3 March 2016
EMA/172711/2016

Comments received from public consultation on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

The draft of this module was released for public consultation between 15 December 2015 and 29 February 2016. The module has been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using a specific template.

The comments received are published, identifying the sender's organisation (but not name). Where a sender has submitted comments as an individual, the sender's name is published.

The European Medicines Agency thanks all those who participated in the public consultation for their contributions.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<February 25, 2016>

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
Asociación Española de Farmacéuticos de la Industria (AEFI)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
175-177		Comment: The appropriate regulatory term for describing the manufacturing changes could be either a variation or extension application, due to the fact that in accordance with Annex II of Commission Regulation (EC) No 1084/2003 the manufacturing change consisting on “modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source” should be submitted as an extension application. Proposed change (if any): 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 **or as an extension** application to the marketing authorization.	
554		Comment: EMA web page on the Good Pharmacovigilance Practice (GVP) informs that some modules stay void (module XII is one of them). Proposed change (if any): Remove the citation to the GVP module XII (no longer available)	
623 - 627		Comment: The inclusion on the PSURs of all the requested details (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) suppose a significant administrative burden, therefore we suggest the pragmatic approach of providing this information	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		on request, where needed. Proposed change: “Marketing authorisation holders should ~~include in PSURs~~ **have available, on request,** 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.”	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3rd February 2016

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
Cell and Gene Therapy Catapult
[redacted]

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Cell Therapy Catapult thank you for the opportunity to comment on this document. We think it is a well written and clear document and have no general comment other than we hope the guideline will be considered in your development of guidance specific to GVP requirements for ATMP	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
190-192		Comment: *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* We suggest some examples of significant and non-significant. changes would be helpful for the industry Proposed change (if any): Comment: Proposed change (if any): Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

[redacted] for the German Biologics Register RABBIT, German Rheumatism Research Centre, Berlin, Germany

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	In general, we agree with the aims and approaches laid down in the document. We also agree that it is important to be able to distinguish orginator products from biosimilars. However, we doubt that it is feasible as well as necessary to collect batch numbers in prospective pharmacoepidemiological studies such as the biologics registers in rheumatology. Therefore, they also cannot be expected in the PSUR from the companies who receive reports from the registers. Our reasons are the following: The biologics registers are designed to assess the long-term safety of new substances. The physicians contributing to the data do this on a voluntary basis within their busy practices. Every additional burden that is posed upon them has to be substantiated by an important scientific question. Of course it is necessary to know whether a patients was exposed, e.g. to Remicade or Remsima. All registers collect the trade names. However, to detect a signal occurring in a specific batch of a substance, huge numbers of cases in these batches are needed. In addition, in our register as well as in others, the data are collected every six months for the previous six months. If a batch should have a real problem, this would be detected much earlier by spontaneous reporting. We would like to explain our hesitation with a short example: In our biologics register RABBIT, about 1,000 patients per year are observed under treatment with Humira. To	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	our knowledge, Humira is produced in about 50 batches per year. It is not known how many of these batches reach the German market. If we assume that only 10 batches per year are distributed in Germany and our patients are exposed to these batches equally, we have 100 patient-years per batch. If we now take the most frequent serious adverse event, serious infections with an incidence of 4/100 PY, we would not be able to detect even a threefold increase in the incidence ($p>0.05$, exact test) in one batch. If there are packages from more batches on the market, this becomes worse, if substance from all 50 batches would be used in our patients, we would not detect even an eightfold increased risk. This example was made with a drug with high exposure in our data. For other drugs the problem is worse. Therefore, batch numbers are not suited to detect risk increases in routine observational data. It is certainly advisable to include batch numbers in spontaneous reporting in order to detect a problem in a specific batch quickly. For observational cohort studies it should not be required because it substantially increases the work load without any scientific or safety advantage.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: It should not be required for pharmacoepidemiologic studies such as the biologics registers. Proposed change (if any): 456/7: When spontaneously 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) Comment: The following is impossible and not necessary for data from the registers. Proposed change (if any): 462: Competent authorities and marketing authorisation holders should also encourage reporters to record information on product names ~~and batch numbers~~. If there is reason to suspect that a problem arises from a specific batch, a~~A~~ follow-up procedure shall be put in place to obtain the batch number where it is not indicated in the initial report. Comment: The detection of "any differences between originator products and biosimilars" already needs need very large sample sizes as they are collected e.g. in the registers. It is unrealistic to expect that it will be possible to detect new batch-specific differences by routine pharmacovigilance. The processes	

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		mentioned should not apply to cohort studies. Proposed change (if any): "Processes should be particularly sensitive to detect meaningful~~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~~ meaningful 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)"	
		Comment: The following is neither feasible nor useful for the registers. 620: "When reporting suspected adverse reactions resulting from spontaneous reporting, 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)]"	

Please add more rows if needed.

29th February 2016

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
The European Biopharmaceutical Enterprises (EBE) and The European Federation of Pharmaceutical Industries and Associations (EFPIA)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The EFPIA & EBE trade associations appreciate that many of the previous pharmaceutical industry comments to the 2014 biological concept paper have been taken into account in this draft GVP Module document for biological medicinal products. Nevertheless, we have a number of general and specific comments for further improvements. In particular, we have the following key concerns on aspects of the draft guidance that do not address the realities and practicalities of marketing biological products both globally as well as in the European Union. These concerns take into account the acknowledgement that a key biological product marketed for decades by many companies is insulin for which many of the provisions stipulated in this draft guideline, appear to be excessive. Key concerns: • Batch Traceability and Product Identification (how these will be handled in the PSUR/PBRER) • Batch Traceability and individual Member State Implementation • Immunogenicity and the need to link to the outcomes (how these will be handled in the RMP) • Collaboration between MAHs (practicalities and logistics)	
	Batch traceability and Product Identification: EFPIA & EBE welcome the acknowledgement of the concept of differences (“drift”) in the safety profiles between the originator and its biosimilar and support the steps being taken to ensure traceability throughout the lifecycle of all products. This Guideline emphasizes the importance of batch traceability and quite rightly so, but overall does not appear to acknowledge the sheer practical challenges of obtaining batch numbers when a suspected ADR is reported for any product and especially biological medicinal products where the reporter may not even be aware of the batch number. This again refers to some biological products such as insulins or even more recent products, which may be initiated in a hospital setting but thereafter will be prescribed in a general practice setting in many countries. MAHs may routinely and repeatedly request this information on follow-up (if not provided at the first	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	notification) but the response rate, even in the face of such follow up is very low. Specific considerations include the fact that biologicals, even if prescribed and/or dispensed in the hospital setting, may be subject to substitution (substitution: practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber) due to change in the Hospital Pharmacy supply. This is an issue to traceability and even determination of the product actually administered, as the prescriber may not be aware that the patient received a biosimilar in place of the product that was actually prescribed. While prescribing practices/interchangeability are responsibilities of the Member States, the document does not appear to take into account the enormous challenge of following up individual cases when trying to link biosimilars to particular patients. In certain situations, e.g. TNFis, there may be multiple biosimilars that are potentially used interchangeably. Implementation of the recommendations of the Falsified Medicines Directive (Directive 2011/62/EU) will provide additional tools (2-d barcode) to improve traceability but these are, as yet, unproven. Nevertheless, there is no experience yet to determine whether or not these recommendations will meet their objectives. In the interim and until there is a consistent system in place across the EU that reliably tracks batch numbers of medicines dispensed to patients and follows this throughout the entire treatment pathway, it is unrealistic to expect such information to be collected via current routine pharmacovigilance activities. The guideline furthermore indicates that batch numbers should be routinely reported in PSURs/ PBRERs when these periodic reports based (by international consensus) on ICH E2C (R2) and in the EU reflected in GVP Module VII are simply not designed, nor indeed are intended, to reflect such aspects unless they have given rise to a safety signal. In the absence of a safety signal, batch numbers should not routinely be included in the PSUR/PBRER. EFPIA & EBE recommend therefore further and better education of HCPs in this matter and support the implementation of the WHO proposal for a Biological Qualifier (BQ). The latter provides an additional safeguard and reflects the global challenge of PV.	
	Batch Traceability and Member State Implementation According to the new delegated act (Commission Delegated Regulation (EU) 2016/161) laying down the detailed rules for the safety features appearing on the packaging of medicinal products for human use, the Member States	

