1 8 December 2015
2 EMA/168402/2014 DRAFT for public consultation

3 Guideline on good pharmacovigilance practices (GVP)

4 Product- or Population-Specific Considerations II: Biological medicinal 5 products

Draft finalised by the Agency in collaboration with Member States for submission to ERMS FG	17 November 2015
Draft agreed by the European Risk Management Strategy Facilitation Group (ERMS FG)	24 November 2015
Draft adopted by Executive Director	8 December 2015
Start of public consultation	15 December 2015
End of consultation (deadline for comments)	29 February 2016
Anticipated date for coming into effect after finalisation	Q2 2016

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P.II.A. Introduction

A biological medicinal product (hereon referred to as 'biological') is a medicinal product that contains an active substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physio-chemical-biological testing, together with the production process and its control [Directive 2001/83/EC, Annex 1, Part I, Section 3.2.1.1(b)].

Biologicals encompass a very wide and diverse array of medicines. These include medicinal substances derived from blood and plasma, biotechnology-derived medicines (e.g. using recombinant DNA technology), all types of prophylactic vaccines and advanced therapy medicinal products (ATMPs). This GVP Module does not apply to vaccines and ATMPs as separate specific guidance already exists for these products (see GVP Module P.I and the Guideline on Safety and Efficacy Follow-up - Risk Management of Advanced Therapy Medicinal Products[1]).

Unless specified otherwise in particular sections, this Module applies to reference biological medicinal products as well as 'similar biological products' (hereafter referred to as 'biosimilars') and products which contain the same or closely related active substance (based on the international non-proprietary name (INN)) as (an)other authorised medicine(s) but not authorised as biosimilar (e.g. different interferon a/b inhibitors, different normal human immunoglobulins). These products are herafter referred to as 'related biological medicinal products'.

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA, and which has shown similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise (see Guideline on Similar Biological Medicinal Products[2]).

The legal requirements for pharmacovigilance and the Good Pharmacovigilance Practices (GVP) apply to biologicals just as they do for other medicines, and the guidance of this Module does not replace any of these. However, as outlined below, biologicals are associated with several specific challenges in pharmacovigilance. This Product-Specific Considerations Module P.II is therefore intended to be read and followed alongside the other GVP Modules when developing and implementing pharmacovigilance for biologicals to ensure these challenges are addressed. P.II.A describes some of the specific issues and challenges and P.II.B. provides guidance on addressing these in the context of the main pharmacovigilance processes described in GVP Modules. P.II.C. provides guidance related to operation of the EU network.

Although separate guidance exists on donor traceability of medicinal substances derived from blood and plasma (see Guideline on Plasma-derived Medicinal Product[3]), the general principles of pharmacovigilance and patient traceability in this Module also apply to such products.

Relevant guidelines to be considered include the Guideline On Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins, the Guideline on Comparability of Biotechnology-derived Medicinal Products After a Change in the Manufacturing Process, the Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues, the Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues and the Guideline on process validation for the

[1] See http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf
[2] See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
[3] See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500109627.pdf

manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission[4]. Guidelines with pharmacovigilance requirements existing for specific biosimilars should also be considered.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note[5] and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

References to the legislation are provided as follows: Directive 2001/83/EC as amended is referenced as DIR, Regulation (EC) No 726/2004 as amended as REG and the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC as IR.

As regards the use of the term "competent authority" in GVP, in particular in Section B, the term is to be understood in its generic meaning of an authority regulating medicinal products and/or a national authority appointed for being in charge of all or individual pharmacovigilance processes. For the purpose of applying GVP in the EU, the term "competent authority", used anywhere in GVP, covers the competent authorities in Member States and the Agency. The term "organisation" in GVP covers marketing authorisation holders, competent authorities of Member States and the Agency.

P.II.A.1. Pharmacovigilance aspects specific to biologicals

Unlike chemically synthesised medicines which can usually be easily characterised and reproduced across different manufacturers, biological active substances are complex molecules produced usually using complex manufacturing processes with many upstream/downstream steps that are specific to a given manufacturer and shape the overall safety, quality and efficacy profile. The manufacturing process (including choice of cell line, raw/starting materials, fermentation and purification process, final formulation) is as much a determinant of the product's quality as the active substance, and minor changes in any manufacturing step can affect the product quality, and subsequently its safety and efficacy. Advances in biotechnology and analytical sciences will continue to allow greater characterisation and control of biologicals, but it is this fundamental complexity that creates the specific challenges for biologicals in pharmacovigilance.

P.II.A.1.1. Immunogenicity

As with any medicinal product, the safety profile of a biological is determined partly by the direct or indirect pharmacological, including immunogenic, properties of the active substance (e.g. exaggerated immunomodulation/immunosuppression), as well as of the excipients and/or process-related impurities (e.g. host cell proteins) due to host/disease-related susceptibility (e.g. drug-induced allergic reactions, auto-immunity, inflammatory events). For biologicals and non-biologicals alike, the basic principles of benefit-risk assessment in other GVP Modules apply to these potential or identified risks. However, due to their much more complex nature, biologicals pose a greater potential risk of immunogenicity compared to non-biologicals and require specific consideration. This is discussed in detail in the Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins[6].

For the purpose of this Module, 'immunogenicity' refers to an unwanted immune response that is considered potentially clinically relevant, may require product-specific pharmacovigilance and risk management activities and may be unrelated to identified risks associated to the active substance, product class or common excipients.

