ASK

Attitude, Skills, and Knowledge in Oncology Biosimilars

Implementing biosimilars: a case study on pharmacovigilance best practice

Interactive discussion:
Marta Trojniak and Glenn Myers

Educational funding

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An interactive webinar: please participate

Questions for the panellists

- Throughout this session, **please pose your questions to the panellists in the Q&A box**
- Please note: you will **NOT** be able to ask questions via the chat function
- The speakers will look to incorporate your questions throughout the webinar to facilitate discussion

Interactive questions

- There will also be interactive questions displayed on the screen
- Please choose your answer by selecting the options when they appear on the screen

NOTE: If you are watching the archive footage, you will not be able to take part in any polls

Panellists

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Panellist disclosures

- All panellists are receiving a speaker honoraria for this ASK webinar

Within the last 12 months:

  - MT has no relevant disclosures

  - GM received fees from Merck, Eisai, Novartis, Apobiologix, AstraZeneca, Sanofi, Bristol Myers Squibb (BMS) and Ipsen, and reports commercial relationships with Amgen, Gilead, Roche and IMV Inc.

Learning objectives

At the end of this webinar, delegates should be able to:

- Identify and assess key areas where post-marketing monitoring of biosimilars may provide important information on clinical safety and efficacy of biosimilars

- Implement effective strategies for ensuring comprehensive monitoring and reporting of events that may impact efficacy and safety of biosimilars

- Adopt measures to ensure the quality and completeness of the data for individual case safety monitoring and show how it can improve safety and clinical uptake of biosimilars

Pre-learning assessment

When implementing new biosimilar medications, how often does your patient communication include details on self-reporting adverse events?

- **A** Routinely
- **B** Often
- **C** Sometimes
- **D** Rarely
- **E** Never

Please select one answer

Introduction

Interactive question – NAMING

Naming conventions can be variable between regulatory authorities around the world, which can make tracing biosimilars difficult. Which of the following examples would make it difficult to differentiate between a biosimilar and the innovator biologic for tracing purposes?

A Filgrastim (Grastofil)

B Filgrastim-aafi

C Filgrastim

D Nivestym®

E Filgrastim (Nivestym)

