Identification and traceability of biological products

Dr Peter De Veene

EU QPPV, Roche

On behalf of EBE

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Outline

- Biopharmaceuticals & Pharmacovigilance
- Traceability & Pharmacovigilance
- Legal Requirement
- Stakeholders
- Proposal for QRD template
- Other avenues to explore
- Conclusions

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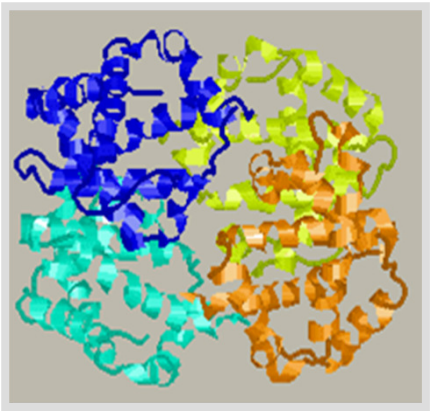
Biopharmaceuticals have specific characteristics



- A complex production process
- Limited predictability of preclinical to clinical data
- A high potential for immunogenicity
- Adverse events can often be related to an exaggerated pharmacology
- Delayed onset adverse reactions

Giezen et al. Drug Safety 2009

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‘Typical’ Safety Issues

Table I. Differences between biopharmaceuticals and small molecules, and examples of safety-related problems related to these differences[1,2,7-9]

Biopharmaceuticals vs small molecules	Examples of safety-related problems
Large complicated molecules and often mixtures of different isoforms	
Relatively unstable	Formation of aggregates can influence the immunogenic potential
Complex production and purification process/(small) changes in manufacturing process can influence safety	Pure red cell aplasia in patients treated with epoetin alfa following manufacturing changes
Manufactured in living cells	The host cell used and contamination with host cell DNA and host cell material can influence the immunogenic potential, e.g. natural interleukin (IL)-2 was reported to be less immunogenic than IL-2 produced by *Escherichia coli*
Potential for immunogenicity	Thrombocytopenia after treatment with recombinant thrombopoietin due to neutralizing antibodies blocking endogenous thrombopoietin
Limited predictability of preclinical to clinical data due to species-specific action and immunogenicity of human proteins in animals	Cytokine storm in TeGenero phase I trial Human interferon has a different pharmacological effect to mouse interferon in mice
Adverse events often related to exaggerated pharmacology	Tuberculosis with the use of the tumour necrosis factor-α inhibitor infliximab

Giezen et al. Drug Safety 2009

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Traceability & Pharmacovigilance

- Traceability
  - Product-level → batch number
  - Patient-level → good record keeping
- Identifiable product → brand name
- Automatic Substitution and INN-prescribing
  - Decision to treat should remain with the prescribing physician

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Traceability for biological products:

The need to ensure no disconnects between prescribing, dispensing and AE reporting

AE Report

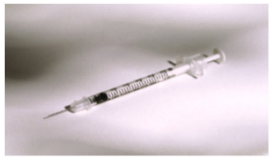
In the event patient experiences an AE, reporter knows exactly which brand the patient was dispensed

Prescription by brand

Prescription by INN

Pharmacist dispenses per physician stated brand or contacts physician to agree change

Pharmacist dispenses an available or cheapest biological with same INN



AE Report

In the event patient experiences an AE, reporter does not have immediate access to the precise brand dispensed to the patient

Issue: National practice of INN prescribing for biologics does not allow physicians rapid access to the precise brand dispensed when reporting AEs

Legal Requirements

Article 102 of the medicinal products Directive 2001/83/EU, as amended by Directive 2010/84/EU, deals with the identification of medicinal products when reporting adverse events. Article 102(e) provides clarification specifically for biological medicinal products. The provision reads as follows:

The Member States shall:

…

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to ***identify clearly any biological medicinal product prescribed****,* ***dispensed, or sold in their territory*** *which is the subject of a suspected adverse reaction report, with due regard to* ***the name of the medicinal product****, in accordance with Article 1(20), and the* ***batch number*** *[Emphasis added].*