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	can exempt (under certain conditions) “healthcare institutions” (defined as follows: “hospital, in- or out-patient clinic or health centre”) from the obligation to verify the safety features (which include the unique identifier, which in turn includes among its element the “name”, the “common name”, and the “batch number”) (refer to recital 25 and article 26 at http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.032.01.0001.01.ENG). Therefore, the above traceability requirement and, in particular, reliance upon bar code-scanning technology in the hospital will also be dependent upon the way each Member State implements the delegated act. It is inevitable that it will not be possible to adopt this provision consistently and in the same frame across the Member States. As a result, reliance on such technology will not necessarily be sufficient to ensure proper traceability and identification of the biologics given to patients in the EU and additional measures are required. In recognition of the challenge, it needs to be assured that methods for ensuring traceability are thoroughly discussed and agreed with Member States to ensure that PV requirements are realised. In addition, EFPIA & EBE recommend adopting measures at national levels to encourage prescribing biological medicines by brand/invented name and/or preventing inappropriate switches (switching: decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment) and/or substitution practices. Even though prescribing practice and product interchangeability, and particularly switching and substitution between biologicals are beyond the scope of this GVP module, EFPIA & EBE consider that it is important to emphasise that not only traceability, but also keeping track of the patient’s therapeutic history, is key to assuring that the objectives of protecting public health are met.	
	Immunogenicity and the need to link to clinical outcomes Per the draft immunogenicity guideline EMEA/CHMP/BMWP/14327/2006 Rev. 1 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/10/WC500194507.pdf) , *immunogenicity should always be related to the clinical consequences* and the extent to which these constitute a safety concern warranting inclusion in the RMP as an important identified or potential risk. As such, the draft	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	immunogenicity guideline is much clearer. We therefore consider that, for the purposes of this GVP too, the concept of immunogenicity should be consistent. As such, it should be restricted to immunogenicity-related outcomes that constitute a clinical concern sufficient to warrant classification as an important risk and inclusion in the RMP with the need to conduct specific pharmacovigilance and risk management activities. EBE and EFPIA accept that the overall data for immunogenicity needs to be carefully evaluated **prior to determining whether or not the outcomes of immunogenicity should be included in the safety specification** and other sections of the RMP but, as currently written, the draft guideline appears to be contradictory. On the one hand it implies that the "consideration" of whether or not immunogenicity should be **routinely** included in the safety specification of the RMP but on the other hand it states that it should only be included if the immunogenicity is associated with safety concerns or uncertainty. We are sure that this was not intended but industry`s experience is that wording can be interpreted literally in circumstances such as a PV inspection, so it is very clear, unambiguous and not subject to individual interpretation on how immunogenicity is reflected in the RMP and PSUR/PBRER.	
	Collaboration between MAHs (practicalities and logistics) Whilst EFPIA and EBE appreciate that close collaboration between MAHs is important and highly desirable particularly in matters of public health, we would like to highlight that the logistical challenges of doing this should not be underestimated for many reasons but in particular for legal concerns regarding sharing of company confidential information. We suggest that the approach proposed by CMDh for sharing the safety concerns of the innovator company with subsequent generic companies in order to promote consistency, could also be considered when there is a need for a biosimilar applicant to adopt the RMP of the innovator company. This could be achieved for example by the creation of a "safe harbour", which is hosted by the EMA. It is acknowledged that it is possible to obtain an RMP document under "Access to Documents" (Policy 0043) in the EU but this is time consuming for all parties including EMA. We would welcome further dialogue on this matter e.g. at a future Industry Stakeholder platform meeting in order to develop practical and workable strategies for close collaboration between MAHs, including sharing of important information as safety specifications and risk minimisation tools that would be	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	common for their respective products.	
	Other General Comments **Cross reference to other guidelines** EBE and EFPIA acknowledge that cross reference to other guidelines in the GVP modules is usual, however, the number of guidelines given in cross references in this GVP module is particularly numerous and diverse and spans multiple disciplines including regulatory, quality, manufacturing and pharmacovigilance. Although we are clearly not advocating the reproduction of large sections of other guidelines (such as the final version of the immunogenicity guideline) in this GVP module, it should, nevertheless, aim to be as standalone a document as possible in order to promote a better understanding of its content and to minimise the need for frequent cross- referral to other guidelines. For example, it would be useful to give the main definitions in an appendix of this GVP module (including related biological medicinal products and similar biological medicinal products and to provide further clarity on certain terms to avoid subjective interpretation, such as significant and minor manufacturing changes, difference between related Biological medicinal products and similar biological medicinal products. EFPIA and EBE assume that the significant interdependencies of the final biological document with other guidelines and templates still in draft (e.g. the revised RMP template and draft immunogenicity guideline) will be taken into account and that the respective dates of coming into effect are coordinated as much as possible. **Processes and Mechanisms** EFPIA and EBE consider it to be extremely important that processes and mechanisms are developed and in place when this guideline is finalised to facilitate sharing of important information to promote consistency where needed. This would certainly apply when the signal and risk assessment and risk management processes of either the MAH of the reference product/originator or the MAH of a biosimilar identify a change in the safety profile of the active substance, particularly if associated with an update to the SmPC and/or Risk Management Plan or other regulatory action considered to be applicable to both innovator and biosimilar(s). It would be most helpful, in the interests of clarity and transparency, if the guideline could specify that MAHs of innovators and biosimilars will be:	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	- Routinely informed of the outcome of the signal assessment process by other companies where this results in a change in the safety profile of the active substance (e.g. a new ADR, or important risk), and of any related recommendations e.g. for additional monitoring and regulatory actions. - Provided with adequate documentation to evaluate if the signal identified by another company is product specific or not.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 135-136		Comment: 'potentially clinically relevant' would be open to interpretation. As such, it could be literally interpreted to include any associated adverse event, even if not medically serious or necessarily requiring a specific pharmacovigilance and risk management activities. Per the draft immunogenicity guideline, immunogenicity should always be related to the clinical consequences and the extent to which they constitute a safety concern warranting inclusion in the RMP as an important identified or potential risk. As such, the draft immunogenicity guideline is much clearer. We therefore consider, for the purposes of this guideline too, that it should be restricted to immunogenicity-related events that constitute a clinical concern sufficient to constitute an important risk and inclusion in the RMP with the need to conduct specific pharmacovigilance and risk management activities. Proposed change: For the purpose of this Module, 'immunogenicity' refers to an unwanted immune response that is considered potentially clinically relevant **and of sufficient safety concern to** ~~may~~ require specific pharmacovigilance and risk management activities~~ and~~. This may be unrelated to identified risks associated to the active substance, product class or common excipients.	
Lines 175-176		Comment: As further clarified in the text subsequent to this section, not all manufacturing changes require a comparability exercise. Proposed change: Addition of the following wording: "Manufacturing changes may be more complex for biologicals. ~~**They**~~ **The marketing authorisation applicant should consider if these** need to be supported by a comparability exercise (…)"	
Line 200		Comment: It would be helpful if some examples of manufacturing changes having	