[4] Available on the EMA website: http://www.ema.europa.eu
[5] See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/08/WC500191777.pdf
[6] See http://www.ema.europa.eu

In most cases, immunogenicity to a biological will be without clinical significance, such as a transient appearance of antibodies, and will not impact on the risk-benefit balance of the product. However, on rare occasions, immunogenicity could result in serious and life-threatening reactions.

Sources of immunogenicity for biologicals are multi-factorial and involve one or more of product-related factors (e.g. choice of cell line, post-translational changes and alterations to the 3D structure during downstream processing, impurities, choice of product containers), treatment-related factors (e.g. route of administration, dosing frequency) and patient/disease-related factors (e.g. genetic background, concomitant medications, and nature of the underlying disease and immune status).

The clinical consequences of immunogenicity may include partial or complete loss of efficacy of the product due to induction of neutralising antibodies, altered pharmacokinetics due to antibody binding, general immune effects such as anaphylaxis, formation of immune complexes and potential induction of cross-reactivity with endogenous proteins or other auto-antibodies.

Specific evaluation of immunogenicity is required during product development and prior to authorisation of biotechnological medicines (see the Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins [7]). However, non-clinical models and analytical methods/bioassays cannot always reliably predict immunogenicity in humans. Furthermore, the limited sample size of pre-authorisation studies and/or rarity of the disease to be treated may not allow rare consequences of immunogenicity to be evaluated prior to authorisation. Uncertainty in relation to immunogenicity should be reflected in the risk management plan (RMP) (see P.II.B.1.) and requires specific activities/surveillance in the post-authorisation phase if necessary.

For biosimilars in particular, initial marketing authorisation is based on demonstrated and accepted similarity of quality, safety and efficacy, in accordance with the comprehensive comparability exercise. This exercise is designed to exclude any relevant differences between the biosimilar and the reference medicinal product. However, the Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues[8] notes that “Data from pre-authorisation clinical studies are usually insufficient to identify rare adverse effects. Therefore, clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment”.

Following on from characterisation of immunogenicity at the time of initial marketing authorisation, the next challenge relevant to any biological relates to changes to manufacturing or quality, and the fact that immunogenicity, and thereby an altered safety and efficacy profile of a product, can potentially be introduced at any time post-authorisation.

P.II.A.1.2. Manufacturing variability

Marketing authorisation holders of medicinal products make frequent changes to the manufacturing process of their products post-authorisation. This happens for many reasons including for example changes in source materials, in facilities or in regulatory requirements.

Manufacturing changes may be more complex for biologicals. They need to be supported by a comparability exercise and submitted by the marketing authorisation holder as a variation to the marketing authorisation to determine that the pre-and post-change product is comparable, to the extent that quality, safety, and efficacy is not adversely affected. In accordance with the Guideline On Comparability Of Biotechnology-derived Medicinal Products After a Change in the Manufacturing Process[9], demonstration of comparability is a sequential process, beginning with quality studies. If a

[7] See http://www.ema.europa.eu
[8] See http://www.ema.europa.eu
[9] See http://www.ema.europa.eu

marketing authorisation holder can provide evidence of comparability through physico-chemical/analytical and biological assays, then non-clinical or clinical studies with the post-change product are not warranted. In other cases, the process change may require supportive non-clinical and/or clinical data and specific pharmacovigilance requirements. Recital (17) of Regulation (EU) No 1235/2010 states that "Risk management plans are normally required for new active substances, biosimilars, medicinal products for paediatric use and for medicinal products for human use involving a significant change in the marketing authorisation, including a new manufacturing process of a biotechnologically-derived medicinal product". The Guideline On Immunogenicity Assessment Of Biotechnology-derived Therapeutic Proteins[10] also refers to the need to consider risk management planning if changes in immunogenicity (see P.II.A.1.1.) are possible. Judgements on what constitutes a 'significant' change in the manufacturing process can only be made on a case-by-case basis, based on the comparability exercise.

Most manufacturing changes do result in a comparable product, and the need, extent and nature of non-clinical and clinical comparability studies will be determined on a case-by-case basis. However, it will not be possible to predict immunogenicity based on physico-chemical/analytical and biological assays alone, and supportive clinical studies (if requested) will not always be able to detect rare consequences of any altered immunogenicity before approval of a manufacturing change. Biologicals are therefore potentially subject to this dynamic quality profile, with the potential for serious new risks (safety or efficacy) to emerge at any time point in the product life-cycle due to changes in product quality or characteristics (which may also be related to product handling and patient characteristics).

These potential changes are relevant not only within a product (e.g. 'drift' in quality specifications over time), but also across products with the same INN. In the long-term post-authorisation period, the originator, biosimilar(s) and related biological product(s) may potentially exhibit different safety profiles as these products evolve through their life-cycle. Whether or not an updated risk management plan (RMP) (see P.II.B.1.) was implemented to support approval of a given manufacturing change, it underlines the importance for biologicals of continuous, life-cycle pharmacovigilance and risk management to rapidly detect any important changes in product safety and efficacy over time.

P.II.A.1.3. Stability and cold chain

Strict process controls are in place for biologicals to ensure that manufacturing processes and standards remain within the authorised specification. Beyond the point of manufacture and release, overall product stability is maintained by adherence to appropriate storage/handling conditions, cold chain and good distribution practices (see the Guidelines on Good Distribution Practice of Medicinal Products for Human Use[11]).

