IGBA Position on Identification of Biological, including Biosimilar Medicines

2019 Update of Facts & Figures

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Successful traceability and identification are possible without an addtional identifier

- No additional identifier is needed for successful traceability and identification in case of adverse event reporting and both are possible in a framework where biosimilar products and their respective reference products share the same International Non-Proprietary Name (INN)
- Unique identification of a medicinal product is ensured either with
  - Invented/"brand" names
    - or
  - INN + MAH (especially in countries with INN prescribing or where an invented/"brand" name is not available or not legally enforceable)
    - Marketing Authorisation Holder (MAH) is responsible for Pharmacovigilance
- It is the worldwide implementation of the WHO standards and the strengthening of national pharmacovigilance systems, and not an additional identifier, which will support patient safety and public health.

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2019 Update
Supporting Facts & Figures

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EU EudraVigilance demonstrates that identification is possible without a BQ

- EMA adopted a guideline to enhance pharmacovigilance for biological medicines:
  - the product name and the batch number have to be included in adverse event reporting and in all product packaging throughout the supply chain
- EU approved biosimilar medicines have generated more than 700 million patient days of safe clinical experience [2]
- The Vermeer study (Vermeer et al. Drug Safety (2013) 36: 617—625) reviewed over 2 million unique ADR reports in the European Union Eudravigilance system from 2004-2010, with product attribution rates ranging from 90-96%

[2] Biosimilar Medicines Clinical Use: An Experience Based-EU Perspective

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Publication reveals high level of product indentification in multisource markets

2011-2016 study revealed that adequate identifiers were reported for **96.7%** of the suspected Biologicals

Product identifiability remained consistently high over time for classes of biologicals for which biosimilars were introduced

European system for identification of ADRs to the **level of the manufacturer** is **robust**

https://bit.ly/2NwhBhf

Identifiability of Biologicals in Adverse Drug Reaction Reports Received From European Clinical Practice

Niels S. Vermeer[1], Thijs J. Giezen[2], Sofia Zastavnik[3], Elena Wolff-Holz[4] and Ana Hidalgo-Simon[3]

Biologicals are established treatment options that require pharmacovigilance adapted to their specific nature, including the need for products to be identifiable up to the specific manufacturer in reports of adverse drug reactions (ADRs). This study explored the identifiability of 10 classes of similar and related biologicals up to the level of the manufacturer in ADR reports received from European clinical practice between 2011 and June 2016. Adequate identifiers were reported for 96.7% of the suspected biologicals, ranging from 89.5% for filgrastim to 99.8% for interferon beta-1a. The product identifiability remained consistently high over time for classes of biologicals for which biosimilars were introduced during follow-up. The overall batch traceability was, however, only ensured for 20.5% of the suspected biologicals and needs further improvement. This study shows that the European system for identification of ADRs to the level of the manufacturer is robust, allowing for the timely detection of potential product-specific safety signals for biologicals.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Adverse drug reactions (ADRs) to biologicals may be product-specific or batch-specific, resulting from changes in manufacturing. Due to the increased availability and use of biosimilars in Europe, the product identifiability up to the manufacturer in ADR reports has received scrutiny.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We investigated the product identifiability in ADR reports received from European clinical practice between 2011 and 2016. We focused on classes of biologicals for which similar or related (bearing the same generic name) products are available.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We show that product identifiers are available for 96.7% of the suspected biologicals in ADR reports. The identifiability remained robust over time for biologicals for which biosimilars were introduced. Traceability of individual batches was identified as an area for improvement.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The high level of product identification is reassuring, and confirms that product-specific safety signals can be timely identified in multisource markets with multiple similar and related biologicals. Fears of poor product identification when switching between products are not justified.

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Publication reveals strong pharmacovigilance data via product name reporting

- A Dec. 2017 publication [1] systematically reviewed the periodic safety update reports (PSURs) of 3 biosimilars marketed worldwide for the assessment of the post-approval safety monitoring
- These 3 biosimilars collectively represent nearly 350 million patient days of treatment worldwide
- The data show that spontaneous adverse drug reactions are reported by brand name in the majority of cases and are attributable to a specific medicine.