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		manifested into changes in safety and/of efficacy could be added and to illustrate how these may be related to product handling or patient characteristics Proposed change: Please provide examples of safety and efficacy changes, which may be as a result of product handling and how this relates to patient characteristics.	
Lines 202-204		Comment: Please provide examples of innovators and biosimilars having potentially different profiles in the long-term post-authorisation period.	
Line 244-250		Comment: While EFPIA and EBE are supportive of the text emphasising traceability of specific products and batch numbers in pharmacovigilance, it is also important to emphasize a longitudinal record, especially when patients may be exposed to multiple versions of a biological medicinal product during the course of therapy (e.g. the originator product and one or more biosimilars). Proposed change: This is particularly important in cases when **there is the potential for** different products, **including products** with same INN, **to be** ~~are~~ either intentionally inappropriately switched or automatically substituted without the prescriber's consent. **A well-maintained record of the therapeutic history of the respective patient can help identify the cause of the problem faster.**	
Lines 277-282 vs line 333		Comment: EFPIA and EBE completely agree that the potential for immunogenicity and associated clinical consequences should be fully evaluated as part of the initial marketing authorisation application. As currently written, however, the guideline implies that immunogenicity should be included in the safety specification, **regardless of whether or not** it is considered to be an important identified or potential risk based on outcomes or uncertainties. For an initial MAA, the Applicant should not be automatically required to discuss immunogenicity in the safety	

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		specification unless it is considered to be a safety concern as there is no provision for this in prevailing guidelines or templates. It is also likely that this was not the intent of the current wording. Where immunogenicity has been fully evaluated and found not to constitute an important (identified or potential) risk or where there is no clear uncertainty (missing information), then there should be no requirement to automatically discuss (include) immunogenicity in the safety specification of the EU – RMP. This principle also applies to line 333, which introduces the concept of immunogenicity as a "theoretical risk" to be discussed in the pharmacovigilance plan when this concept is not otherwise defined and when the RMP is only indented to discuss important identified or potential risks Proposed change: The potential for immunogenicity and associated clinical consequences (see P.II.A.1.1.) should be fully evaluated **and discussed** as part of the initial marketing authorisation application (or variation) **in the relevant sections of the Summary of Clinical Safety. This should only be included** ~~and discussed~~ in the safety specification **of the RMP when the** ~~with appropriate~~ conclusions **warrant their classification as an important risk (identified or potential)** ~~drawn on whether or not a product may pose such a risk~~ in the post-authorisation phase.	
Line 305		Comments: The current wording is not sufficiently specific as it implies that any ADR /risk should be included and reflected in the RMP when in fact it should only be **important risks or missing information.** Proposed change: **Important** Risks **and / or missing information relating to uncertainties** identified from differences within the comparability exercise with	

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		regard to.....	
Line 337		Comment: As currently worded, " the MAA/MAH" implies that all the listed points are applicable to all circumstances and products when this may not be the case. Proposed change: In this section, the MAA/MAH should discuss, **where appropriate and applicable:**...	
Line 333-335		Comment: As noted above, and whilst EFPIA and EBE agree with the principle, this section of the guideline introduces the concept of a "theoretical risk" when this is neither defined nor exists as a concept in any other guideline. The RMP as a whole and the PV Plan specifically is not designed to address "theoretical" risks. Proposed change: Delete reference to theoretical risk altogether and move the point from this section of the guideline as it should not be included in the PV Plan. Move the concept to section P.II.B.1, which addresses general principles as this appears to be more appropriate.	
Lines 338-340		Comments: The estimation of the number of doses delivered or administered in each country for each batch is quite difficult to anticipate. Deviation in the estimated number can raise questions, such as to provide a rationale in case of higher delivery/ administrations. Will the MAH be required to inform CAs? Proposed change: "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 **as far as possible**;	
Lines 341-342		Comments: Providing background AESIs is important, but providing this information by age group is gratuitous. Patients taking biologicals are often medically complex; stratifying AESIs by age will be only modestly informative. Better would be a priori	

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		development of an expected rate by indication (e.g. TNFis are used in several very different medical populations). Proposed change: 'activities performed to measure background rates for AESIs **preferably by indication and if possible,** in the age group targeted by the product**'**	
Lines 352-354		Comment: The relevant time period should be agreed with Competent Authority at the time of submission of manufacturing change variation. Also it is recommended to include additional information on the batch-specific PV required and cross reference GVP Module XV and relevant sections in PII (RMP update and managing ADRs). Proposed change: '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 an ~~**relevant**~~ **agreed** time period **at the time of submission of manufacturing change variation** ~~after the manufacturing change'~~ **. This period of surveillance will start after approval of the variation once new batches are on the market**. **This could include communication(s) to HCPs in affected countries reminding them of the need to report batch number for biological medicines (refer to GVP Module XV for types of safety communications, also see P.II.B.1.2.3 and P.II.B.2).**	
Lines 412-416		Comment: The sentence (lines 414-415) could be reworded. Further clarity is required on when the MAH could or should submit an updated RMP based on a manufacturing change. Proposed change: 'Even minor changes to a manufacturing process can potentially	

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		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 **if a new important potential or identified risk has been identified** based on the risk analysis or previous experience.	
Lines 479-482		Comment: EFPIA & EBE agree that Real World Data sources provide high-quality measures of drug utilization in actual clinical practice. However, EFPIA & EBE do not agree that available electronic health records (EHR) or health insurance claims databases provide a complete measure of patient exposure, to the extent that these data sources do not capture all patients exposed to a given product. Except for extremely rare cases, no registry with 100% patient capture exists. Therefore, while it is possible to use statistical methods to make projections or extrapolations from EHRs or medical insurance claims databases to the whole population exposed to a given medicine, such methods require extensive data manipulation and strong assumptions. Proposed change: Consider removing the reference to EHR or adding an appropriate caveat for their use as follows: "…. marketing authorisation holders should make every effort to obtain data on actual usage of the product (i.e. rather than aggregated relying exclusively on sales data) from available electronic health records from other 'real-world' data sources.	
Line 490-495		Comment: With regard to PSURs, EFPIA & EBE consider that each product should follow its own reporting cycle and should not automatically be grouped for review with other products, which may have differing safety profiles. In addition, EFPIA & EBE consider that changes in the safety information must be made on a per product case-by-case basis and that it is not appropriate to suggest that 'Unless there is	

