Attitude, Skills, and Knowledge in Oncology Biosimilars

ASK 'Implementing biosimilars: a case study on pharmacovigilance best practice' transcript

Slide 1

Marta Trojniak: Hello. Welcome, everybody, to the webinar on "Implementing biosimilars: a case report on pharmacovigilance best practice." Many thanks to the audience for being here and we wish you an interesting session.

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Marta Trojniak: So before starting, I'll give you some information about this webinar. The ASK webinar is supported by grant funding from Pfizer. PCM Scientific is the medical education company acting as scientific secretariat and organiser for this programme.

The activity is run independently of the financial supporter and all content is created by the faculty. No funder has had input into the content of the activity.

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Marta Trojniak: This is an interactive webinar, so please participate. Please post your questions in the Q&A box. The chat function will be disabled. We will look to incorporate your questions throughout the webinar to facilitate discussion.

There will be also interactive questions displayed on the screen, so please choose your answer by selecting the options when they appear on the screen. Obviously if you are watching the archived footage, you will not be able to take part in any polls.

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Marta Trojniak: I would like to introduce you to my colleague: Glenn Myers is a clinical pharmacist working in the Dr. Sheldon H. Rubin Oncology Clinic in Moncton, New Brunswick, Canada.

My name is Marta Trojniak and I'm a clinical pharmacist working in the Paediatric Research Institute, Trieste, Italy.

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Marta Trojniak: These are our disclosures.

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Marta Trojniak: Regarding learning objectives of this webinar, we would like to draw your attention to key elements of pharmacovigilance best practice.

After completing this webinar, you 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 which 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 uptakes of biosimilars.

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Marta Trojniak:

Let's start with a pre learning assessment to see what your attitudes in your daily practise are. So please answer the question whether it appears on the screen. 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 choose your answer.

Oh great, so very good; 50% of you clicked on routinely and 50% sometimes. So sometimes your patient communication includes the details on self-reporting adverse events.

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Marta Trojniak: During this webinar you will have the chance to learn more about the importance of adverse event reporting.

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Marta Trojniak: Now let's start with the introduction; here we've got the first interactive question.

You will learn during this session that naming conventions can be variable between regulatory authorities around the world, which makes tracing difficult.

The question for you is, “which of the following examples would make it difficult to differentiate between a biosimilar and the innovator biologic for tracing proposes?”

Please select one answer:

(A) filgrastim (Grastofil),
(B) filgrastim-aafi,
(C) filgrastim,
(D) Nivestym®,
(E) filgrastim (Nivestym).

There is an error in the polling mechanism, so the correct answer is (C): filgrastim alone is only the international non-proprietary name and does not allow to identify a specific product and manufacturer, which is required to accurately product traceability.

Marta Trojniak: OK, so now Glenn will continue the presentation on “pharmacovigilance best practice.”

Please Glenn, go ahead.

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Glenn Myers: Alright, thank you so much, Marta, for that great intro and I think that was a good kind of question to get us warmed up for our discussion.

Now, when we think about pharmacovigilance, especially when it comes to biosimilars, or when it comes to any drug therapy, the overarching benefit and purpose of pharmacovigilance is to enhance patient care and safety to ensure that the risk benefit ratio is maintained throughout the course of the drug's lifespan.

It provides us this information to make an appropriate risk–benefit profile to the drug, because this may change over time depending on reporting or as a result of any manufacturing practices.

The other thing with pharmacovigilance that's really important, especially when it comes to biologics and biosimilars, is assessing any high-risk manufacturing changes – as this may change the actual structure and function of the biologic as we do make these products in living organisms.

So, when we look at pharmacovigilance from a broad perspective around the world, we collate a lot of different information from individual case reports, whether it be published in the literature, case reports from health authorities, from hospitals - both in your local jurisdiction and nationally.

We use this information to process the case reports and then provide reports which are disseminated by the National Health authorities, continental health authorities, the drug companies, various hospitals, or even published in the literature, to give us a better example of what the risk–benefit ratio is for that drug, as it's on the market for a longer period of time.