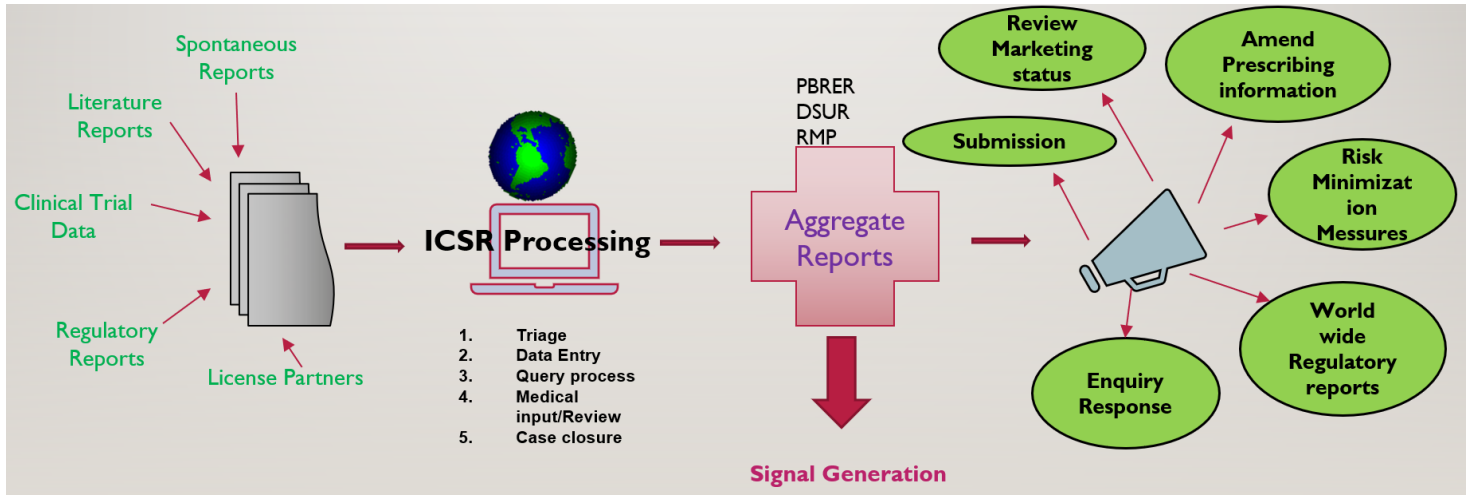
Please select one answer

Aims of pharmacovigilance

Enhance patient care and safety[1]

Provide reliable information for assessment of the risk–benefit profile of medicines[1]

Assess manufacturing processes for high-risk changes[2]



4 stage process[3]

1. Detection
   - Individual case safety reports
     - Solicited sources
     - Unsolicited sources
2. Assessment
3. Understanding drug safety profile
4. Prevention of adverse events

DSUR = development safety update report; ICSR = individual case study report; PBRER = periodic benefit–risk evaluation report; RMP = risk management plan.

1. World Health Organization. Available at: https://bit.ly/3neRwpl (accessed Nov 2021). **2.** Speaker insight. **3.** Image from Global pharmacovigilance. Available at: https://bit.ly/3E1DD4J (accessed Nov 2021).

Product names and information

Biosimilars and originators may exhibit different safety profiles[1]

- Need to clearly identify which product is associated with an adverse event

Detailed and accurate information is required

- More detail required than INN alone – different approaches in different countries[2]
- Batch number – important for identification[3]
- Patient details[3]
  - Naïve patient – data recording
  - Previously switched patient – report both names

INN = international non-proprietary name.

1. Dolinar and Reilly, *GaBI. Journal*. 2014:3(2);58–62. **2.** Kang et al., *Ann. N.Y. Acad. Sci*. 2021:1491;42–59. **3.** Speaker insight.

Product names and information

Biosimilars and originators may exhibit a different safety profile[1]

- Need to clearly identify which product is associated with an adverse event

- EuropaBio 2016 survey[1] on physician preferences on SmPCs details reported
  - 90.5% use SmPC label frequently or occasionally as an information source
  - 87.2% deemed a clear statement on origin of data helpful or very helpful
  - 78.7 to 82.9% preferred biosimilar SmPCs with additional information

- Naïve patient – data recording
- Previously switched patient – report both names

SmPCs = summaries of product characteristics.

1. Hallerston et al., *Regul. Toxicol. Pharmacol*. 2016:77;275–281.

Naming confusion

Confusion over naming could lead to questions concerning[1]	Prescription mix-ups
	Intentional or unintentional switching[2]
	Traceability and detection of ADRs post-marketing
	Adopt new technologies to aid clarity[2] – e.g., 2D barcode
A 2013 ASMB-commissioned survey regarding biosimilar naming among European physicians reported[3]	53% mistakenly felt identical non-proprietary name implied identical structure
	61% mistakenly said identical non-proprietary names imply medicines are approved for the same indications
	24% recorded only non-proprietary name of biologics

ADR = adverse drug reaction; ASMB = Alliance for Safe Biologic Medicines.

1. Generics and Biosimilars Initiative. Available at: https://bit.ly/3G6WGMM (accessed Nov 2021). **2.** Speaker insight. **3.** Dolinar and Reilly, *GaBI. Journal*. 2014:3(2);58–62.