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		adequate evidence of a potential difference in safety profile between the biosimilar and reference product, recommendations and regulatory actions resulting from a PSUR assessment for biosimilar product should be in line with that for the reference product, and vice versa.' It is important to assess each change individually and to determine if it is appropriate if the new safety finding is unique to the product/batch or class. Proposed change: delete ~~However on a precautionary basis if there is inadequate evidence of a product specific aetiology, recommendations and regulatory actions resulting from a signal assessment for biosimilar or related biological medicinal product should be applied to the reference product/originator, and vice versa~~	
Lines 492-495 / 543-545		Comment: EFPIA & EBE feel that this sentence is not required here in lines 492-495 as it is repeated in lines 543-545. Proposed change: delete this sentence: ~~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~~	
Lines 504-506		Comment: It is suggested that PSUR submission dates may be amended after a manufacturing change. It is unclear under which circumstances the 'merits' of such a change could outweigh the major impact of desynchronising the EU PSUR from the rest of the world. Taking into account the global aspects of pharmaceutical development, it is essential that the scheduling based on a harmonized date such as the IBD, is not impacted. If there are concerns that the change may significantly impact the safety profile of the product, timely interim safety updates should be used. These can be agreed e.g. as post-authorisation measures of the	

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		manufacturing change. Proposed change: Following a significant change to the manufacturing process, the cycle of submission of the PSURs **will remain harmonised internationally for similar/related products, and interim safety updates can be used to address any concerns regarding the impact of the change on the risk profile of the product.** ~~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)~~.	
Lines 594-599		Comment: It would be beneficial to add in additional details here on how the Agency expects MAHs to communicate the importance of reporting adverse events after long-term use. Also, consider further cross-reference with GVP Module XV. Proposed change (if any): It should be communicated to patients and healthcare professionals that adverse reactions may arise even if a medicinal product has previously been well tolerated, **e.g.** due to ~~**e.g.**~~ **a** manufacturing variability or changes or long-term/delayed onset effects, and that this ~~**awareness makes**~~ reporting of adverse reactions, even those after long term use or with ~~**not yet**~~ **un**known/expected features, ~~**more**~~ **is** important. **Refer to GVP Module XV for methods of safety communications.**	
Lines 609-631		Comment: The importance of MAHs involvement in the preparation of the communication is to be highlighted. EFPIA and EBE recommend that the roles and responsibilities of the MAHs for signal management and safety communications need to be described and to add cross-reference to other sections on MAH responsibilities.	
Lines 623 - 627		Comment: The format and content of the PSUR/PBRER, which is that of ICHE2C	

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		(R2), was not designed or intended to evaluate individual cases or to include the detailed information on batches outlined in the draft guidance (i.e. 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), especially if it not relevant to the evaluation of a new safety signal or new information on a known important or potential risk. This aspect is also reflected in GVP Module VII (VII.B.5.5.2 Subsection3), which clearly states that inclusion of patterns of use should be on the basis that it is relevant for the interpretation of safety data. With respect to batch numbers, inclusion could be appropriate if relevant to the evaluation of a safety signal that has been detected in the interval covered by the PSUR. If not relevant to the evaluation of a new signal or to any other evaluation contained in the PSUR, then it should not be necessary to include the above-mentioned long list of information stipulated in relation to batch numbers. Furthermore, the requirement to routinely include such information is deviating from content and format of a document that is not only based on international consensus but is also submitted to multiple regulatory authorities internationally. Finally, routinely including in the PSUR all batch related details such as “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” is a significant administrative burden for the marketing authorisation holder in the absence of any benefit to the evaluation of safety, when such information is not relevant. This information should be held by the marketing authorisation holder and should be used when relevant for the evaluation of safety, including any new signals. Ongoing signalling processes should be able to sufficiently cover the evaluation of batch related issues.	

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		Proposed change: "**Only where relevant to the interpretation of safety data, including a new safety signal that has been detected in the interval covered by the PSUR**, Marketing authorisation holders should include in PSURs the following **a summary of relevant** 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."	
Lines 698-700		Comment: The sentence should be reworded for a better clarity: Proposed change: "...provide advice on the RMP ~~subject to their review,~~. In particular, for biosimilar **RMPs the PRAC** should ensure as appropriate that the pharmacovigilance plan and risk minimisation plan ~~of the RMP for a biosimilar~~ include similar activities as for the reference medicinal product."	
Lines 702-715		Comment: The information included in this section is acknowledged though no specific reference is made to raising awareness on the use of biosimilars in relation to inform patients and tracking of the product name and batch number for biological medicinal products. In addition, it should be clarified how benefit-risk can vary between EU member states for a centralised approved product. Proposed change: e.g. "(...) and should support healthcare professionals **(incl. pharmacists and alternative drug dispensers)** with communication materials in order to facilitate **timely** communication with patients with a view to ensuring informed therapeutic choice **(including eventual change of treatment)**, adequate risk minimisation and reporting of suspected adverse reactions **and the importance of traceability of batch and product name.**"	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 February 2016

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
EGA – European Generic and Biosimilar Medicines Association
Contact: [redacted]

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid and http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf).

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The EGA and its sector group the European Biosimilars Group (EBG), representing together the European generic and biosimilar medicines industries, referred jointly as EGA in this document, welcome this opportunity to comment on the draft EMA Good Pharmacovigilance Practice for Biological medicines (GVP P-II). In this response we wish to provide both general considerations as well as in the next section, specific comments covering specific parts of the proposed text. **DEFINITIONS** The GVP P II for biologicals applies to reference biological medicinal products, biosimilars and related biological medicinal products. Such scope definition can be misleading, as both biosimilars and related biological products fall under the definition of a biological medicinal product according to Annex 1 of Directive 2001/83/EC, part I, Art. 3.2.1.1.. The difference between originator and biosimilar medicines is the regulatory process used for their respective approval. As such, we invite the EMA to ensure a harmonised and coherent approach to pharmacovigilance for all medicines scientifically defined as biologicals. Biosimilar and related biological medicinal products, as defined for the purpose of this Module, **need not and should not be singled out** unless there is a scientifically compelling argument to treat these biologicals differently from a pharmacovigilance perspective. Moreover, the need to distinguish between biosimilar and related biological medicinal product in terms of pharmacovigilance activities is not justified. Furthermore, the use of 'biosimilars' vs. 'biosimilar and related biological product' brings confusion to the overall understanding of the document, giving little or no background why different approach is needed, more clarity and simplification in that regard would be required. **2012 PHARMACOVIGILANCE LEGISLATION** The official deadline for the transposition of the new pharmacovigilance provisions into national law was 21 July 2012. Delays in EU Member States' (MSs) transposition and consequential practical implementation via guidelines drafting and updating, which are in most cases still ongoing, have not yet allowed for the new pharmacovigilance system and provisions to fully deliver. Regarding transposition of the legislation into national law: • 25% of the EU MSs (6 EU MSs) transposed the legislation into national law by the	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

EU official deadline.

- Majority of countries (71%, 20/28 EU MSs) did the transposition in the year following the deadline.
- The last EU MS (Slovenia) transposed the legislation in March 2014.

The key priority appears to now be to **closely monitor, support and stimulate the implementation by EU Member States of Article 102 (e) of Directive 2001/83/EC as amended**, and address in particular the current challenges of biological product identification by batch number which concern all marketed biological medicines to ensure full traceability in case of ADR reporting.

EGA Recommendations:

1. Pursue and complete the pharmacovigilance legislation implementation.

Immediate efforts should concentrate on the full roll out and finalisation of the implementation of the pharmacovigilance legislation. A more strategic approach, e.g. with a work plan for example in place, would be recommended.

2. Foster a dynamic exchange of best practices among EU MSs pharmacovigilance competent authorities.

The transposition of the EU legislation into national law is now complete, however national systems and operators in the system need to adapt their working procedures and tools. Acknowledging national specifics, good pharmacovigilance implementation practices exchange would benefit all and allow for a more coordinated and efficient way forward.

