% vs 0.0% for SB3 and RP[d] 0.7% in both groups[e]

Bevacizumab biosimilars

- **Low rate of ADA development (0.6% of patients)** in bevacizumab RP clinical trials across tumour types[2]
- **Similar low rate of ADA development in comparability trials** of patients with NSCLC and other indications receiving biosimilar bevacizumab and originator bevacizumab[2]

Abs, antibodies; ADA, antidrug antibody; AE, adverse event; MAb, monoclonal antibody; NR, not reported; NSCLC, non small-cell lung cancer; RP, reference product.
[a]Results from neoadjuvant setting; [b]Results from the single switch treatment arm vs continuing arm in adjuvant phase of the study; [c]Safety results of the phase III trial in metastatic breast cancer population; [d]Reported results are safety results of the phase III trial in early breast cancer patients (neoadjuvant period); [e]Safety results of the phase III trial in early breast cancer patients (neoadjuvant + adjuvant period).

1. Barbier L, et al. *Br J Cancer.* 2019;21:199–210; 2. Taïeb J, et al. *Clin Colorectal Cancer.* 2020;S1533-0028:30143–2.

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What measures can be taken to manage the side effects associated with MAb biosimilar infusions?

Infusion-related reactions are the most common side effects of MAbs and are usually manageable

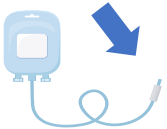
Premedications are considered as standard procedure for minimizing the risk of IRRs with MAbs

Administration strategies

Premedication, which may include paracetamol, antihistamines, corticosteroids (NSAIDs used on rare occasions)

Depending on the type of MAb and the severity of the IRR

Slow down infusion rates, interrupt infusion, fractionate dose or reinitiate the treatment



Other measures

Induce pharmacological desensitization and temporary immune tolerance or fractionate the dose

Medical therapy

Use of oxygen, beta-agonist agents, corticosteroids, intravenous fluid therapy or antipyretics

IRR, infusion-related reaction; MAbs, monoclonal antibodies; NSAIDs, non-steroidal anti-inflammatory drugs.

Caceres M, et al. *Ther Clin Risk Manag.* 2019;15:965–77.

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What are the practical challenges associated with ensuring MAb biosimilar stability and appropriate storage and preparation of products?

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Pharmacist,
The Japan Agency for Medical Research and Development,
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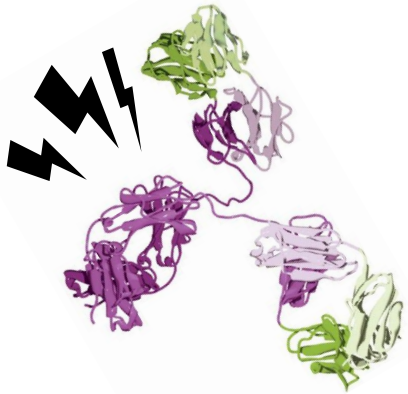
What is the impact of storage conditions on the stability of MAb biologics for solid tumours?

Physical factors during storage and handling can influence MAb stability

MAbs are complex proteins that are susceptible to chemical and physical processes, which promote their degradation and denaturation

Temperature changes and other stress factors may alter the molecular structure of MAbs



Structural changes introduce physical instability into the MAb and alter its physical properties

- Including formation of soluble aggregates and insoluble precipitates, and adsorption onto surfaces

Instability of MAbs results in loss of therapeutic efficacy

Elevated temperature is a key stress factor and may lead to instability of MAbs with irreversible aggregation and loss of protein function

MAb, monoclonal antibody.

Laptos T and Omersal J. *Exp Ther Med.* 2018;15:3161–8.

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What steps should be taken to ensure the appropriate storage of MAb biologics for solid tumours?

Correct transportation and storage of MAbs is key for maintaining their stability

Maintain cold-chain 'temperature-controlled' security

- During transport to the hospital pharmacy

Store between 2 and 8˚C

- Until preparation is under controlled aseptic conditions or administration

Protect from light

- MAbs are kept in secondary packaging to protect the solution from light
- This is to prevent oxidation reactions, which can compromise chemical stability of MAbs

MAb, monoclonal antibody.

Laptos T and Omersal J. *Exp Ther Med.* 2018;15:3161–8.