Practical example – naming conventions

- The Cancer Vanguard partnership developed generic guidance for development of policies for biosimilar adoption[1]

- The guidance policy recommends prescribing by brand name to reduce accidental substitution
  - i.e., INN (brand name), e.g., Filgrastim (Zarzio®)

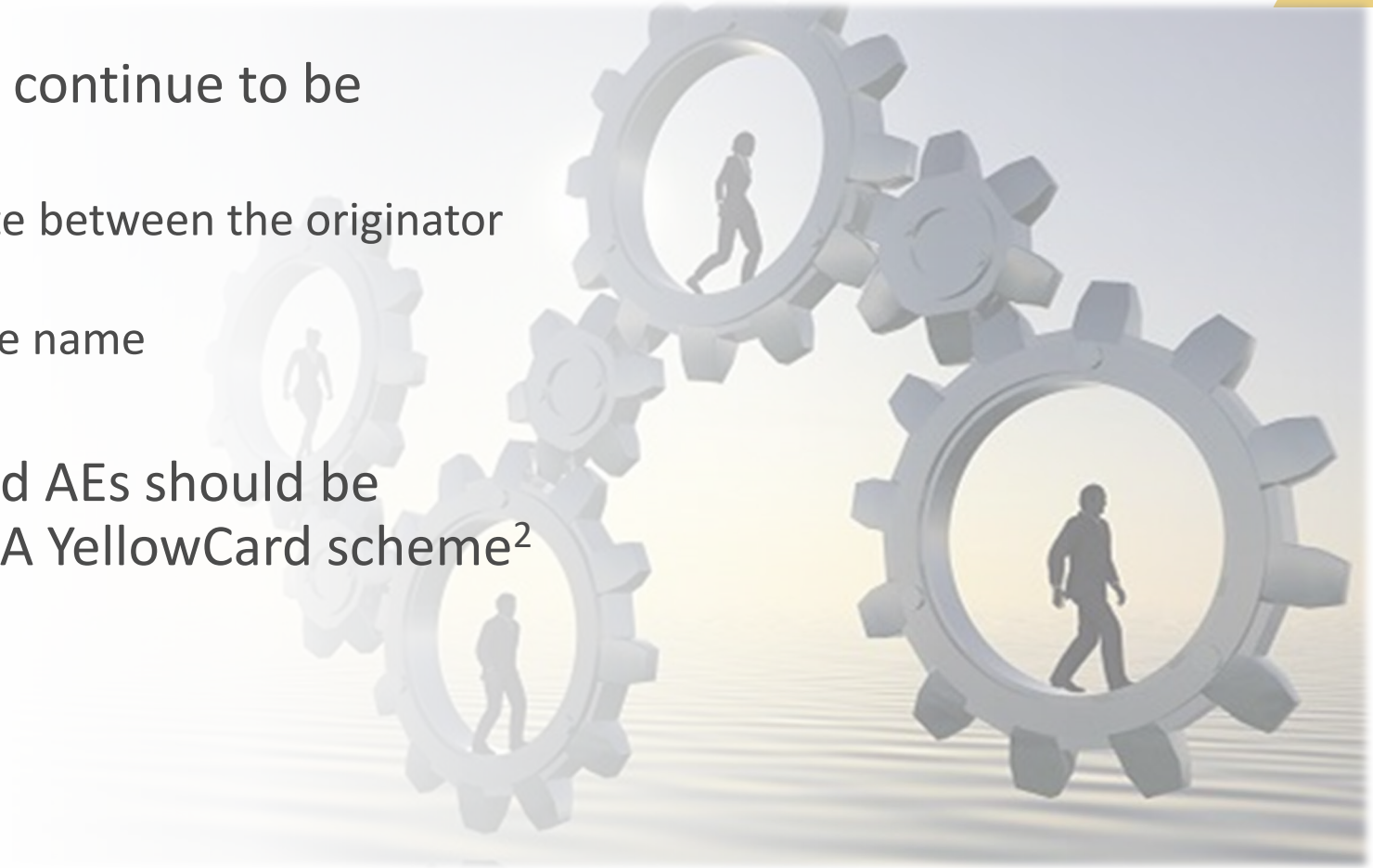
Regulatory body[2,3,4]	Naming convention	Example
EMA (EU)	INN + brand name Other identifiers used, e.g., tracking via batch number	Filgrastim (Zarzio®)
PDMA (JP)	Reference product INN + BS (biosimilar qualifier) + approval order code Note: naming system does not allow for substitution at the pharmacy level[2]	Bevacizumab BS1
FDA (USA)	INN + 4-letter suffix	Replicamab-hixf

AE = adverse event; EMA = European Medicines Agency; FDA = Food and Drug Agency; INN = international non-proprietary name; PDMA = Pharmaceuticals and Medical Devices Agency.