3. Raise awareness and provide an education platform for patients and healthcare professionals.

Awareness raising, education and encouragement of healthcare professionals (HCP) and patients to systematically record and report detailed exposure information, with special attention paid to batch number reporting.

4. Limit further product information/labelling changes.

Further product information/labelling changes do not appear as an immediate area of primary focus while the recent pharmacovigilance changes are still in their implementation phase and impact is yet to be as assessed.

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TRACEABILITY OF BIOLOGICAL MEDICINES

Biological medicines are subject to specific regulations and guidelines for development, approval and post-approval. The EU pharmacovigilance legislation specifically calls out for ADR report to include brand name and batch number in order to ensure that ADRs are accurately ascribed to the correct causative product and batch.

Biosimilar companies databases (source: PSUR) do confirm that as far as brand name recording is concerned, compliance with the EU obligation is really high. Below are some illustrative data from EGA members.

Brand name recording Teva:

Number of ADR reports for marketed biosimilars	What is the % of cases reported		What is the % of brand name recording in ADR reports	What is the % of brand name recording?	
	To the company directly	Via the authorities		Of reports sent to the company directly?	Of reports provided via the authorities?
1006	90.76%	9.24%	98.21%	99.56%	84.95%

Brand name recording Sandoz (reporting periods in 2014):

Biological substance	**Total Spontaneous AEs/ADRs reported**	**Reported as 'Unknown'**
Epoetin alfa	285	7 / 2%
Somatropin	1335	22 / 2%
Filgrastim	279	18 / 6%

This is in line with the EMA statistics (Source: Presentation Sabine Brosch, EMA, at 12th EGA International Biosimilar Medicines Conference, London, 4 April 2014) which show that for the period 1/7/2012 – 28/2/2014, 90% of ADR cases on biologicals reported did include the

Stakeholder number (To be completed by the Agency)	General comment	Outcome (To be completed by the Agency)

corresponding brand names.

As is defined in the Guideline on good pharmacovigilance practice (GVP) Module VI[1]: *'For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number. A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products is presented in an appendix to the GVP guidance.'*

This mandatory follow up is valid for both Marketing Authorisation Holder (MAH) and National Competent Authority (NCA) and is also subject to inspections.

The batch number recording as part of ADR reporting is an essential feature of the EU pharmacovigilance system that requires attention and concerted multi-stakeholder efforts.

RAISE AWARENESS AND PROVIDE CONTINUOUS EDUCATION

Recent experience shows that the overall awareness of HCPs of their recently introduced obligations in the context of the pharmacovigilance legislation implementation is rather limited and as such is preventing the legislation provisions to translate into improved outcomes in the practice.

It therefore appears as an essential step for regulatory authorities to actively engage with professional organisations to **pursue the continuous training** on the new provisions e.g. recording of product information, essential ADR reporting elements, intense monitoring and black triangle.

"*Efforts to improve the traceability should, in the short-term, be focused toward encouraging health professionals and patients to systematically record and report detailed exposure information*" (Vermeer, 2015)

Recent interactions with healthcare professionals have for instance indicated that some hospital software providers do not yet account for the mandatory nature of batch number recording in the context of ADR reporting (i.e. no -mandatory- 'field' is foreseen to enter/record this information).

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

Continuous education of HCPs on their obligations would certainly speed up the upgrading of professional tools which are essential in today's healthcare practice.
The pharmacovigilance legislation introduced some provisions to allow better patient awareness on the medicines they are prescribed and their involvement into spontaneous reporting.
Patient awareness raising is clearly anticipated to greatly improve the overall traceability of treatments and medicines.

OTHER POSSIBLE CONSIDERATIONS
The need for collaborative efforts among the various stakeholders is essential to the success of any future action in this field.

Future considerations on how to **enhance the ADR reporting quality and accuracy** through, e.g., the improvement of ADR reporting systems should be explored in greater detail for their practical feasibility and cost-effectiveness: gaps and bottlenecks in the ADR reporting process which may cause poor product and batch traceability of biological medicines should be identified.

Further studies on cost-effective means to achieve strengthened information recording systems (e.g. FMD, peel off label), learning from other fields (pharmaceutical – e.g., vaccines- or other) and trying to reduce the human factor/human error in the system.

The EU pharmaceutical industry is currently investing a large amount of resources in the set-up of EU databases and various telematics platforms and will continue to do so in the years ahead. The potential support of these existing and ongoing initiatives on how to make the systems evolve to include the latest technologies indicates they should be assessed for their potential to enhance batch identification in the context of ADR.

It is anticipated that improvement of information recording systems can be achieved very simply through communication and awareness raising activities before envisaging sophisticated technological IT solutions.

The EGA does not support the introduction into the EU of the voluntary final WHO proposal on the Biological Qualifier (BQ), as published by the WHO INN Expert Committee in January 2016. Even passive use (i.e. voluntary, outside of any legal requirement) is not

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	deemed appropriate as it could lead to misperception and confusion as to the nature of the product at stake: a version of the active substance. **Traceability requires strong systems, not yet another identifier.** To date, the EU system and naming policy has proven fit for purpose and experience confirms the robustness of the approach: no system has, to date, proven superior in allowing identification of medicines. In addition to the EU approach to naming and reporting ADRs in the pharmacovigilance system, there are plenty of initiatives and systems already in place or under active implementation: unique brand names tested by the authorities not to be confused with other products already on the market, 2D bar codes and ISO IDMP standards (global, tested and interoperable). With the Falsified Medicines Directive (FMD), there is already a unique identifier foreseen for each product i.e. in the format of serialisation. In addition, these serialised numbers will be linked to a batch number in the same system. The inclusion of the batch number will facilitate the inclusion of a batch number in the reporting of Adverse Drug Reactions for pharmacovigilance purposes. Furthermore, the WHO has not yet reached a decision and an impact assessment is to be carried out followed by what seems to be a 3-year pilot implementation before any formal WHO adoption. These steps will be essential for the WHO proposed random four letter code to be tested in real conditions with physicians, pharmacists, patients, electronic systems and official databases, drug safety specialists, payers to be sure it does not cause more harm than it does good.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
69-74		Comment: The description of the scope might be confusing. Biological products are "reference medicinal products" only in the context of an application for marketing authorization for a biosimilar product. Proposed change (if any): Unless specified otherwise in particular sections, this Module applies to **all biological medicinal products regardless of the regulatory pathway of approval or market exclusivity status, i.e. it applies to originator biological medicinal products** ~~reference biological medicinal products as well as~~ and 'similar biological **medicinal** products' (hereafter referred to as 'biosimilars') **as well as** ~~and~~ to products which contain the same or closely related active substance but not authorised as biosimilar (e.g. different interferon a/b inhibitors, different normal human immunoglobulins). These products are **hereafter** referred to as 'related biological medicinal products'.	
117-118		Comment: The *complex manufacturing process with many upstream/downstream steps* is specific to a manufacturing process, not to the manufacturer. The same manufacturer can have different processes for the same product (either in parallel at different sites, or over time). Proposed change (if any): (...) complex manufacturing processes with many upstream/downstream steps that	

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		~~are specific to a given manufacturer and~~ shape the overall safety, quality and efficacy profile	
153-154		Comment: As acknowledged in the *Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins*, non-clinical models and in-vitro assays are usually not predictive for humans. So the rule/exception is vice-versa the description here. Proposed change (if any): However, non-clinical models and analytical methods/bioassays ~~cannot always reliably~~ **can usually not** predict immunogenicity in humans.	
167-170		Comment: Altered safety and efficacy may also be a consequence of an altered immunogenicity, not only an "introduced" immunogenicity. For the sake of clarity a change of wording is also proposed. Proposed change (if any): (...) and the fact that immunogenicity can potentially be introduced **or altered** at any time post-authorisation ~~and thereby~~ **potentially resulting in** an altered safety and efficacy profile of a product.	
190-192		Comment: EGA fully supports that significant manufacturing changes should be assessed on a **case-by-case basis**. Examples on what constitutes 'significant' might be misleading. No change proposed.	