More so than for non-biologicals, non-adherence to these processes and standards can affect the stability and quality of biologicals, which in turn may introduce immunogenicity (see P.II.A.1.1.) or contamination. Though very rare, particularly for a product that has already been released, such defects and deviations would usually affect isolated batches.

Life-cycle pharmacovigilance at the levels of products and batches is therefore an important issue for biologicals (see P.II.A.1.4.).

P.II.A.1.4. Product traceability

As a consequence of manufacturing variability over time in the post-authorisation phase within and across products with similar active substances, a key requirement for pharmacovigilance of biologicals

[10] See http://www.ema.europa.eu
[11] See http://ec.europa.eu

is the need to ensure continuous product and batch traceability in clinical use. This is especially important for biologicals compared to chemically-synthesised medicines due to a greater inherent variability in product characteristics.

Whether originator, biosimilar or related biological product, it is essential that different products with the same INN can be readily distinguishable in order that newly emerging and product-specific safety concerns and immunogenicity (see P.II.A.1.1.) are rapidly detected and evaluated throughout a product life-cycle, and that supply can be traced to locations/patients if necessary. As any given product usually retains the same product name following a significant change to manufacturing process, batch traceability is an important aspect to be considered in any associated updates to risk management plans (see P.II.B.1.).

As product name and batch information is included in product packaging, this information is available to be recorded and reported at all levels in the supply chain from manufacturer release to prescription, dispensing and patient administration. Biologicals constitute a very diverse array of products for a wide range of therapeutic areas and the clinical settings for prescription, dispensing, supply and administration are equally diverse. Traceability needs therefore to be fully integrated in different healthcare settings and infrastructure that may vary across products and between countries, such as the infrastructure for electronic data recording and record linkage. Most products will be supplied in a hospital setting and, if record linkage does not exist, other methods need to be used to collect exposure information, such as routine bar code scanning at all points in the supply chain. National health authorities should also work towards better integration and automation of prescription information.

It should be noted that prescribing practice and product interchangeability, and particularly switching and substitution between biologicals, are beyond the scope of this Module as they fall under the scope of the individual Member States. Best clinical practice dictates that the product name and batch number of an administered biological should always be recorded by healthcare professionals (and ideally provided to the patient) (see P.II.B.1.4.). This is particularly important in cases when different products with the same INN are either intentionally switched or automatically substituted without the prescriber's consent.

P.II.B. Structures and processes

P.II.B.1. Risk management system

All marketing authorisation applications submitted in the EU after 2 July 2012 (through the centralised marketing authorisation procedure) or 21 July 2012 (through the mutual recognition marketing authorisation procedure or the decentralised marketing authorisation procedure) should contain a risk management plan (RMP) that must be approved by the competent authorities prior to the granting of the marketing authorisation. The submission of a risk management plan, or an update thereof, is also normally required for medicinal products for which the initial application was submitted before the above dates if a significant change in the marketing authorisation, including a new manufacturing process of a biotechnology-derived medicinal product [Recital (17) of Regulation (EU) No 1235/2010] (see GVP Module V).

As a general principle, any post-authorisation updates to the RMP for a reference product/originator should be similarly applied to the relevant biosimilars and related biological products, and vice-versa, unless justified, e.g. where available information suggests that the clinical concern prompting the update was product-specific (i.e. not related to the active substance or other common excipients). All parts of a RMP are required for a biosimilar, with the exception of RMP part II, module SI "Epidemiology of the target population".

P.II.B.1.1. Content of the risk management plan

P.II.B.1.1.1. RMP part I "Product overview"

The origin of an active substance of a biological should be included as important information about its composition (see GVP Module V, with biological as a stated example).

P.II.B.1.1.2. RMP part II "Safety specification"

P.II.B.1.1.2.1. RMP module SVII "Identified and potential risks" and RMP module SVIII "Summary of the safety concerns"

In accordance with the requirements of GVP Module V, the safety specification should include important identified risks, important potential risks and missing information.

The potential for immunogenicity and associated clinical consequences (see P.II.A.1.1.) should be fully evaluated as part of the initial marketing authorisation application (or variation) and discussed in the safety specification with appropriate conclusions drawn on whether or not a product may pose such a risk in the post-authorisation phase. Immunogenicity may occur during the life-cycle of a biological but is not in itself a specific safety concern. If no particular concern or uncertainty arises from the evaluation of the dossier, inclusion of immunogenicity as a potential risk is therefore not required. Immunogenicity may otherwise be included in the safety specification if there is a rationale to do so, based on information assessed as part of the initial application/comparability exercise, an a priori concern or residual uncertainty. In such instances, this should be defined as much as possible (including any specific potential clinical risks with case definitions) so that specific pharmacovigilance measures to address the uncertainty can be developed (see P.II.B.1.1.3.). The Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins[12] as well as any relevant available product/class-specific guidance on immunogenicity evaluation (e.g. the Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use[13]) should be used in order to determine the most appropriate strategy to further evaluate the potential risk.

In case of a significant change to the manufacturing process requiring an amendment of the RMP (see P.II.B.1.2.), potential immunogenicity and clinical consequences should be discussed in the safety specification. If no specific potential clinical concern has been identified (other than the significant manufacturing change with uncertain clinical consequence), the missing information listed in the updated safety specification may make reference to "immunogenicity following a significant change to the manufacturing process".