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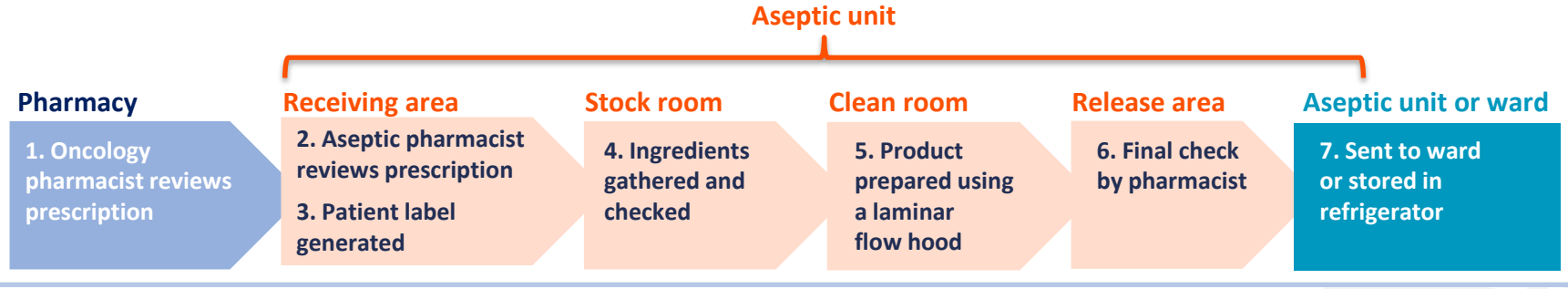
What are the practical steps undertaken by the pharmacy team to prepare Mab biologics for parenteral administration in patients with solid tumours?

Aseptic technique for preparing MAb infusions is important to ensure sterility and safety of the reconstituted product

The aseptic preparation pathway[1]



Validity checks at each step to ensure traceability and safety[2,3]

- Reduces risk of microbial contamination
- Reduces risk of errors in preparation
- Ensures that the prepared MAbs are appropriate for the patient
- Reduces level of MAb product degradation

MAb, monoclonal antibody.

1. Leeds Teaching Hospitals NHS Trust. Chemotherapy preparation – the Pharmacy Aseptic Unit. Available at: www.leedsth.nhs.uk/a-z-of-services/leeds-cancer-centre/your-treatment/chemotherapy/chemotherapy-delivery/chemotherapy-preparation/chemotherapy-preparation-the-pharmacy-aseptic-unit/ (accessed 26 January 2021); 2. Laptos T and Omersal J. *Exp Ther Med.* 2018;15:3161–8; 3. Beaney AM. On behalf of the Royal Pharmaceutical Society and the NHS Pharmaceutical Quality Assurance Committee. 2016. Available at: www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Quality%20Assurance%20of%20Aseptic%20Preparation%20Services%20%28QAAPS%29/rps---qaaps-standards-document.pdf (accessed 27 January 2021).

How can hospitals implement best practice for preparing and storing MAb biologics?

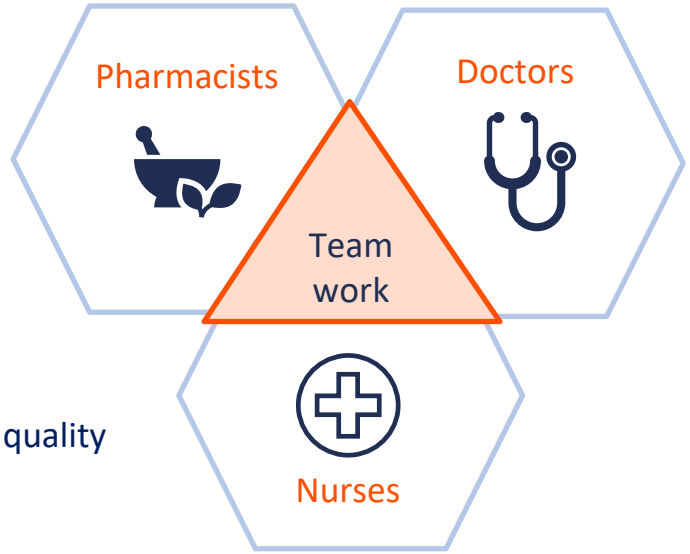
Optimizing the delivery of MAb biologics

Collaboration is needed between pharmacists, doctors and nurses to facilitate accurate and timely administration of MAb biologics for patients[1,2]

Follow approved standard operating procedures

Use clear, unambiguous labelling to prevent errors

Incorporate a system of quality assurance



Ensure all healthcare staff have a clear understanding of their roles and responsibilities

Stay informed about MAb biologic prescribing and preparation practices

MAb, monoclonal antibody.

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