Pharmacovigilance of Biologics:  
Workshop summary – 20th of May 2015, Amsterdam, The Netherlands

This document gives an overview of the results of the work that has been presented and discussed at the workshop organised on the 20th of May 2015 in Amsterdam, with a focus on the outcome of discussions from the break-out sessions in the afternoon. The objective of the workshop was to present the findings from the pilot study conducted in the Netherlands, a simulation study and to discuss potential solutions and recommendation to improve practices for tracking and tracing biological medicinal products in clinical practice and thereby strengthen the accuracy of adverse drug reaction (ADR) reporting. The overall aim of the workshop was to give directions for future research (including similar work in other EU Member States) and policy-making in the area of pharmacovigilance for biologics.

Below, the outputs of the workshop are described in a summarised form, a more extensive account will be published in peer reviewed journal papers, which are in preparation at the time of writing. The program of the workshop is attached as Annex I, a list of participants is attached as Annex II.

Background to the workshop  
(Recombinant) biologics differ from small molecule medicines. In contrast to small molecule medicines, biologics have highly complex structures and are sensitive to changes in their manufacturing process (1), which could have an effect on their quality and or safety/efficacy profiles. In light of this the so-called pharmacovigilance legislation in the EU specifically calls out the need to report adverse drug reactions (ADR) for biologics by brand name and batch number in order to ensure that ADRs are accurately ascribed to the correct causative product and batch (2).

ADR data is collected by national pharmacovigilance centres and marketing authorisation holders (MAHs) at the national level and is aggregated in EudraVigilance, an EU ADR database that supports signal detection and analysis. In a recent study of the data recorded in EudraVigilance, Vermeer et al. concluded that for the majority of entries into the EudraVigilance database unique products are identifiable at the level of the brand name, especially for products where biosimilars are available (96.2%). At the same time, it was reported that only 21.1% of ADR reports for biological medicinal products found in EudraVigilance contained batch numbers (3). It is hypothesised that inaccurate or incomplete ADR reporting may decrease the chance to detect safety signals and/or incorrectly attribute safety signals to a product (4).

Preparatory work  
The Escher team has conducted a number of analyses that aim to identify gaps in the ADR reporting process that may cause poor product and batch traceability of biologics as well as to identify the impact of gaps on signal detection. The objectives of these analyses were:

1. To evaluate practices and information recording systems in hospital and community settings for tracking and tracing medicinal product information and reporting ADRs in the Netherlands, specifically with regard to brand name and batch number
2. To estimate the potential impact of misclassification of biological products during ADR reporting on safety signal detection for biologics.

Summaries of the results presented are mentioned below, more details and more extensive analyses can be found in the forthcoming peer reviewed publications.

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1 Biological medicinal products (biologics) are produced by in or derived from a biological source; a subset of the biologics is the recombinant biologics, which are produced by genetic engineering techniques. For the purpose of this project we focus on recombinant biologics (excluding vaccines), to which we refer to as ‘biologic’ in the continuation of this document regarding the work that has been done.
1. Traceability of biologics in clinical practice

Introduction
Currently, we have limited knowledge about where and how product (brand) names and batch numbers for biologics are recorded and available in clinical practice, and how this relates to brand name and batch number reporting in ADR reports.

Aim
To evaluate information recording systems and practices in the Dutch hospital and community setting for tracing biological medicinal product information and the association with brand name and batch number availability in ADR reports for biologics.

Methods
1. Hospital and community pharmacists were surveyed to assess the different information recording systems and practices for brand name and batch number recording for biologics in clinical practice.
2. To explore the association with ADR reporting quality, we performed an analysis of ADR reports for recombinant biologics in the Netherlands from 2009 to 2014 with data from the database of the Netherlands Pharmacovigilance Centre Lareb.

Results
Hospital setting - The assessment of the information recording systems and practices revealed that brand name recording in the hospital setting ranges between 60%-80%, depending on the information system, whereas batch numbers were not recorded except for biologics compounded or formulated in the hospital pharmacy.
Community setting - The brand name recording in the community pharmacy was approximately 90% whereas batch number recording was very limited.