1. Cancer Vanguard Partnership and NHS. Available at: https://bit.ly/3niD7IF (accessed Nov 2021). **2.** Generics and Biosimilars Initiative. Available at: https://bit.ly/3cDPqKJ (accessed Nov 2021). **3.** Generics and Biosimilars Initiative. Available at: https://bit.ly/2Z94LzQ (accessed Nov 2021). 4. Generics and Biosimilars Initiative. Available at: https://bit.ly/3kX3qns (accessed Nov 2021).

Practical example – naming conventions

- If the originator and biosimilar both continue to be prescribed:[1]
  - Pharmacy systems need to differentiate between the originator and biosimilar
  - i.e., including brand name in the profile name
- Additional monitoring and suspected AEs should be reported using the (voluntary) MRHA YellowCard scheme[2]
  - Providing brand and batch number



AE = adverse event; MRHA = Medicines and Healthcare products Regulatory Agency.

1. Cancer Vanguard Partnership and NHS. Available at: https://bit.ly/3niD7IF (accessed Nov 2021).

Reporting

Interactive question – REPORTING

Company X produces a biosimilar monoclonal antibody for treatment of HER-2 positive breast cancer. All patients within the regulatory authority are switched to the biosimilar. What post-marketing information is important to include with the tailored risk management program?

A Common adverse events expected with drug therapy

B Changes to manufacturing processes that may change safety of efficacy of biosimilar

C Storage issues or alerts that may change physiochemical properties of biosimilar

D Cost-savings from switching to biosimilar from innovator

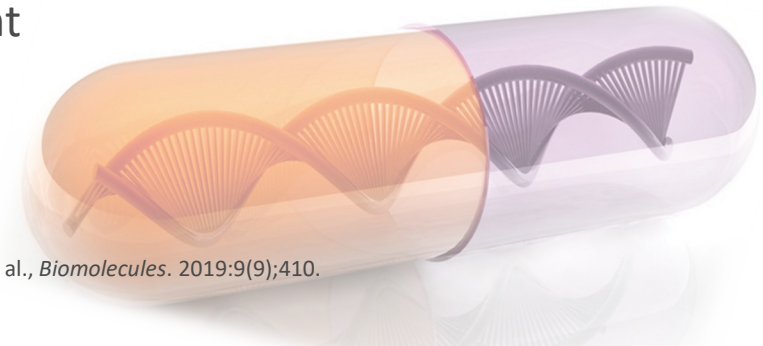
E Immunogenicity concerns with biosimilar (e.g., increased anti-drug antibodies, reduced efficacy on switching)

F B, C, E are correct

Please select one answer

Post-marketing adverse events

- Safety concerns associated with biologics may be detectable outside the time frames of the controlled clinical trials[1]
  - Limited sample size of clinical trials
  - Rarity of ADRs
- Clinical trials are used for comparisons of efficacy and equivalence[2]
  - Sample size linked to comparison of equivalence
- Hypothetical study of 1,000 patients[3]
  - Chance of detecting doubling of treatment-related AE from 5–10% = 82%
  - Chance of detecting doubling of treatment-related AE from 1–2% = 17%
- Abbreviated licensing pathway of biosimilars limits amount of pre-market-authorisation safety data[4]
  - Strengthens necessity for post-approval safety monitoring and risk management



ADR = adverse drug reaction; AE = adverse event.

1. Oza et al., *J. Postgrad. Med*. 2019:65(4);227–232. **2.** Isakov et al., *Am J Ther*. 2016;23(6):e1903–e1910. **3.** Berlin et al., *Am J Public Health*. 2008;98(8):1366–1371. **4.** Kabir et al., *Biomolecules*. 2019:9(9);410.