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202		Comment: The INN principles may be not sufficient to identify the same or a different active substance, e.g. compare Interferon alfa/beta versus Epoetin alfa/beta. Proposed change (if any): (…) but also across **all** products with ~~the same INN~~ **containing the same active substance.**	
214-215		Comment: Immunogenicity is an expected effect. It may occur even with best maintained products. Product degradation (e.g., formation of aggregates) during storage may further enhance the immunogenicity. Proposed change (if any): non-adherence to these processes and standards can affect the stability and quality of biologicals, which in turn may introduce **or alter** immunogenicity	
216-117		Comment: Stability and cold chain deviations after batch release are not only specific to a certain batch, but usually affect several batches within a certain part of the logistics chain. For example, storage conditions at a specific warehouse may affect several batches. Proposed change: Though very rare, particularly for a product that has already been released, such defects and deviations would usually affect **defined clusters.** ~~isolated batches.~~	
239-241		Comment: Please see also 'general comments' Please note that pharmacovigilance legislation provisions are still to be fully	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		implemented (i.e. raise awareness on each stakeholder's role in ADR reporting). We should aim first to gather a deeper understanding of what is actually needed from operators in the system, rather than looking for new solutions as IT tools. Especially taking into consideration the intense investments needed and some of possible IT tools/processes that could potentially support still to be implemented in upcoming years.	
246-248		Comment: Following the new pharmacovigilance legislation implementation one of the key deliverable was to educate and engage patients, also in ADR reporting. In addition, according to No.5 Europeans patients' rights 'when you are treated, your healthcare provider must make a medical record of the treatment provided. As a patient you have the right to a copy of this medical record in order to secure continuity of care and be treated by a doctor of your choice, also if you continue treatment in another Member State.' http://ec.europa.eu/health/patient_safety/docs/2015_eu_patients_factsheet_en.pdf Proposed change: Please rephrase accordingly.	
248-250		Comment: The sentence '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.' is partially misleading. 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. In addition, best clinical practice dictates that the product name and batch number of	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		an administered biological should always be recorded by healthcare professionals (and ideally provided to the patient) (see P.II.B.1.4.). We agree with the fact that policies for substitution and interchangeability of medicines pertain to EU Member States competence and should be left out of the present EMA pharmacovigilance guidance document. In the EU, we are not aware of any Member State where substitution occurs for biological medicines. According to our latest information, substitution of biological medicines by the dispensing pharmacist is either forbidden by law or even in instances where public procurement or tendering processes are engaged, clinical decision makers are involved in the decision (e.g. at the level of formulary committee in hospitals). In essence **only switching under the supervision of a clinical decision maker occurs** and we would suggest that the sentence be reworded accordingly. Proposed change (if any): **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~~ **versions of the same active substance (products with the same INN, either reference medicinal product and its biosimilar(s) or versions of the originator product pre- and post-manufacturing changes)** are **available concomitantly on the market** ~~either intentionally switched or automatically substituted without the~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~prescriber's consent~~." Comment: The statement that immunogenicity is not a safety concern per se, is highly appreciated and should remain in the guidance to clarify that the potential or known/identified clinical consequences may be of concern but not immunogenicity per se. It is proposed to stress this point also in the introduction (P.II.A.1.1).	
280-281			
302-304		Comment: beside a specific indication also other non-product related factors, e.g. routes of administration or dose-regimen, may be absent for the related product. Proposed change (if any): (...) or where elements of the safety specification/summary of concerns are specific to a particular **use (e.g.** indication **or route of administration)** that is absent in some products (however, potential for off-label use would need to be considered).	
318		Comment: Routine pharmacovigilance activities as signal management up to batch is possible and part of signal management. Batch-specific safety management does not appear needed in this sentence, might be misleading. Proposed change (if any): The need and plans for continuous life-cycle signal detection and pharmacovigilance specific to the product ~~and sensitive to~~ **including** batch-specific **issues** ~~safety signals~~, particularly following a significant change to the manufacturing process, should be discussed.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
338-340		Comment: Please note that the RMP is a planning tool how to mitigate possible risks, not a reporting tool and the feasibility of additional pharmacovigilance activities of routine recording and reporting number of doses delivered or administered in each country for each batch is questionable. Proposed change: ...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;~~	
409-411		Comment: In consideration of the practical recommendation for the risk analysis (as described in 421-433), a change in wording is proposed to stipulate the requirement for the evaluation, which may result in the need to submit an updated RMP. Proposed change (if any): If the comparability evaluation identifies a potential impact of the manufacturing change in terms of clinical relevance, the ~~change requires~~ **need to submit** ~~submission of~~ **an update to the RMP should be evaluated and discussed**, unless otherwise justified. This **evaluation, discussion and/or** justification would need to be made on a case-by-case basis.	
412-416		Comment: Changes that lead to a comparable product following the ICH-Q5E comparability exercise should not trigger any additional measure as these changes are defined as not altering the benefit/risk ratio of a product. Therefore reference should be added to ICH Q5E.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
441-442		Comment: Conventional signal detection is designed to catch all signals, irrespective if specific to single causes such as batches, countries, indication, and route of administration. In case of any detected signals the root cause for this signal will be evaluated which may be connected but is not limited to the batch. Batch specific signal evaluation after manufacturing changes should only be considered/requested for cases when the comparability evaluation identifies a potential impact of the manufacturing change in terms of clinical relevance Proposed change (if any): ~~If the product name has not changed, particular~~ **For cases when the comparability evaluation identifies a potential impact of the manufacturing change in terms of clinical relevance, particular** attention should be paid to **describe how** ~~ensuring~~ batch-specific signal ~~detection and surveillance~~ **evaluation can be done** in order that the pre and post-change products can be easily distinguished during a relevant time period after the manufacturing change.	
469		Comment: Reference to chapter P.II.B.1.3. is broken since no such chapter exists in the document: … (see P.II.B.1.3.). Please amend with the correct reference.	
483-485		Comment: Routine PSUR reporting of detailed data such as batch numbers/codes of delivered/sold batches, the sizes of them and to which regions/countries the respective batches have been delivered is out of the scope of the PSUR and not feasible. However, in case of any signals an effort should be made to trace back to	