The Netherlands Pharmacovigilance Centre Lareb received 1523 spontaneous ADR reports for recombinant biologics. For 76% of these ADR reports, a brand name was identifiable, whereas only 5% of the ADR reports contained a batch number. Brand name reporting was highest for community pharmacists (96%), while hospital pharmacists were most likely to report a batch number (36%). Hospital pharmacists have direct access to the compounding protocol, the only source where batch numbers are recorded and can be traced for biologics compounded in the hospital pharmacy, which may explain the high percentage of batch number reporting in the hospital setting, where compounding of biologics takes place more often than in other settings.

Conclusion
This study shows a positive association between brand name and batch number recording in clinical practice and the quality/completeness of ADR reports. The results of the study highlight the need to improve practices for tracing biological medicinal products in clinical practice in order to strengthen ADR reporting.

2. The effect of exposure misclassification – a simulation study

Background and objective
The availability of accurate product-specific exposure information is essential in the pharmacovigilance of biologicals, because differences in the safety profile may emerge between products containing the same active substance. In spontaneous ADR reports subjects may however be misclassified with regard to their product-specific exposure status, which could result in a delayed
detection of potential product-specific risks. The purpose of this study was to explore the effect of drug exposure misclassification on the ability to timely identify product-specific risks along signal detection in spontaneous reporting systems.

**Methods**
We evaluated the absolute effect of exposure misclassification (i.e. delay in number of cases and/or years to detection) for three test cases within a simulated data model. Furthermore, the impact of exposure misclassification was studied in general terms by varying the model parameters, and assessing the impact of misclassification in relative terms.

**Results**
We found that exposure misclassification results in the largest delay in identification of risks that have a weak association with the biological of interest, and in situations in which the biological associated with the unique risk has a large market share. By contrast, the detection of strong drug-event associations was found to be relatively robust to low levels of exposure misclassification.

**Conclusion**
Drug exposure misclassification may result in delayed detection of product-specific risks in spontaneous reporting systems. The absolute delay is however highly dependent on the characteristics of the drug-event combination, and the potential impact of exposure misclassification on public health should therefore be assessed for each drug-event combination individually.

**Conclusions from break-out sessions**
Two break-out sessions were held during the afternoon. These break-out sessions discussed current challenges in identifying products (session 1) in clinical practice and the quality of reporting (session 2), see Figure 1. The summary of the break-out session below is a reflection of the discussion, and will not necessarily be supported by individual participants.

1. **Identifying products in clinical practice**
   - Products (esp. packaging/labeling) → Clinical practice
2. **Quality of reporting and signal detection**
   - Reporting to Lareb → ADR reporting → Reporting to MAH → Safety signal detection

*Figure 1: Structure of break-out sessions.*
**Break-out 1: Traceability of biologics in clinical practice**

The results of the preparatory analyses show that it is important to increase awareness in (potential) reporters about the need to report brand name and batch number for biologics. Educational activities play a key role here. As part of this, the dialogue between different stakeholders (health care professionals, policy makers, companies etc.) needs to be strengthened. This dialogue will also enable better understanding of any hurdles that may be encountered when implementing new policies and regulations.

At the same time, roles and responsibilities need to be clarified (e.g. for pharmacists, MAHs and physicians) and those responsible for appropriate traceability need to be empowered. Without adequate technical support limited progress can be made, and any activities that aim to increase awareness will have limited impact.

To produce real change in the current system, a sense of urgency needs to be present, convincing case studies and scenarios (also from other areas) can be of value here. The technology for tracking/tracing medicinal products is available (RFID, GS-1 barcodes) but needs to be simplified to be used by health care professionals in an effective manner. It may be important to look for synergies with other initiatives that could benefit from the same technology, such as the discussion around falsified medicines, quality control (e.g. batch recalls) or aiding to general efforts to improve pharmaceutical care (e.g. by reducing medication errors due to better tracking and tracing system).