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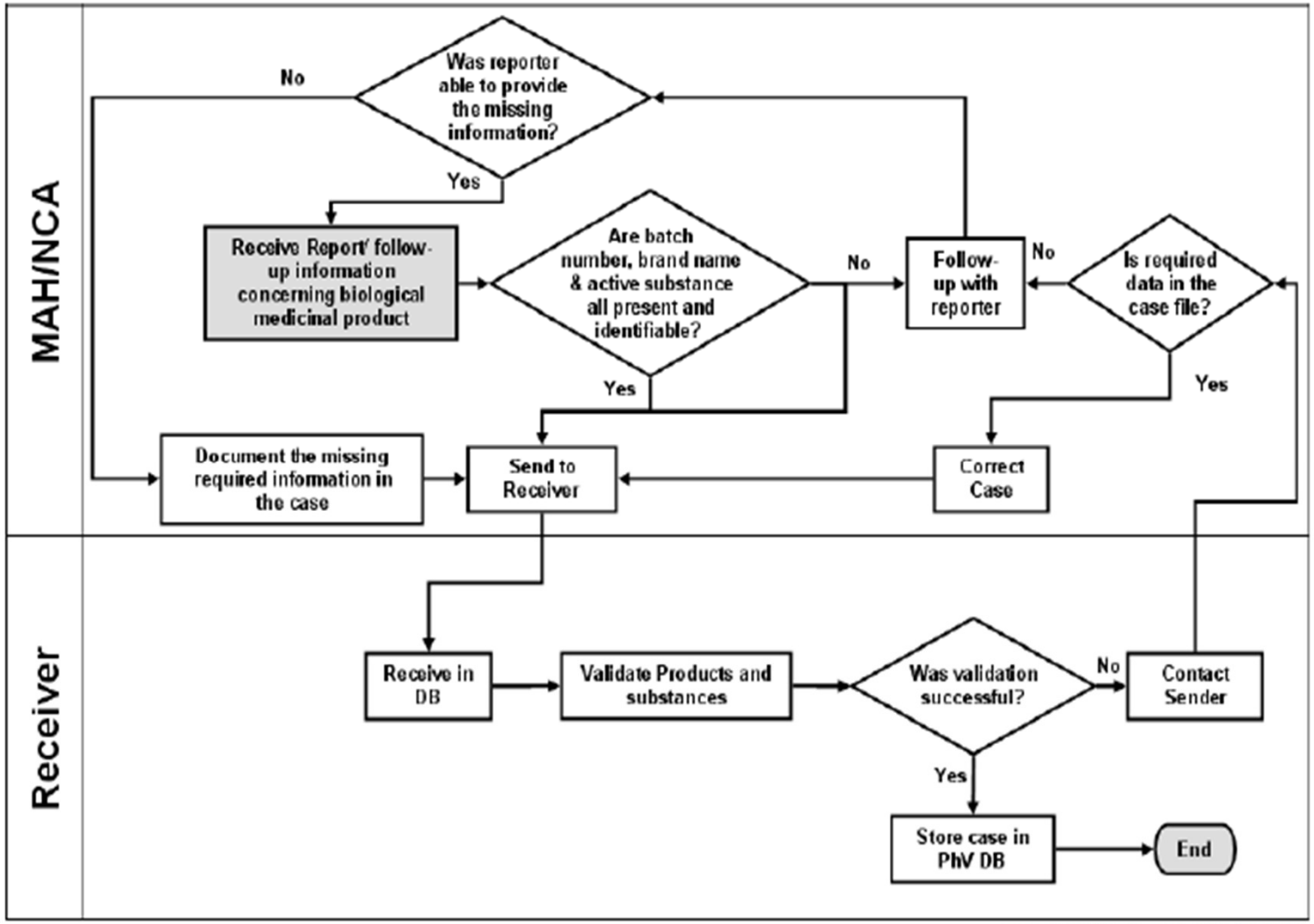
Appendix 1. Identification of biological medicinal products



Stakeholders / Communication

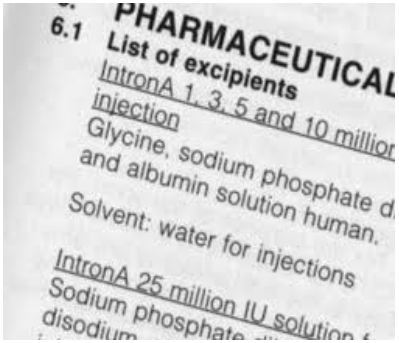
Patient

Regulators

Prescriber

MAH

QRD template proposal


6.1 PHARMACEUTICAL
List of excipients
IntronA 1, 3, 5 and 10 millior
injection
Glycine, sodium phosphate d
and albumin solution human.
Solvent: water for injections
IntronA 25 million IU solution
Sodium phosphate
disodium

- Inconsistent use of texts already included for biologics
  - Erythropoiesis-stimulating agents (ESAs)
  - Rituximab
- Suggestion to include standardised text in SmPC for all biological products (innovator products as well as biosimilars)
  - To alert physicians to record the name of the prescribed product in the patient notes
  - In order to improve traceability
  - Amended text also to be considered for inclusion in the Package Leaflet in view of patient reporting

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Other avenues to explore

- Counterfeit technology
- Expanding existing technologies
  - E.g. peel-off sticker
  - E.g. vaccines
- Web-based information
- Prescribing software

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Conclusions

- Biopharmaceuticals are complex products with specific safety issues compared to small molecules
- Identification and traceability are essential for pharmacovigilance processes
  - Reporting brand name
  - Batch number

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Recommendations

- Multifaceted approach needed involving all stakeholders
- EMA to provide guidance to NCAs to require that prescribers are made aware of the exact biologic dispensed which may be achieved by brand name prescriptions without automatic substitution

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