Post-marketing adverse events

A strong pharmacovigilance strategy must[1]

- Include a summary of potential risks and safety specifics
- Identify any area where there is a lack of sufficient information

Report high-risk changes to manufacturing processes[2]

Such changes may produce clinically significant changes to

- Quality
- Purity
- Function

1. Kabir et al., *Biomolecules*. 2019:9(9);410. **2.** Sardella et al., *Ther Adv Drug Saf*. 2021;12: DOI:10.1177/20420986211038436.

Practical example – change in drug delivery system causing ADRs

Excipient induced immunogenicity – epoetin and PCRA

Patients developed neutralising antibodies to erythropoietin after treatment with epoetin

- 3 cases developed between 1988–1997[1]
- 191 cases between 1998–2004[1,2]
- 92% of cases in patients who had received Eprex®[2,3]

Incidence rate rose between 1998–2002 after a change in formulation

- Change that replaced human serum albumin with polysorbate-80 as a stabilising agent[3]

Other contributing factors included[1,2]

- Change in delivery from intravenous to subcutaneous administration
- Use of uncoated rubber stoppers

Eprex® now mandated to be administered intravenously and with pre-filled Teflon®-coated syringes[1]

ADR = adverse drug reaction; PCRA = pure red cell aplasia.

1. McKoy et al., *Transfusion (Paris)*. 2008;48(8):1754–1762. **2.** Bennett et al., *N Engl J Med*. 2004;351(14):1403–1408. **3.** Pollock et al., *Clin J Am Soc Nephrol*. 2008;3(1):193–199.

Post-marketing guidelines

- Many regulatory bodies require post-market pharmacovigilance[1]

Regulatory Guideline	Pharmacovigilance
EMA (EU)	Risk management pharmacovigilance plan must be submitted; clinical safety monitored closely after marketing authorisation
MHRA (UK)	Risk management pharmacovigilance plan must be submitted; clinical safety monitored closely after marketing authorisation
WHO	Pharmacovigilance plan submitted with marketing authorisation application; describe planned post-marketing activities
FDA (USA)	Any risk evaluation and mitigation strategy for the reference product applies. Post-marketing studies or additional clinical trials could be mandated
BGTD/Health Canada	Risk management plan submitted prior to marketing authorization; periodic safety update reports. Serious adverse drug reactions reported within 15 days
PMDA (JP)	Post-authorisation safety studies monitored on a continuous basis
TGA (AU)	Risk management plan outlining pharmacovigilance procedures to be implemented submitted with biosimilar application

BGTD = Biologics and Genetic Therapies Directorate; EMA = European Medicines Agency; FDA = Food and Drug Administration; MHRA = Medicines and Healthcare products Regulatory Agency; PMDA = Pharmaceuticals and Medical Devices Agency; TGA = Therapeutic Goods Administration; WHO = World Health Organization;

1. Mysler et al., *Rheumatol. Int*. 2016:36(5);613–625. **2.** Table adapted from: Kabir et al., *Biomolecules*. 2019;9(9):410.

Individual case safety reports (ICSR)

- As under-reporting of AEs is highly prevalent, literature searches may be required to identify potential ICSRs[1]
  - i.e., journals, newspapers, and other media
  - Possible that safety cases may not be reported officially but may gain attention in the public media

- Practical example – using social media to monitor ADR mentions of adalimumab
  - Study compared ADR mentions on Twitter with systematic reviews, FAERS, and DIDs
  - Total 10,188 tweets collected
    - 801 true ADRs (2,617 potential ADRs identified automatically)
  - The most frequently and infrequently experienced ADRs were similar across all sources
  - Moderately frequent ADR experiences were more likely to differ
    - Dermatological ADRs most mentioned in FAERS

ADRs = adverse drug reactions; AEs = adverse events; DID = drug information database; FAERS = US FDA adverse event reporting system.