For biosimilars and related biological products, the summary of safety concerns should, as a minimum, be the same as the reference/originator product unless otherwise justified. Such justification may include the situations where a particular risk associated with the originator was known to be associated with a component/factor/manufacturing process (other than the active substance) that is not associated with the biosimilar or related biological product, or where elements of the safety specification/summary of concerns are specific to a particular indication that is absent in some products (however, potential for off-label use would need to be considered).

Risks identified from differences found within the comparability exercise with regard to seriousness and frequency of adverse reactions for the biosimilar as compared to the reference product should be reflected and discussed in the RMP and the need for additional pharmacovigilance/ risk minimisation measures should be assessed.

[12] See http://www.ema.europa.eu
[13] See http://www.ema.europa.eu

Any other proposed differences in the safety specification of a biosimilar compared to the reference product should be duly justified based on the outcome of the comprehensive comparability exercise.

P.II.B.1.1.2.2. RMP module SVI "Additional EU requirements for the safety specification"

For all biologicals, the potential for infections caused by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process should be presented in relation to the potential for transmission of infectious agents.

P.II.B.1.1.3. RMP part III "Pharmacovigilance plan"

P.II.B.1.1.3.1. RMP part III section "Routine pharmacovigilance activities".

The need and plans for continuous life-cycle signal detection and pharmacovigilance specific to the product and sensitive to batch-specific safety signals, particularly following a significant change to the manufacturing process, should be discussed. In this context, the pharmacovigilance plan should include a discussion around clinical settings of product use and how this may impact on routine product name and batch recording and reporting (e.g. whether used in primary or tertiary care, if non-prescribed use) and what additional activities or risk minimisation measures may be required to support product traceability (e.g. provision of 'sticky' labels, bar coding).

In this section, the MAA/MAH should therefore discuss:

- the clinical settings of product use and how this may impact on product name/batch recording and reporting;
- measures that will be introduced to routinely follow-up on case reports to obtain information on product name and batch number(s) (see also GVP Module VI App 1);
- signal detection activities performed to identify batch-specific safety issues;
- any adverse events of special interests (AESIs), with definitions, identified as important potential risks for which specific safety surveillance will be put in place (see also GVP Module P.I and P.II.B.1.1.3.2.);
- any clinical consequences of a potential emerging immunogenicity (as a theoretical risk) to be monitored throughout the product life-cycle, unless a potential for immunogenicity (see P.II.A.1.1.) and its clinical consequences are listed in the safety specification as a specific concern.

P.II.B.1.1.3.2. RMP part III section "Additional pharmacovigilance activities"

In this section, the MAA/MAH should discuss:

- any additional measures introduced in collaboration with the national competent authorities to support traceability of the product (e.g. provision of "sticky" labels, bar coding, etc.) and estimate the number of doses delivered or administered in each country for each batch;
- activities performed to measure background rates for AESIs in the age group targeted by the product;
- activities performed to continuously monitor ADR reporting frequencies/rates for AESIs based on available data on exposure and comparing such rates to relevant defined background rates (using methods such as observed to expected analyses) (see also GVP Module P.I.);
- use of existing patient registries or other data sources (or establishment of a new registry if existing data sources are inadequate) (see GVP Module VIII App 1);

- any other post-marketing activity, e.g. post-authorisation safety studies, whether interventional or non-interventional;
- for a biosimilar, any specific safety monitoring imposed to the reference medicinal product or product class and its relevance for the concerned product.

For significant changes to the manufacturing process that require an RMP update (see P.II.B.1.2.), given that the product name usually does not change, there should be a particular emphasis on batch-specific pharmacovigilance for a relevant time period after the manufacturing change.

Immunogenicity

If the potential for immunogenicity is included in the safety specification as a specific concern (see P.II.B.1.1.2.), relevant strategies for the evaluation of immunogenicity and associated clinical consequences in the post-authorisation setting should be proposed as an additional pharmacovigilance activity. Where applicable, the principles for immunogenicity evaluation should follow the Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins[14] as well as any relevant available product/class-specific guidance on immunogenicity evaluation (e.g. the Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use[15]).

Depending on the nature of any potential immunogenicity and the data that generated the concern, the plan may include bio-analytical methods (e.g. in vitro assays, serology studies), non-clinical studies, interventional clinical studies or observational/epidemiological approaches. Any analytical and clinical endpoints relevant to the potential risk, including those related to safety and efficacy (e.g. in order to evaluate potential effects of neutralising antibodies), should be clearly defined to increase their sensitivity to evaluate the risk in passive surveillance (e.g. via targeted follow up) and/or additional pharmacovigilance/epidemiological studies.

For these reasons, determination of the optimal strategy for evaluation of immunogenicity in the RMP should be a multidisciplinary approach, with input from experts in quality, non-clinical, clinical and pharmacovigilance.

If a new clinical risk is identified that may have an immunogenic aetiology, it should be fully explored in any subsequent risk evaluation. Whether the risk is specific to a specific product or batch and the potential root cause should be assessed in order to evaluate the ability for risk minimisation or elimination (e.g. improved assays, manufacturing steps).

Post-authorisation safety studies

Use of existing registries or establishment of new registries collecting observational data for new biologicals should be considered where relevant to evaluate any specific areas of concern. A comparator or non-exposed group should be preferably included in the registry. Joint disease registries should be encouraged.