Harmonization plays an important role as well: at the public sector level by introducing EU legislations in an harmonized fashion, at the MAH level by harmonizing the practices & procedures and at the health system level by harmonizing IT systems (and allowing information exchange).

Furthermore, more data is needed to confirm the current gaps regarding the traceability of biologics (and medicinal products in general) in clinical practice. For this, an assessment in other Member States is needed.

**Break-out 2: Quality of reporting and signal detection**

One of the observations during this break-out session was that product labelling is a critical first step in the chain and one of the areas that needs to be optimised. In addition to labelling, the information recording systems need to be strengthened to be able to record the information in a quick and effective manner. However, due to the variety in IT systems that are currently in place there needs to be alignment in a feasible matter in order to facilitate a ‘closed loop’ system that allows tracking and tracing of medicinal product information throughout the entire hospital healthcare setting.

However, the IT and information delivery framework requires a clarification of the accountability and adapt the ‘ways of working’ for each stakeholder involved. For this it is important to look at the feasibility for each stakeholder with regard to other responsibilities and workload and whether the right incentives are in place. Total traceability and reporting of ADRs (100% coverage and product traceability) may not be achievable, at least not on the short term. Therefore, it is important to identify targets that sufficiently address the public health needs and the overall objectives of the EU pharmacovigilance system, while expecting realistic efforts from prescribers, pharmacists, patients, MAHs and other stakeholders.

Pharmacovigilance systems request information from doctors, patients and pharmacists that report ADRs. Often, these reporting systems operate in a ‘passive’ manner; they highlight the information that is needed, but if this information is not provided, follow-up provides only limited possibilities to retrieve the missing information. The question arises what we need to do to complete reports or retrieve information that is now missing. How can follow-up activities be performed more effectively in order to obtain the missing information needed for product traceability?
Conducting cross-European analyses and sharing best practices are needed to support learning and information exchange. European (public-private) collaborations can guide the way here, particularly in areas where the European system is fragmented, such as pharmacovigilance. Best practices or examples can also come from outside of the field of the recombinant biologics discussed here, for example, blood products and vaccines can be learning devices.

**Next steps**
The results from the workshop and the analyses presented will be incorporated into the peer-reviewed publications, which will be prepared/submitted during the summer of 2015.

**References**
Annex I - Program of the workshop

Agenda – Escher workshop - May 20, 2015
‘The pharmacovigilance of biologics - traceability and reporting’
Location: Hermitage (Amstel 51), Amsterdam

10:00  Registration

10:30  Welcome & objectives for the day  Marieke De Bruin (Utrecht University)
       Pieter Stolk (Escher/Exon Consultancy)

10:45  Availability of information in clinical practice
       & reporting (incl. brief Q&A)  Kevin Klein (Escher/Exon Consultancy)

11:15  The effect of exposure misclassification –
       a simulation study (incl. brief Q&A)  Niels Vermeer (Utrecht University)

11:45  Reflection on the results:
       Eugène van Puijenbroek (Lareb)
       Mariette Driessens (VSOP)
       Fabio Bisordi (EBE)
       Suzette Kox (EGA)

12:15  Wrap-up of morning session/set-up of afternoon  Marieke De Bruin (Utrecht University)
       Pieter Stolk (Escher/Exon Consultancy)

12:20  Lunch Break

13:00  Break-out sessions (parallel: 45 mins. x 2)
       1. Identifying products in clinical practice
       2. Quality of reporting and signal detection

14:30  Coffee Break

15:00  Plenary wrap-up  Marieke De Bruin (Utrecht University)
       Pieter Stolk (Escher/Exon Consultancy)
       - Reporting back from break-outs:
         o Implications for policy-making
         o Follow-up research questions
       - Final remarks

16:00  End of meeting
## Annex II List of participants

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<th>Name</th>
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<td>Brian</td>
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<td>ISOP/NDA</td>
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<td>Graatsma</td>
<td>Medicatieveiligheid.info</td>
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<td>Universität Basel</td>
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