- ➢ Brand names remain the most frequently and reliable data element
- ➢ In countries where brand names are not available, INN and MAH serve as unique identifiers of a medicine

TABLE 1 Safety Monitoring Experience with 3 Biosimilars with Total Patient Days of Treatment After Approval

EPOETIN ALFA Binocrit/Epoetin alfa Hexal/Abseamed/Novicrit	SOMATROPIN Omnitrope/Scitropin	FILGRASTIM Zarzio/Zarxio/Filgrastim Hexal
Total spontaneous (HCP, non-HCP) AEs/ADRs reported through August 31, 2016, n = 355	Total spontaneous (HCP, non-HCP) AEs/ADRs reported through September 30, 2016, n = 1,603	Total spontaneous (HCP, non-HCP) AEs/ADRs reported through September 15, 2016, n = 533
Reported as: Abseamed, n = 97 Binocrit, n = 229 Epoetin alfa Hexal, n = 18 Epoetin alpha Sandoz, n = 1 Erythropoietin Sandoz, n = 1 Novicrit, n = 1 **Unknown:** Erythropoietin alfa/epoetin alfa/ erythropoietin, n = 8	**Reported as:** Omintrope, n = 1,531 Scitropin, n = 15 Somatropin BS, n = 22 **Unknown:** Somatropin, n = 35	**Reported as:** Zarzio, n = 455 Zarxio, n = 18 Filgrastim Hexal, n = 20 Filgrastim Sandoz, n = 3 Filgrastim BS, n = 1 **Unknown:** Filgrastim, n = 33 **Unknown:** G-CSF, n = 3
206,303,772 patients days through August 31, 2016 (date of PSUR: October 21, 2016)	***120,461,390 patient days*** through September 30, 2016 (date of PSUR: November 14, 2016)	***15,924,538 patient days*** through September 15, 2016 (date of PSUR: October 31, 2016)

ADR = adverse drug reaction; AE = adverse event; BS = biosimilar; G-CSF = granulocyte-colony stimulating factor; HCP = health care provider; PSUR = periodic safety update report.

[1] Sagi et.al., Pharmacovigilance of Biologics in a Multisource Environment, JMCP, Vol. 23, No. 12, December 2017

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DanBio confirms successful identification of products sharing same INN [1]

Danish national recommendation to use biosimilars – highest uptake of all EU countries:

- nearly 100% use of biosimilar Inflximab
- nearly 80% use of biosimilar Etanercept

Danish Executive Orders (Dec 2015) ensure traceability through:

- Physicians shall make records of brand name and batch number in patient records and provide brand name and batch number when reporting ADRs
- Increased focus on product information in reporting forms, e.g.
  - Pop up-message for biological medicinal poducts in HCP e-form
  - specific field for batch number in consumer e-form)

➢ Very high reporting of batch numbers for biosimilar medicines (75.4 % for Infliximab; 72.7% for Etanercept)

➢ Danish Agency‘s report published on a biannual basis

Reporting of batch no, infliximab and etanercept

Product	Active substance	Number of reports	Batch number, initial report	Batch number, on follow up	Total batch no (% of reports)
Not specified	Infliximab	9	-	-	-
Remicade	Infliximab	73	2	3	5 (6.8)
Remsima	Infliximab	142	71	36	107 (75.4)
Not specified	Etanercept	6	-	-	-
Enbrel	Etanercept	23	4	2	6 (26.1)
Benepali	Etanercept	22	9	7	16 (72.7)
TOTAL		275	86	48	134 (48.7)

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[1] Benedictine Lunddahl, Head of Pharmacovigilance, Danish Medicines Agency, March 2017

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Australia supports unique identification with product‘s trade name and INN

IGBA welcomes the Australian Government’s decision taken in January 2018

- to maintain the existing naming convention for biological, including biosimilar medicines, i.e. using the Australian biological name (without a specific identifier suffix)
- to strengthen the adverse event reporting. This includes making the product's trade name, as well as the non-proprietary name, a mandatory field when reporting an adverse event to the Therapeutic Goods Administration (TGA),
- to avoid the complexity and potential confusion that would be associated with introduction of a suffix-based system with retrospective coverage
- to align with the EU which has the largest experience with biosimilars sharing the same INN than their respective reference products and excellent product identification results in case of ADR reporting.