Biosimilars and related biological products

Any specific safety monitoring imposed on the reference medicinal product or product class should be adequately addressed in the pharmacovigilance plan unless otherwise justified (e.g. if the safety concern was specific to the originator product and not included in the safety specification of the biosimilar or related biological product). Where applicable and feasible, competent authorities should encourage MAHs of biosimilars and related biological products to participate in any pharmacoepidemiological studies already in place for the reference product/originator, unless otherwise justified (see P.II.B.1.1.2.).

[14] See http://www.ema.europa.eu
[15] See http://www.ema.europa.eu

P.II.B.1.1.4. RMP part V "Risk minimisation measures"

Evaluation of any new clinical risks associated with a biological product should include a root cause analysis in order to evaluate the ability for risk minimisation or elimination via analytical studies/bioassays (e.g. improved assays, manufacturing steps).

As a general principle in order to improve traceability of biological medicines, all Summary of Product Characteristics (SmPC) for biologicals (also with relevant appropriate wording in the package leaflet (PL)) should include a statement strongly recommending that the name and batch number of the administered product should be clearly recorded in the patient file. Related wording should also be included in relevant educational material, direct healthcare professional communication (see P.II.B.6.) and product promotional material as applicable. Use of other tools such as sticky/tear-off labels in the product packaging should also be considered to facilitate accurate recording in patient files and provision of information to patients. Use of available bar code-scanning technology and infrastructure should also be encouraged where appropriate.

Risk minimisation activities in place for the reference medicinal product/originator should, in principle, be included in the RMP of the biosimilars and related biological products, and vice-versa. Any deviation from this (e.g. when the risk minimisation is linked specifically to the reference product) should be justified.

P.II.B.1.2. Updates to RMP due to manufacturing changes

P.II.B.1.2.1. Potential impact of a manufacturing change

If the comparability evaluation identifies a potential impact of the manufacturing change in terms of clinical relevance, the change requires submission of an update to the RMP, unless otherwise justified. This justification would need to be made on a case-by-case basis.

Even minor changes to a manufacturing process can potentially have unpredicted significant clinical effects. In cases when the comparability exercise or evaluation has not necessarily identified a potential impact of clinical relevance, marketing authorisation holders and/or competent authorities submission of an updated RMP with the variation to the manufacturing process may still be appropriate based on the risk analysis or previous experience.

It is not possible to give specific guidance on what may constitute a clinically relevant impact of a manufacturing change in every situation, and judgements have to be made based on the findings of the comparability exercise or other quality or clinical evaluation that supports the variation to the process, as well as any other relevant precedents or experience.

P.II.B.1.2.2. Risk analysis

To support this process and ensure that Recital (17) of Regulation (EU) No 1235/2010 is adhered to, all applications for a variation to the manufacturing process of a biological should routinely include a risk analysis from the marketing authorisation holder on the potential significance and the need, or not, for an update to the RMP. This process is in line with the concepts envisaged in ICH-Q5E (Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process) and ICH-Q10 (Pharmaceutical Quality System)[16].

The risk analysis from the marketing authorisation holder may be a short statement with appropriate justifications or a more complex evidence-based analysis if required by the nature of the change (particularly if there is precedent for the type of change resulting in a clinically significant impact).

[16] See http://www.ema.europa.eu

If the marketing authorisation holder has already decided that an RMP update is required, a risk analysis is not necessary and the RMP should be submitted with the quality variation. In other cases, the risk analysis should be submitted with the quality variation.

P.II.B.1.2.3. Update of the RMP

If the MAH considers that an update of the RMP is required, it should be provided with the application warranting such update. Otherwise if the competent authority concludes on the need for an RMP update, it should provide to the marketing authorisation holder recommendations on the nature of the changes expected in the RMP. A RMP update should be submitted as soon as possible to allow for its approval in the context of the variation to the manufacturing change.

Updates to the RMP should address the safety specification, pharmacovigilance plan and risk minimisation measures. If the product name has not changed, particular attention should be paid to ensuring batch-specific signal detection and surveillance in order that the pre and post-change products can be easily distinguished during a relevant time period after the manufacturing change.

Following an update to the RMP, subsequent PSURs (see P.II.B.3.) should specifically evaluate reports and any other information that might indicate a new clinical risk related to a process change. This evaluation should relate to the specific concern included in any updated safety specification of the RMP based on the manufacturing change. The cycle of submission of the PSURs may also be amended (and re-instated) accordingly in line with the updated RMP.

P.II.B.2. Management and reporting of adverse reactions

The requirements for the management and reporting of suspected adverse reactions outlined in GVP Module VI apply equally to biologicals and non-biologicals. In addition, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, competent authorities shall ensure that all appropriate measures are taken to identify clearly any biological 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 (see GVP Annex I) and the batch number [DIR Art 102(e)]. When reporting suspected adverse reactions, competent authorities and marketing authorisation holders shall provide all available information on each individual case (see GVP Module VI), including the product name and batch number(s) [IR Art 28(3)h)]. For this purpose, Member States and marketing authorisation holders should therefore encourage health care professionals to provide patients/carers with information on the product name and batch number(s) of any biological administered, regardless of the point of prescription/supply/administration and technical infrastructure that may exist. Competent authorities and marketing authorisation holders should also encourage reporters to record information on product names and batch numbers. A follow-up procedure shall be put in place to obtain the batch number where it is not indicated in the initial report. The business process map included in GVP Module VI App 1 should be followed.