1. Oza et al., *J. Postgrad. Med*. 2019:65(4);227–232. **2.** Smith et al., *Drug Safety*. 2018;41(12):1397–1410.

Practical example of voluntary reporting – UK Yellow Card scheme[1]

- Run by the MHRA and is the UK system for collecting and monitoring information on safety concerns involving medicines and medical devices
  - i.e., suspected side effects or AEs

- The purpose is to provide an early warning that the safety of a medicine or medical device may require further attention or to flag issues that may not have been previously indicated

- The scheme relies on voluntary reporting
  - Can report online – mhra.gov.uk/yellowcard
  - Can give a report to a healthcare practitioner
  - Can report via the yellow card mobile app

AE = adverse event; MHRA = Medicines and Healthcare products Regulatory Agency.

1. MHRA YellowCard scheme. Available at: https://bit.ly/3joHUaD (accessed Nov 2021).

Practical example of mandatory reporting – Vanessa's Law

- Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)[1]
  - Amendment of the Food and Drugs Act
  - Provides post-marketing oversight over therapeutic products
  - Allows certain actions to be taken when a serious health risk is identified

Vanessa's Law
Protecting Canadians from Unsafe Drugs Act

Serious Adverse Drug Reaction and Medical Device Incident Reporting

- Law enacted in 2014 and mandatory reporting effective in Dec 2019[2]

- Mandatory institutional reporting of
  - Serious ADRs
  - MDIs

PATIENTS FOR PATIENT SAFETY CANADA | PATIENTS POUR LA SÉCURITÉ DES PATIENTS DU CANADA

- Patients for Patient Safety Canada (PFPSC) aim to raise awareness about reporting ADRs and MDIs[2]

ADR = adverse drug reaction; MDI = medical device incidents.

1. Government of Canada and Health Canada. Available at: https://bit.ly/3B7Osk0 (accessed Nov 2021). **2.** Patients for Patient Safety Canada. Available at: https://bit.ly/3m1yGCN (accessed Nov 2021).

Practical example – paper-based monitoring[1]

Hospital-based observational study monitoring signalling suspected ADRs in a Portuguese oncology department

Biosimilars: rituximab CT-P10 (Truxima®) or trastuzumab CT-P6 (Herzuma®)

Paper-based ADR reporting form developed for each biosimilar

Completed by the attending clinician	Clinical secretariats sent the reports via an electronic platform to the pharmacovigilance department • Analysis of seriousness, expectedness, and causality of suspected ADRs

ADRs = adverse drug reactions.

1. Rigueiro et al., *Eur. J. Hosp. Pharm*. 2021:28(Suppl 1);A154.

Paper-based monitoring example (cont.)

Results

- 35 patients received rituximab; 59 patients received trastuzumab

Most reported ADRs for rituximab CT-P10

- Chest discomfort (19.1%; n=4))
- Odynophagia (9.5%; n=2)

Most reported ADRs for trastuzumab CT-P6

- Back pain (4.8%; n=1)
- Headache (4.8%; n=1)
- Pain in extremities (4.8%; n=1)
- Tachypnoea (4.8%; n=1)
- Tremor (4.8%; n=1)

The results of this study showed that carrying out active pharmacovigilance programmes in oncology pharmacy practice is feasible and that such activities contribute to better characterisation of the safety profiles of medicines

ADRs = adverse drug reactions.

1. Rigueiro et al., *Eur. J. Hosp. Pharm*. 2021:28(Suppl 1);A154

Transportation and storage monitoring

- Biologics have complex structures with high sensitivity to[1]
  - Humidity
  - Medium composition
  - Temperature
  - Shaking and vibration[2]
  - Shear strain during stirring[2]

- Suggested monitoring includes[3]
  - Environmental conditions in the warehouse, transports, and at delivery points
    - Cold chain storage and good distribution practises
  - Monitors should be fitted with alarms
  - Data should be securely stored
  - Monitoring software should be secured, compliant, and in real-time

1. Alsharabasy, *Arch. Biotechnol. Biomed*.2017:1(1);033–053. **2.** Zapadka et al., *Interface Focus*. 2017;7(6):20170030. **3.** Hoffman. Available at: https://bit.ly/3prqZbg (accessed Nov 2021).