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		the root cause which may result in the display of such data, but only on case-by-case basis, not routinely. Proposed change (if any): 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 **for relevant clusters of cases, on a case-by-case basis.**	
496		Comment: Reference to chapter P.II.B.1.5. is broken since no such chapter exists in the document: … (see P.II.B.1.5.). Please amend with the correct reference.	
515-516		Comment: Signal detection is designed to identify all signals, irrespective if specific e.g. to batches, countries, indication, route of administration. It is expected that signal management is sensitive to identify clinical symptoms or outcomes of potential immunogenicity response in timely and precise manner. According to existing guidelines, any signal should be validated taking into account other relevant sources of information. If a signal was detected, a clear traceability exercise should be performed up to the batch level. Proposed change (if any): All steps of signal management should be performed at the level of the product name, as well as the active substance**. In case of a signal any effort should be made to identify any common root cause, such as** ~~and, if feasible, at the level of the~~ batch, **distribution deficiencies in cold chain logistics**	

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		of special countries, indications, route of administration and batch identification.	
517-522		Comment: Detecting any differences between originator products and biosimilar or related biological products seem not to be in line with the overarching "Guideline on similar biological medicinal products" as it is stated: "There is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product, e.g. in the context of a change in the manufacturing process, once the Marketing Authorisation has been granted" Proposed change (if any): 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).	
534		Comment: References to chapters P.II.B.1.3. and P.II.B.1.5. are broken since no such chapter exists in the document: … (see P.II.B.1.3. and P.II.B.1.5.). Please amend with the correct reference.	
538-540		See comment 515-516 Proposed change (if any): Any ~~batch-specific~~ signals should be evaluated in the	

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		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.	
551-552		Comment: The concept of additional monitoring is connected to a limited period of time. REG Art. 23(1)(b) says: "Medicines containing new active substances or new biologicals remain on the list for five years". The current statement is too general and could therefore be misleading. Proposed change (if any): According to REG Art. 23(1)(b) additional monitoring applies to all biologicals authorised after 1 January 2011 **as long as they are on the EMA list** (see GVP Module X).	
624-627		Comment: see comment on 483-485	
633-639		Comment: The scope of this section is not understood. According to the Annex of 726/2004 all biologicals are to be authorised by the European Community. We cannot see a role of the competent authorities in Member States in this.	
669-670		Comment: see comment on 551-552 Proposed change (if any): Biological medicinal products authorised after 1 January 2011 are included in the additional monitoring list under the mandatory scope **for five years**.	

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676		Comment: Reference to chapter P.II.B.1.5. is broken since no such chapter exists in the document: ... (see P.II.B.1.5.). Please amend with the correct reference.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 February 2016

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
EuropaBio – the European Association for Bio-Industries [redacted]

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EuropaBio welcomes the opportunity to submit these comments and observations on the draft Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014). EuropaBio welcomes this draft GVP Module which is particularly relevant to developers and manufactures of biological medicines, providing the regulators expectations to ensure compliance with the requirements of the EU pharmacovigilance legislation, and thus the ongoing safety of biologicals post-marketing authorisation. EuropaBio is appreciative that the EMA and Heads of Medicines Agencies' European Risk Management Strategy Facilitation Group have taken into account many of our comments on the concept paper on the key elements of pharmacovigilance activities for biologicals which was issued for targeted consultation in 2014. We are pleased to see the emphasis on traceability of biological products in clinical use. Although in general we support the proposed content of the draft GVP Module, we believe that the following points require further consideration before finalisation of the GVP Module on pharmacovigilance considerations for biologicals.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Role of Member States in ensuring traceability of biological medicinal products We welcome references in this guideline to the need to integrate traceability of biological medicinal products in different healthcare settings and infrastructures, including hospital settings, and to rely on various methods to collect information, such as bar code scanning. We support the need to ensure that the product's brand name and batch number are recorded at all levels in the supply chain. According to Recital 25 and Article 26 of the Draft Delegated Regulation laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use, we note that, under certain conditions, Member States can exempt healthcare institutions, defined as "hospital, in- or out-patient clinic or health centre", from the obligation to verify the safety features, which include the unique identifier, which in turn includes the name, the common name and the batch number. Therefore, the above traceability requirement and, in particular, reliance upon bar code-scanning technology in hospital settings (where the vast majority of biological medicines are prescribed and dispensed to patients) will also be dependent upon the way the Member States implement the delegated act. As a result, reliance on such technology will not necessarily be sufficient to ensure traceability of biologicals given to patients in the EU, and additional measures are required.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	We would therefore recommend having a clear separation between activities falling under Member State responsibilities and what is expected from the marketing authorisation holder in terms of traceability. For example, it will not be possible for marketing authorisation holders to establish clear alternatives to collect exposure information if record linkage does not exist. Methods for ensuring traceability should be discussed and agreed with Member States to ensure that pharmacovigilance activities are realised. **Sharing of risk knowledge** There are many places throughout the draft GVP Module which call for close collaboration between the EMA/National Competent Authorities and marketing authorisation holders or between marketing authorisation holders with regard to sharing risk knowledge, the need to ensure robust traceability practices, etc. While collaboration in the area of pharmacovigilance is to be welcomed in terms of public health benefits, it would be helpful if regulators could suggest some tangible strategies to ensure these groups can work together as envisaged in this guidance. **Updates to the RMP of reference products and biosimilars** It is well acknowledged that all biologicals (including biosimilars) are unique products and the safety profiles may change overtime independently from another and that this should be reflected in the RMP. As there are independent updates to the RMP for reference	

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products and for biosimilars throughout their respective lifecycles, it is important that neither product's label is automatically updated with the findings of another product in the absence of positive confirmation of a specific safety finding for the concerned product.

While we are in agreement that the RMP of a biosimilar should be reflective of that of the reference product it would be helpful if a mechanism could be proposed whereby marketing authorisation holders will be made aware of any such post-authorisation updates to the RMP.

Acknowledgement of confidentiality of manufacturing process data

EuropaBio fully supports the requirement that biosimilars should share the safety concerns of the originator product. It is suggested at lines 298-299 that exceptions may apply subject to justification, for example 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. Since a biosimilar manufacturer will not have access to the manufacturing process of the originator, it should be acknowledged in this GVP Module that there may be differences in the summary of safety concerns for related biological products.

Ensuring alignment with relevant guidelines

It is recommended that the date for coming into effect of the finalised

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	GVP module on pharmacovigilance considerations for biologicals is synchronised with that of the revised GVP Module V (Risk management systems) and the related RMP template, to ensure a supporting regulatory framework is in place. Finally, with regard to section P.II.A.1.1. Immunogenicity, it would be helpful if the EMA and ERMS FG would take into consideration relevant comments received in response to the recent public consultation on the Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
133		Comment: Consider adding that often immunogenicity events may be of delayed onset. Proposed change: "...compared to non-biologicals and require specific consideration. **Furthermore, immunogenicity type reactions associated with biological medicinal products are of delayed onset, that is, the adverse clinical signs do not manifest until after the start of treatment, sometimes weeks or months after administration.**"	
156-166		Comment: It is clear in this section that immunogenicity assessment cannot be conclusive during the development of a biological medicinal product and therefore specific activities (even if this is considered as routine monitoring) should continue in the post-authorisation phase where appropriate. Proposed change: "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~~ **as appropriate**."	