If the RMP of a biological specifies certain activities to be performed to collect information on defined clinical endpoints (e.g. immunogenicity endpoints), specific laboratory/assay data, case definitions (see P.II.B.1.3.) and questionnaires may be developed and referred to in the RMP for the follow-up of targeted adverse reactions, in addition to the capture of product name and batch information.

Where marketing authorisation holders and competent authorities consider utilising their websites to facilitate the collection of reports of suspected adverse reactions by providing reporting forms or appropriate contact details for direct communication (see GVP Module VI), any such activities should

be used to communicate, promote and facilitate the capture of product names and batch information in reports of adverse reactions.

P.II.B.3. Periodic safety update report

The requirements for signal management in GVP Module VII apply equally to biologicals and non-biologicals (see P.II.C.1.2. for the assessment of PSURs for biosimilars).

P.II.B.3.1. PSUR section "Estimated exposure and use patterns"

To support the processes for signal management (see P.II.B.4.), marketing authorisation holders should make every effort to obtain data on actual usage of the product (i.e. rather than aggregated sales data) from available electronic health records and other 'real-world' data sources.

In addition, marketing authorisation holders should make every effort to include batch numbers/codes of delivered/sold batches, the sizes of them and to which regions/countries the respective batches have been delivered during the PSUR-period. This information will support analysis of batch numbers provided/included in individual reports more meaningful, and particularly the evaluation of data before and after a significant change to the manufacturing process.

P.II.B.3.2. PSUR section "Overview of signals: new, ongoing, or closed" and "Signal and risk evaluation"

The guidance in P.II.B.4. should be applied to the signal evaluation process within PSURs, i.e. case-by-case judgements are required on whether or not the signal applies to a single product or to all products with the same active substance. However, on a precautionary basis, if there is inadequate evidence or suspicion of a product-specific aetiology, recommendations and regulatory actions resulting from a signal assessment for a biosimilar or related biological medicinal product should be applied to the reference product/originator, and vice versa.

In reference to P.II.B.1.5., and in accordance with the Guideline on Comparability of Biotechnology-derived Medicinal Products after a Change in the Manufacturing Process[17], following a significant change to the manufacturing process (which will normally require submission of an updated RMP), PSURs should specifically evaluate reports and any other information that might indicate a new clinical risk related to a process change. The required data referred to above on batch-specific exposure patterns will support such evaluation. This should be presented in the context of the specific concern that is included in any updated safety specification of the RMP on account of the manufacturing change.

Following a significant change to the manufacturing process, the cycle of submission of the PSURs may also be amended (and re-instated) accordingly in line with the updated RMP (providing that the merits of this outweigh the requirement for a harmonised cycle across similar/related products).

P.II.B.4. Signal management

The requirements for signal management in GVP Module IX apply equally to biologicals and non-biologicals. As with all medicinal products, biologicals require continuous pharmacovigilance in order to detect and evaluate potential new clinical risks (safety or efficacy) that may emerge during a product life-cycle. However, this is especially important for biologicals for the reasons described in P.II.A.1. and particularly due to the inherent variability in manufacturing process that may potentially alter the immunogenicity of a product and induce clinical consequences.

[17] See http://www.ema.europa.eu

Signal detection for biologicals should therefore be specific to the product, as well as the active substance. All steps of signal management should be performed at the level of the product name, as well as the active substance and, if feasible, at the level of the batch.

Processes should be particularly sensitive to detect any acute and serious new risks that may emerge following a change in the manufacturing process or quality of a biological, any other potential changes or trends in its safety profile over time or any differences between originator products and biosimilars or related biological products and between batches of the same product (this is particularly important following a significant change to the manufacturing process given that the product name usually does not change).

Post-authorisation exposure information is needed for signal management for biologicals but biologicals are often prescribed and/or dispensed in the hospital setting and the required exposure information may not be available in population-based databases. Marketing authorisation holders should make every effort to obtain data on actual usage specific to a product (see P.II.B.3.) and explore all methods and data sources to obtain reliable and updated information. Denominator data and data of suspected adverse reaction (see GVP Module IX) should be analysed to support continuous signal detection and particularly detection of any apparent changes in suspected adverse reaction reporting rates or trends that could indicate new signals (particularly following manufacturing changes). Some active substances/medicinal products may also be subject to an increased frequency of data monitoring and a significant change in the manufacturing process of a biological may, on a case-by-case basis, justify specific signal detection activities (see GVP Module IX). Any such requirements should be specified in the risk management plan (see P.II.B.1.3. and P.II.B.1.5.). Continuous disproportionality analysis and 'observed vs expected' methods (see GVP Module P.I, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology [18] and the Guideline on the Use of Statistical Signal Detection Methods[19]) should also be consulted as needed.

Any batch-specific signals should be evaluated in the context of batch-specific exposure data, including numbers/codes of delivered/sold batches, their sizes and the regions/countries where the respective batches have been delivered. Implementation of strengthened processes for routine pharmacovigilance will facilitate earlier detection of new risks and changes in product safety/quality over time.