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Glenn Myers: When we look at the first aspect of pharmacovigilance, product names become extremely important because we need to differentiate between a biosimilar and its innovator biologic. As you can imagine from our example before, if we use just the name filgrastim for all our biosimilars, it would be very confusing to try to identify and classify which biosimilar could be associated with potentially increased adverse events.

It's really important to have a unique naming system for biosimilars, because, again, we need to be able to trace back certain manufacturing changes or certain adverse events to a specific batch or even a or a specific biosimilar product and not just the innovator.

The naming conventions for biosimilars have changed over the years and will vary depending on the jurisdiction you're in, as per the question, so the international non-proprietary name is really insufficient by itself to name a biosimilar. Depending on where you're at it will have a different naming convention, as we will see moving forward into the into the next slides.

It is extremely important, because if I was to say to you, I want a chocolate bar, but I don't tell you what kind of chocolate bar I want, then as you can imagine it becomes very difficult to know what chocolate bar I want.

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Glenn Myers: So, there was a survey assessing some of this information on the product information leaflet, and from this survey what they gathered from physicians was that 90.5% of physicians actually used the label as an information source for a biosimilar or for a biologic.

I think it's really important the information that is contained within a summary of a product, the product monograph or product characteristic, does outline where the information comes from – whether it's from the original clinical trial that was done, or if it was from a post-marketing analysis, or even if it was from a random analysis done by the manufacturer, because this helps the clinician make a decision for the risk–benefit ratio.

Only a small percentage of physicians from the survey deemed the potential additional contents in the information not helpful. So that's why it is helpful to have the information about safety and adverse events within the product monograph or the product details.

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Glenn Myers: Naming confusion has been a hot topic since biosimilars first were presented to the market, because, as you can imagine, there is a potential for mix up if the naming convention isn't consistent within that certain health authority. What it can lead to is potentially unintentional switching at the pharmacy, or even the hospital level, if we're not aware of what specific biosimilar product the patient is actually getting or the innovator biologic.

I think the most important thing is that if we do not have a consistent naming strategy for naming biosimilars, we have a very hard time tracing back adverse events, or even manufacturing changes, to that specific biosimilar. It's very difficult to educate the public, and educate the patient, on that risk–benefit ratio if we don't know what biosimilar it's associated with.

The other thing that it becomes really troublesome for, is our local systems in the hospital, whether it be physician order entry systems, or electronic medical records, or even barcoding in the pharmacy because if we don't have a specific barcode that coordinates to a specific naming convention, then it can make it very difficult to ascertain what product is causing an issue when we do a retrospective review of the evidence.

There was a 2013 survey regarding biosimilar naming that was done with physicians in Europe. It did identify that, for physicians, there is a really high risk for mix-up when there isn't a clear naming structure identified. So, about 53% mistakenly felt identical non-proprietary names implied identical structure – which is the case for generic drugs but not for biosimilars. Then, about 60% of physicians said that identical non-proprietary names imply medicines are approved for the same indication, which we know with biosimilars that's certainly not the case in all cases. Then, only about 25% recorded only non-proprietary names of the biologics. So, again with the naming convention it becomes very important for biosimilars, not as important for generic drugs, but it becomes much more important for these products because they can have subtle changes that can lead to changes in safety later on.

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Glenn Myers: We're going to use our practical example here to display this. The practical example we're going to use is from the cancer vanguard in London, England. They developed a guidance policy for naming conventions of biosimilars and came up with a policy that used the international

non-proprietary name with the brand name in brackets so that we can differentiate from one biosimilar to another, but also the biosimilar to the innovator.

This becomes very important because this naming policy is actually the same that's used by Canada, but we see differences around the world. In Japan, for instance, they use a naming convention where they use the INN but they also use an approval order code. So, in the case of this bevacizumab product, it's BS1. In the USA, the FDA use the international non-proprietary name followed by a four-letter suffix that really has nothing to do with the drug.