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U.S. pharmacovigilance data not supportive of INN suffix

"Many currently licensed originator biologics in the Unites States have shared non-proprietary names for decades with no pharmacovigilance concerns." [1] – only since the advent of biosimilars some groups assert that there is a problem. But no physician or pharmacist survey was ever conducted to evaluate if these groups are concerned with differentiating the 75+ biologics that already share INNs

- FDA has approved 20 biosimilar products, all with a 4-letter suffix, but only 7 are marketed (status June 2019)
- First public presentation of US Zarxio pharmacovigilance data provided at the DIA Biosimilars Conference in October 2017 [2]:
  - 994,443 patient days of exposure collected until then
  - 65 case reports since US launch of which 62 (95%) contain the brand name
- Data from FDA's Adverse Drug Report System Public Dashboard shows that biosimilar medicines could be identified by their proprietary (brand) name in **99.1%** of reported cases [3]
- No data exists to demonstrate that added non-memorable suffixes in the U.S. will improve the U.S pharmacovigilance system
- **IGBA strongly urges the FDA to re-evaluate the use of a product-specific suffix for biologics naming**

[1] McCamish M, Gallaher A., Orloff J., Biosimilar by name and biosimilar by nature. Table 1. The RPM Report. July/August 2013
[2] Carlos Sattler, MD, Head of Medical Affairs, Sandoz Inc, DIA Biosimilars Conference, Bethesda, MD, October 24/25, 2017
[3] Pink Sheet. "Biosimilar Suffixes Appear Superfluous In Adverse Event Reporting." Available: https://tinyurl.com/y5sf9vz7

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Resolution WHA 46.19 calls for identification via corporate name and INN

- The 1993 Resolution WHA 46.19 on nonproprietary names for pharmaceutical substances requests WHO member states to encourage manufacturers to rely on their corporate name and the international nonproprietary name, rather than on trademarks, to promote and market multisource products introduced after patent expiration.

- In order to ensure consistent traceability, and given the need for identification in case of Adverse Drug Reports (ADRs) and the role of the MAH being responsible for pharmacovigilance, National Regulatory Authorities (NRAs) are therefore strongly encouraged to implement
  - the use of INN + MAH (i.e. linked to corporate) to identify biological products, especially in countries where INN prescribing may also apply to biologicals or an invented/"brand" name is not available or not legally enforceable, and
  - to promote consistent inclusion of the batch/lot numbers into the reports

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WHO has put on hold the INN Biological Qualifier

- The report [1] of the May 2017 WHO Expert Consultation on Improving Access to and Use of Similar Biotherapeutic Products, published in October 2017, revealed on page 4, that following the outcome arising from the meeting
  - *"No consensus was reached on whether WHO should continue with the BQ – it should be noted that WHO will not be proceeding with this at present."*
- WHO further communicated to industry that **WHO has decided to put on hold** the implementation of the International Nonproprietary Names Biological Qualifiers (INN BQ) Recommendation pendig further data collection and experience with uptake and safety of Similar Biotherapeutic Products

- IGBA is consequently no longer participating at the bi-annual Open Sessions to Stakeholders-Consultation on INNs for pharmaceutical substances, to allow the INN Expert Committee to allocate its precious time to many other important items.

[1] https://bit.ly/2gJ4L3o

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Canada supports unique identification with product‘s brand name and non-proprietary name

- On 14 Feb 2019, Health Canada announced the decision that both the brand name and non-proprietary name should be used throughout the medication use process
- Biologics that share the same non-proprietary name can be distinguished by their unique brand names

- Policy Statement on Naming of Biologic Drugs
  - Health Canada’s Canada Vigilance database shows that reporting by brand name is largely successful in achieving accurate product-level attribution of spontaneously reported adverse events for suspected biologics
  - This option avoids any potential perception that different suffixes indicate clinically meaningful differences between a biosimilar and its reference biologic drug
  - https://bit.ly/2VjYmKz

- “What We Heard Report”
  - 75% of respondents supported the use of the brand name with the non-proprietary name to distinguish among biologics
  - https://bit.ly/2EvzQR6

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