For new signals, case-by-case judgements are required on whether or not the signal may apply to the concerned product or to all products with the same active substance. However, on a precautionary basis, inadequate evidence on the specificity of a signal detected for a biosimilar or related biological may justify application of a regulatory action to the reference product/originator, and vice versa. Any new clinical risk suspected to have an immunogenic aetiology should be fully investigated to determine whether the risk is specific to a product name or batch, and evaluate its potential root cause in order to determine the potential for risk minimisation or elimination (e.g. improved assays, manufacturing steps).

P.II.B.5. Additional monitoring

According to REG Art. 23(1)(b) additional monitoring applies to all biologicals authorised after 1 January 2011 (see GVP Module X).

P.II.B.6. Safety communication

GVP Modules XV and XII provide principles and guidance on safety communication. The current guidance addresses specific aspects of communications for biologicals due to their complex

[18] See http://www.encepp.eu.
[19] See http://www.ema.europa.eu

manufacturing processes and compositions as well as to the complex effects they have on the human body including possible adverse reactions caused by immunogenicity (see P.II.A.1.).

Communicating about risks of biologicals poses specific challenges for presenting scientifically, technically and medically complex issues in a language understandable to patients and the general public, and also to healthcare professionals of various specialities. Some technical terms and concepts require careful explanation in order to ensure their proper understanding and avoid social risk amplification[20] due to e.g. biotechnological methods, mainly recombinant DNA technology, which are not commonly known by non-specialists and which may be perceived by some individuals or populations as not natural and negatively interfering with nature, the human body or genes. Social risk amplification may also occur with other technologies used in biologicals like nanotechnology.[21] Poor understanding of biologicals by patients and healthcare professionals as regards manufacturing, mode of action, benefits and possible risks may lead to uncomfortable feelings in patients, depriving them from therapeutic choice, non-adherence to prescribed therapy or inadequate compliance to risk minimisation measures. Hence providing information on the manufacturing process and its variability, the active substance/mode of action as well as the excipients and possible residues should be considered. Due to the complexity of biologicals as well as the target diseases, users may have questions about interactions with other concomitant medication. Specific concerns may also be expressed regarding potential adverse effects after long-term use, with delayed onset, on the reproductive system or in the off-spring. Immunogenicity is a specific source of concerns for biologicals, resulting in information needs to be fulfilled consistently for patients with allergies, autoimmune or inflammatory diseases or immune-compromised conditions. Issues around previous exposure to the same or cross-immunogenic products may also have to be addressed in communication documents. As regards blood- and plasma-derived products, patients may be concerned over transmission of infectious agents. For biosimilars, consultations with patients and healthcare professionals have shown information needs relating to quality, safety, efficacy, extrapolation, comparability and interchangeability. The EMA Questions and Answers on Biosimilar Medicines[22], drawn up in consultation with patient and healthcare professional representatives, and the European Commission's Consensus Information Document "What you need to know about biosimilar medicinal products"[23] may be used as a source for explanations when drafting product-specific communication documents.

Any common concerns and information needs of patients and healthcare professionals which become known before or during an assessment process, should be addressed in the assessment, so that early feedback to the public can be provided.

Building confidence of users in biologicals requires not only communication on product-specific aspects, but also about the mechanisms in place for safety surveillance, and reference in communication documents to the relevant risk management plan summary (see GVP Module V). If applicable, comparability data may be provided. Honest information over areas of scientific uncertainty may be required for building confidence.

Encouraging reporting of suspected adverse reactions requires some specific information for biologicals. It should be communicated to patients and healthcare professionals that adverse reactions may arise even if a medicinal product has previously been well tolerated, due to e.g. manufacturing variability or changes or long-term/delayed onset effects, and that this awareness makes reporting of

[20] The concept of social risk amplification describes changes in risk perceptions at various stages of dissemination of information, e.g. through scientific debates or discussion in the general media.
[21] See EMA "Nanotechnology" webpage at: http://www.ema.europa.eu
[22] See http://www.ema.europa.eu
[23] See http://www.ec.europa.eu

suspected adverse reactions occurring even after long-term use or with not yet known/expected features more important.

With a view to adverse reaction reporting and effective risk management, traceability is a major objective in managing the appropriate use and pharmacovigilance of biologicals (see P.II.A.1.4.) and hence constitutes a specific communication objective for biologicals vis-à-vis patients and healthcare professionals.

Other specific safety communication objectives in relation to biologicals may aim at avoiding errors in storage and handling, in particular as regards cold chain requirements (see P.II.A.1.3.) and administration which frequently requires specific medical devices.

In order to ensure proper understanding, consultation of draft communication documents with patients and healthcare professionals should be undertaken (see GVP Modules XI and XV).

P.II.C. Operation of the EU network

P.II.C.1. Roles and responsibilities

P.II.C.1.1. Marketing authorisation holder and applicant in the EU

Medicinal products developed by means of one of the biotechnology processes listed in the REG Annex, or fulfilling any other criteria of the Annex, shall be authorised by the Union through the centralised authorisation procedure.

P.II.C.1.1.1. Risk management plan

The marketing authorisation applicant is responsible for the submission of the RMP in line with the format and content presented in GVP Module V and section P.II.B.1.1.. In case of significant changes to the manufacturing process, a risk analysis and updated RMP should be submitted (see P.II.B.1.2.).

P.II.C.1.1.2. Reporting of adverse reactions

When reporting suspected adverse reactions, marketing authorisation holders shall provide all available information on each individual case, including, for biologicals, the name and batch number(s) of the administered product [IR Art 28(3)(h)].