So, as you can see, depending on the jurisdiction, there may be different needs for that specific country in terms of naming. It's important that we have a different naming structure so that we can facilitate accurate identification of toxicities as well as manufacturing changes.

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Glenn Myers: Another naming example that we can look at, using the cancer vanguard example, is if we continue to use just the INN, then this can make it very difficult within our pharmacy systems, so the computerised physician order entry (CPOE) or electronic medical record (EMR), for any kind of barcoding or drug checking software to actually differentiate between products. That's something that we've certainly come up with here.

One thing they use in in the UK is something called the MHRA yellow card scheme. This actually allows people to self-report AEs, as well as healthcare professionals to report AEs, but it also includes the brand and batch number as well so that we can accurately trace and identify which product is actually causing the AE.

From your side, Marta, in Italy, why are naming conventions, especially for biosimilars and biologics, so important in your practice?

Marta Trojniak: Well, lack of a specific product name for the Italian pharmacovigilance network means a delay in time taken to detect the product-specific safety signal. We know that biosimilars are a biological medicine that are highly similar but not identical to biological originators. As you previously said, biologics, including biosimilars, are characterised by manufacturing changes during the life cycles and by possible immunologic reactions.

In addition, you have a risk of incorrect storage condition, and so on. This all may affect efficacy or safety. And when we consider switching practices widely used in Italy and automatic substitution, the risk of misattribution of adverse drug reactions to the right product may be really high.

To improve traceability of biologics, the Italian drug agency, AIFA, has been proactively encouraging prescribers to provide the brand name and batch number in the patient records when reporting ADRs, as required by the European legislation.

Furthermore, the Italian electronic adverse event reporting system, VigiFarmaco, helps to prevent any uncertainty when reporting ADRs. In addition, most pharmacy systems support such product identification and traceability when medication is dispensed or administered to patients.

Glenn Myers: Yeah, that's really interesting, Marta. There's still a need for that naming convention to in order to track biosimilars and it becomes really important when in at the pharmacy level and at the patient safety level as well.

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Glenn Myers: OK, so now we're going to move on to reporting.

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Marta Trojniak: Here we've got another interactive question on reporting. Company X produce a biosimilar monoclonal antibody for treatment of HER-2 positive breast cancer. All patients within the regulatory authority are switched to that. What post-marketing information is important to include with a tailored risk management programme?

(A) common adverse events expected with drug therapy,
(B) changes to manufacturing processes that may change safety or efficacy of biosimilar,
(C) storage and issue or alerts that may change physical chemical properties of biosimilar,
(D) the cost savings from switching to biosimilars from innovator,
(E) immunogenicity concern with biosimilars, (e.g., increased the anti-drug antibodies to reduce the efficacy on switching, and
(F) answers B, C, E are correct.

Oh, great, perfect! You all clicked (F), that's the correct answer because a risk management plan should identify, characterise, and minimise important risk specific to the biological product throughout its lifecycle. So that's great.

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Glenn Myers: OK, so by far the most important piece of pharmacovigilance is the recording of post-marketing adverse events, and we talked about this in the first webinar, but with the nature of biosimilar approval for totality of evidence, we only have to perform an equivalent clinical study with the innovator. This is a study that's done in a short timespan to show data for clinically sensitive endpoint and with these studies we may not be able to identify any late-onset toxicities, or even rare toxicities, from the agent.

So, that's why it's really important to have a robust safety plan and pharmacovigilance plan from the manufacturer, so that there's a way that we can identify these adverse events post-marketing. The rule that we used in the first webinar was the rule of three: so if a side effect happens in one in 1000 patients, we usually need 3000 patients to identify one case of this.

As you can imagine, it's very hard to identify these toxicities in the equivalence trials, so that's why we need to have a robust pharmacovigilance system with the manufacturer, but also with the country of origin as well.

