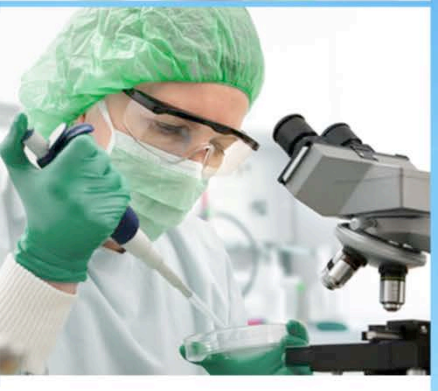

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IGBA Position on Identification of Biological, including Biosimilar Medicines

2018 Update of Facts & Figures

IGBA position: 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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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%
- Data from EudraVigilance database suggests continuous robust levels of product identification of biologicals from European clinical practice
  - an ongoing EMA study of ADR reporting from 2011-2016 revealed overall 95.5% identifiability of classes of biologicals for which biosimilars are approved [1] (=95.5% of more than 49,000 spontaneous ADR reports within the European Economic Area between 01 Jan 2011 and 30 June 2016 were unambiguously attributed to the product dispensed)

[1] A Clinician´s Guide to Biosimilars in Oncology: Understanding the Science of Extrapolation and Interchangeability – Dr. Elena Wolff-Holz

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

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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

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.

[1] Table generated from data shown and discussed at the DIA Biosimilars Conference, Bethesda, MD, October 24/25, 2017

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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 9 biosimilar products so far, all with a 4-letter suffix (status March 2018)
- No reference products have been renamed with suffixes despite stated FDA plans to do so
- Only 3 biosimilars have been launched so far, Zarxio was the first one in September 2015
- 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 - by coincidence, this percentage is similar to biosimilar brand name reporting rates from the EU
- The U.S. pharmacovigilance safety databases have not implemented systems yet to track suffixes (status March 2018)
  - Nonetheless, no reports of problems in differentiating safety reports for biosimilars from their reference products

➢ No data exists to demonstrate that added non-memorable suffixes in the U.S. will improve the U.S pharmacovigilance system

[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

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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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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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Final Recommendation: implement worldwide the WHO SBP standards and strengthen national PV systems to support patients' safety

- Correct and clear product identification is possible through existing tools
  - Consistent and mandatory use of product name (invented/"brand" name+INN or INN+MAH) combined with batch/lot numbers for all adverse event reporting
  - Support with educational efforts towards healthcare professionals and patients, given that new IT tools are increasingly available and used worldwide

- A differentiator, introduced via a suffix-based naming system, does not provide any greater assurance of product quality and cannot ensure its safety
- Instead, patient safety and public health worldwide are best supported by
  - Universal implementation of the WHO SBP standards, which ensures an adequate comparison of the candidate biosimilar to its reference product and consequently confirms product safety, and
  - The strengthening of national pharmacovigilance (PV) systems to improve healthcare stakeholder adherence to adverse event reporting guidelines.

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