P.II.C.1.1.3. Periodic safety update reports

Marketing authorisation holders should include in PSURs the following information on the batches delivered during the PSUR-reporting period: batch numbers, countries/regions where such batches have been delivered, size of the batches and any available information on the number of batches that were delivered per country. All assumptions used for calculations should be provided.

P.II.C.1.1.4. Additional monitoring

For biologicals included in the list of medicinal products subject to additional monitoring according to the mandatory or optional scope [see REG Art 23 (1) and (1a), GVP Module X], it is the responsibility of the marketing authorisation holder to perform the activities described in GVP Module X.

P.II.C.1.2. Competent authorities in Member States

P.II.C.1.2.1. Risk management plan

When assessing the RMPs for biosimilar products and their updates, national competent authorities should ensure that the safety specification, pharmacovigilance plan and risk minimisation plan introduced in the RMP for the reference biological product are taken into consideration for the biosimilars (see P.II.B.1.1.). national competent authorities will assess the risk analysis submitted by the MAHs of a biological medicinal product in the case of a change in the manufacturing process and, based on this assessment, conclude on the need to update the RMP (see P.II.B.1.2.).

P.II.C.1.2.2. Reporting of adverse reactions

Member States shall 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 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 DIR Art 1(20), and the batch number [DIR Art 102(e)]. To fulfil this obligation, national competent authorities should agree with marketing authorisation holders, where applicable, a system to ensure the traceability of the biologicals that are prescribed, dispensed or sold, inform health care professionals and patients of the need to provide the product name and batch number/code when reporting a suspected adverse reaction and make this information available to assessors for signal detection and evaluation of individual case reports.

Member States shall facilitate in their territory the reporting of suspected adverse reactions by means of alternative straightforward reporting systems, accessible to healthcare professionals and consumers, in addition to web-based formats (GVP Module VI). If electronic and web-based reporting forms and data capture tools are developed, consideration should be given to optimise the ability of these to encourage provision of product and batch information. This may include automatic prompts if the product name and/or batch is not provided or drop-down list of available products when a particular active substance is selected.

P.II.C.1.2.3. Periodic safety update reports

For the assessment of PSURs for biosimilars, it is critical that the data can be assessed in parallel to the safety data collected for the reference biological. For the assessment of PSURs for biologicals subject to different marketing authorisations, authorised in more than one Member State, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holder, the PSUR EU single assessment procedure should be followed following harmonisation of the frequency and dates of submission of PSURs in the list of EU reference dates [DIR Art 107e-g]. This assessment shall be performed by a Member State appointed by the CMDh where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure (see GVP Module VII).

P.II.C.1.2.4. Additional monitoring

Biological medicinal products authorised after 1 January 2011 are included in the additional monitoring list under the mandatory scope.

P.II.C.1.3. European Medicines Agency

As for all medicinal products, the European Medicines Agency has the responsibility for coordinating the existing scientific resources for the pharmacovigilance of biologicals such as the coordination of:

- the assessment of the risk analysis submitted by the MAHs of a biological in the case of a change in the manufacturing process and, based on this assessment, provision on a recommendation on the need to update the RMP (see P.II.B.1.5.);
- the PSUR EU single assessment procedure for biologicals containing the same active substance or the same combination of active substances where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure (see GVP Module VII).

For signal detection of biologicals, the Agency should provide rapporteurs, lead Member States and national competent authorities with electronic reaction monitoring reports and other data outputs and statistical reports at the product level rather than at the substance level and provide marketing authorisation holders with appropriate support for the monitoring of the EudraVigilance database at the product level.

The Agency shall maintain and publish the list of biologicals subject to additional monitoring under the mandatory or optional scope.

P.II.C.1.4. Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment Committee (PRAC) shall:

- recommend, upon a request from the European Commission or a competent authority of a Member State, as appropriate, if a biological medicinal product which is subject to the conditions set out in REG Art 23(1a) should be included in the additional monitoring list;
- appoint a rapporteur for the PSUR EU single assessment procedure for biological medicinal products containing the same active substance where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure [DIR Art 107e to 107g] (see GVP Module VII);
- adopt a recommendation on the PSUR EU single assessment procedure for biological medicinal products as identified in the EURD list;
- provide advice on RMP subject to their review, in particular, for biosimilar should ensure as appropriate that the pharmacovigilance plan and risk minimisation plan of the RMP for a biosimilar should include similar activities as for the reference medicinal product.

P.II.C.2. Safety communication about biologicals in the EU

Further to the guidance in P.II.B.6., the following should be considered for safety communications about biologicals in the EU.

Operational details of communication processes may differ according to different scenarios among Member States regarding the use of biologicals, in particular regarding interchangeability and interchange practices of biosimilars. Also, benefit-risk perceptions of biologicals may vary between Member States and cultures. Hence, these differences should be accounted for during the EU-wide coordination of safety communication, while maintaining overall consistency of messages across the EU. Competent authorities in Member States should publish explanations of biological-related terms and concepts and other information for patients, in particular comparability assessments, in the local language and should support healthcare professionals with communication materials in order to

facilitate communication with patients with a view to ensuring informed therapeutic choice, adequate risk minimisation and reporting of suspected adverse reactions. Communication in the EU should be underpinned by transparency on how regulatory decisions were reached and on the roles and responsibilities of each stakeholder in the EU (see P.II.C.1.).