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Glenn Myers: For post-marketing adverse events strong pharmacovigilance practise for a manufacturer has to include several things; it has to include a summary of the potential risks, and safety specifics of that product, but we have to identify the known risks. We also have to summarise the possible risk, but also areas where there may be insufficient information to summarise.

So, let's say in the case of a very rare toxicity that happens in one in 10,000 patients, they have to identify that there's lack of this information from those studies. The way that most regulatory

authorities summarise pharmacovigilance is based on spontaneous reporting systems or SRSs and active surveillance or AS, and both of these are important for post-marketing surveillance of adverse events.

What also becomes important with biosimilars is that we have devices to administer these biosimilars, a lot of the time, and these biosimilars are very sensitive to manufacturing changes. We have to have a way to assess any high-risk manufacturing changes and their potential effect on the biosimilar.

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Glenn Myers: So practical example was the epoetin and the PCRA which occurred in the in the late 90s and early 2000s. This was the example that was used in the handbook; patients actually developed neutralising antibodies to erythropoietin after there was a change in the formulation. So, they changed from serum albumin to polysorbate-80, but they also changed to using uncoded rubber stoppers.

It actually changed the formulation, or the structure of epoetin, where it drastically increased the cases of PCRA, which were which were previously very rare with this product. This is a really good example of post-marketing pharmacovigilance because we were able to identify these increased cases versus historical cohorts of patients who were getting the old version.

And now we have learned from this case to develop a more robust pharmacovigilance strategy for assessing manufacturing changes. Even if it's nothing to do with the product itself, even if it's to do with the device or any big manufacturing changes at the plant, we still have to have a way to assess these to make sure that there's no adverse change to the product.

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Glenn Myers: So, with the post-marketing guidance that's available internationally, this is going to vary depending on the country of origin. As you can see, there's a lot of similarity between the pharmacovigilance strategies from anywhere – from the UK to the EU, to Health Canada, and the US, but the thing to remember here is that not all countries have a robust pharmacovigilance plan.

There are some smaller countries around the world that may not have the ability to perform pharmacovigilance and the monitoring for safety. These are just some good examples, there are also some examples from around the world that may not be as robust. It's really important for post-authorisation studies to occur because they assess major changes to manufacturing and also regularly assess the ADR reports. You'll see that as a very common finding with a lot of these regulatory bodies.

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Glenn Myers: Individual case study reports can also be published in the literature, and they really have nothing to do with an adverse event that's reported to your hospital or to your health authority.

There was an example using Twitter that identified various tweets that associated with case reports of adverse events. So, within this study they collected over 10,000 tweets and there were over 800

ADRs reported. The most frequently and infrequently experienced adverse events were similar across all sources.

I think with this we have to remember that we're not just gathering safety data from reports given at the hospital level or the national level, or at the even at the manufacturer level, but we can even look at the primary literature, something like PubMed or even social media to assess the safety of this and this information may even be gathered by your National Health Authority or the manufacturer to help with the pharmacovigilance plan and the to assess the risk–benefit ratio on a longitudinal basis.

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Glenn Myers: The other practical example we use is the UK Yellow Card scheme: this is a system within the UK where patients, healthcare providers, caregivers, or what have you, can use this yellow card to report an adverse event for a medicine or a medical device. This promotes active reporting of adverse events, not only from the healthcare provider but also from the patient.

What's great about this is that it can be done on many different levels: this can be reported online, it can be a paper-based copy that's given to the health care provider, or it's even available as a mobile app. All of these information sources go to help with the pharmacovigilance strategy for a specific product. This is going to become even more important as more biosimilars do come on the market across the world.

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Glenn Myers: The next example we'll use is from my home country, Canada. Vanessa's law came into effect in December of 2019 and was developed in 2014. The reason why this came out is there was a girl named Vanessa in 2000 who passed away from a serious adverse reaction to a drug. With this law, it really gives the Food and Drugs Act and Health Canada the ability to identify risk proactively, via adverse drug reporting at the hospital level. It then uses this information to provide information to the public on awareness about adverse events associated with drugs.