Practical example – packaging causing ADRs[1]

Two cases of neutralising antibodies to erythropoietin reported

Occurred during a pre-marketing clinical trial of biosimilar epoetin (HX575)

Assessment of the quality attributes of drug-substance and drug product syringes

Increased dimerisation/aggregation found in two drug product batches used to treat the affected patients

- Up to 5% increased aggregation found in individual syringes – levels never found before

Variable levels of soluble tungsten found in the suspect syringes

Most likely derived from the pins used to manufacture the syringes

ADR = adverse drug reaction.

1. Seidl et al., *Pharm Res*. 2012;29(6):1454–1467.

Closing remarks

Post-learning assessment

When implementing new biosimilar medications, will you now routinely include and communicate the importance of the details for patients to self-report adverse events?

A Routinely

B Often

C Sometimes

D Rarely

E I will be unable to

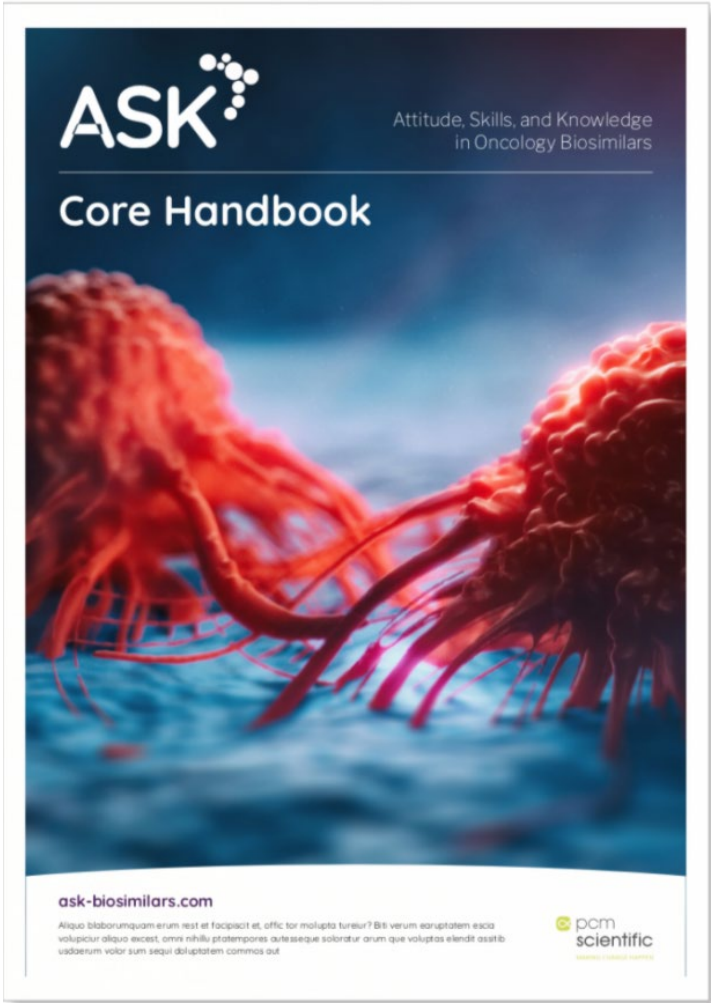
Please select one answer

Free learning resources available

- Handbook
  - English version available now
  - Coming soon in French, German, Italian, Japanese, and Spanish
- Learning chapters – coming soon
- Abstract library – available now
- National guideline summary documents – coming soon
- Subtitled webinar archive footage – coming soon

Find out more via the website:

ask-biosimilars.com



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The archive of ASK expert-led educational webinars will be available with subtitles in French, German, Italian, Japanese, and Spanish and can be found at:

ask-biosimilars.com

Adapting to a changing landscape: switching to oncology biosimilars

Empowering patients as part of a successful biosimilar switching strategy

Implementing biosimilars: a case study on pharmacovigilance best practice

Please remember to complete our evaluation survey – **your feedback is important and valued**

ASK

Attitude, Skills, and Knowledge in Oncology Biosimilars

Thank you for joining this webinar!