What it also does, is it increases the likelihood that healthcare providers will report serious adverse events to their hospital, or to Health Canada, so that we can possibly help mitigate these risks into the future.

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Glenn Myers: The other example comes from Portugal and, again, we don't always have to use electronic systems. This used a paper-based system where they reported adverse events of two biosimilars of rituximab and trastuzumab, and they actually had a paper-based system where they summarised the adverse events that occurred with these two biosimilars and then collated the data.

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Glenn Myers: It had found that there were 35 patients who received rituximab and 59 patients who received trastuzumab, and these were the adverse events that were reported in both these groups of patients. What it shows us is that paper-based systems can still be important at the hospital level. They may be less utilised on a national level due to the pure volume of data, but it shows that the

paper-based pharmacovigilance strategy can still be a useful way of reporting the safety of a biosimilar or a biologic product.

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Glenn Myers: The last thing I just want to mention is, because biologics are very sensitive to temperature and even the device that they're in, it's important that we have a pharmacovigilance strategy within the manufacturing process to help assess any changes to transportation or even storage of that product.

So, let's say there's a breakdown in the temperature monitor in a certain cold chain product. Then this needs to be assessed by the manufacturer and reported to the national jurisdiction in a timely basis, because this can actually change the structure of the product because of how temperature labial the biologic can be. This can vary from biosimilar manufacturer to biosimilar manufacturer, so again, I think it's really important that this is monitored in addition to the adverse event reporting, because this could actually change the structure of a specific lot of that biosimilar and it could potentially be traced back to that lot of that specific biosimilar.

The other thing I just want to mention with this, is that packaging also becomes very important in terms of the device that's used, so we'll go to the next slide to talk about that.

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Glenn Myers: The practical example is two cases of neutralising antibodies to erythropoietin that were reported, this is a practical example, I think Marta, that you had that you had given. It occurred in the pre-clinical marketing of a biosimilar epoetin, and when we looked at the quality attributes of this, there was increased aggregation found in the two product batches used to treat affected patients. It identified that the aggregation levels seen in these specific lots had never been found before. They traced it back to the soluble tungsten found in the suspect syringes that likely developed, causing this dimerization and aggregation.

This is really an example of how the actual injection device, or the medical device, can change the composition of the product, which can in turn potentially change safety or the efficacy in terms of immunogenicity or anti-drug antibodies, or even aggregation or physiochemical properties of the drug.

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Glenn Myers: So now I'll pass it back over to Marta for the closing remarks.

Marta Trojniak: We've come to the end of today’s webinar, so if you have any burning questions, please type them quickly.

I think it has been interesting discussing effective strategies for ensuring accurate monitoring and reporting of adverse events of biologics including biosimilars.

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Marta Trojniak: Before we close, I will just run through the post-learning assessment.

Just to repeat the question from the beginning, “when implementing new biosimilar medications, will you now routinely include and communicate the importance of the details for patients to self-report adverse events?.” Please answer now based on your thoughts.

Glenn Myers: I really hope this is going to be routinely.

Marta Trojniak: Oh, great, lovely. You now declared that your patient communication will routinely include the self-reporting of adverse events. Great, that's brilliant!

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Marta Trojniak: Before you go, I would like to make you aware about the free learning resources available on the ASK biosimilar website. You have an educational handbook on oncology biosimilars in English and this will soon be available in other languages. We've got an abstract library and soon there will be available guideline summary documents.

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Marta Trojniak: The archive of ASK expertly led educational webinars will be available on the website soon, with subtitles in French, German, Japanese, Italian, and Spanish.

So, please check the website. After this webinar, you will find our evaluation survey and we are really interested to have your feedback. This is a new programme, and we would like to know better your needs and thoughts.

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Marta Trojniak: Thank you very much for your attention and for joining this webinar. Thank you so much Glenn, for your wonderful speech today, and thank you, all of you, for your answers and participation. I wish you all the best. Bye-bye.

Glenn Myers: Thanks Marta and PCM. Take care.