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175-176		Comment: As further clarified in the next section, not all manufacturing changes require a comparability exercise. We suggest adding the following wording below. Proposed change: "Manufacturing changes may be more complex for biologicals. ~~They~~ **The marketing authorisation applicant should consider the level of evidence that would be** need**ed** to ~~be~~ support~~ed by a~~ comparability ~~exercise~~ (..)"	
200		Comment: It would be helpful if some anonymised examples of manufacturing changes which have the "potential for serious new risks (safety or efficacy)" could be added in an Appendix to this GVP module to illustrate how these may be related to product handling or patient characteristics.	
201		Comment: The word "drift" is not an appropriate scientific or regulatory term. It implies that a process is not in control, and quality specifications should certainly not "drift". We suggest replacing "drift" by "controlled change". Proposed change: These potential changes are relevant not only within a product (e.g. ~~'drift'~~ **controlled change** in quality specifications over	

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		time), but also across products with the same INN.	
230-232		Comment: We support the need to ensure batch traceability of a product throughout the lifecycle and for this requirement to be reflected in the RMP. Relevant examples of strategies to enhance this and how they have been implemented for current products would be welcomed.	
232		Comment: We suggest adding the sentence below at the end of this paragraph to enhance traceability of the product. Proposed change: "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 section P.II.B.1.). **To enhance traceability, the product name, as per the cross-border healthcare Directive 2011/24/EU, should be used at the point of prescription."**	
248-250		Comment: This sentence should be removed as beyond the scope of this GVP Module. It should be noted that, in some countries, e.g. Ireland, automatic substitution is not permitted.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: ~~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.~~	
277-282		Comment: In the case where immunogenicity has been fully evaluated and found not to be an important risk then there should be no requirement to add this to the safety specification which should be reserved for important identified risks, important potential risks and missing information only. Proposed change: Consider revising the sentence such that there is no requirement to discuss the immunogenicity in the safety specification where immunogenicity has not been found to be an important risk.	
292-297 317-323		Comment: The proposed discussion of significant changes to the manufacturing process will require a new section in the EU RMP template. We understand that the GVP Module V (Risk Management Systems) and the related RMP template are scheduled for updating. Proposed change: It is recommended that the finalised GVP module on	

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		pharmacovigilance considerations for biologicals does not come into effect before the adoption of the revised GVP Module V (Risk management systems) and the related RMP template, to ensure a supporting regulatory framework is in place.	
294-297		Comment: For consistency with language used in other GVP Modules we suggest replacing the word 'may' with 'should'. Proposed change: "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~~ **should** make reference to "immunogenicity following a significant change to the manufacturing process".	
323, 339		Comment: The use of 'sticky' labels and bar coding is presented as both a "Routine pharmacovigilance activity" at line 323, and an "Additional pharmacovigilance activity" at line 339. Proposed change: Please reconcile this discrepancy. We believe that the provision of 'sticky' labels and bar coding should be considered as a routine pharmacovigilance activity.	

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338-340		Comment: Additional measures introduced to support product traceability should not be defined as an additional pharmacovigilance activity, but rather as risk minimisation measures.	
396		Comment: Recording the name and batch number of the administered biological product in the patient file should be the default requirement, not just a recommendation. Proposed change: "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."	
396-399		Comment: The guideline requests marketing authorisation holders to state in SmPCs and PLs the need for tracking names and batch numbers in the patient file. However, it is unclear to whom this responsibility would apply. Our understanding is that the prescribing physician maintains the patient file (medical record), while the pharmacy dispenses the product and would thereby be the only party with access to the batch identifiers. If the intent is that the pharmacy stores this information, we wish to point out that standard practices for	

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		pharmacy record keeping may vary considerably among the EU Member States, and that there may not be mechanisms for batch number tracking in all countries. Proposed change: Please clarify if the party responsible for batch record keeping is intended to be the treating physician, the dispensing pharmacy, or both. It would be helpful if this section could make reference to the Member States responsibility to take all appropriate measures to encourage or mandate the prescription, dispensing, supply and administration of biological medicines by brand/invented name. This is particularly important to ensure traceability and identify the biological medicine which is the subject of a suspected adverse reaction report.	
438		Comment: A clear and predictable timeframe for the submission and approval of RMP updates would be helpful. Proposed change: "A RMP update should be submitted as soon as possible to allow for its **timely** approval in the context of the variation to the manufacturing change."	
450-456		Comment:	

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		In addition to the traceability requirement for biologicals in Article 102(e) of Directive 2001/83/EC (as amended), EU law requires that the brand name should "only be used to ensure clear identification of biological medicinal products" and sets out an obligation for Member States to include the brand name among the "list of elements to be included in medical prescriptions", to be used in the cross-border context, in order to "facilitate the correct identification of medicinal products" (Recitals 4 and 5 and the Annex to the Commission Implementing Directive 2012/52/EU of 20 December 2012 laying down measures to facilitate the recognition of medical prescriptions issued in another Member State). Proposed change: "with due regard to the name of the medicinal product, and the batch number [DIR Art 102(e)]. **Member States shall also ensure that the brand/invented name or, as appropriate, the INN accompanied by the name of the marketing authorisation holder is used to ensure clear identification of biologicals. The brand name should be among the list of elements to be included in medical prescriptions to be used in the cross-border context.**	
504-506		Comment: It is suggested that PSUR submission dates may be amended after a manufacturing change. It is unclear under which circumstances the 'merits' of such a change could outweigh	

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		the major impact of desynchronising the EU PSUR from the rest of the world. Taking into account the global aspects of pharmaceutical development, it is essential that the scheduling based on a harmonized date such as the IBD, is not impacted. If there are concerns that the change may significantly impact the safety profile of the product, timely interim safety updates should be used. These can be agreed e.g. as post-authorisation measures of the manufacturing change. Proposed change: Following a significant change to the manufacturing process, the cycle of submission of the PSURs **will remain harmonised internationally for similar/related products, and interim safety updates will be used to address any concerns regarding the impact of the change on the risk profile of the product.** ~~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)~~.	
517-520		Comment: Considering that the marketing authorisation holders for originator products and biosimilars are different, additional guidance is needed to describe the mechanism allowing marketing authorisation holders to detect differences between originator and biosimilar products during a signal detection	

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		process for a given product. Clarification is requested on the relative responsibilities of the marketing authorisation holders and regulatory authorities.	
558-608		Comment: The section on safety communication seems somehow out of place in this practical, product-specific module. The principles outlined would apply to any safety communication in general, and are not specific to biologicals. A cross referencing to the GVP Module XV should be made instead. Proposed change: • We suggest cross-referencing to the GVP Module XV - Safety Communication. • If, on the other hand, the entire section is maintained in the GVP module for biologicals, we would recommend that the changes suggested below for lines 564-565, 567-569, 570-571, 578-579, 592-593 and 600-603 are taken into account to improve this section with greater clarity.	
564-565		Comment: This sentence should be removed as outside the scope of this GVP Module. Proposed change:	

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		~~Social risk amplification may also occur with other technologies used in biologicals like nanotechnology.~~	
567-569		Comment: This sentence should be removed as outside the scope of this GVP Module. Proposed change: ~~depriving them from therapeutic choice, non-adherence to prescribed therapy or inadequate compliance to risk minimisation measures.~~	
570-571		Comment: We suggest re-wording for greater clarity. Proposed change: "possible residues should be ~~considered~~ **well understood and communicated to patients**.	
578-579		Comment: We are unclear on the purpose of this statement and suggest removing. Proposed change: ~~As regards blood- and plasma-derived products, patients may be concerned over transmission of infectious agents.~~	

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592-593		Comment: We believe this sentence is not appropriate and suggest removing. Proposed change: ~~Honest information over areas of scientific uncertainty may be required for building confidence.~~	
600 – 603		Comment: It would be helpful to state which aspects are required to ensure traceability, i.e. the name and batch number(s) of the administered product. Proposed change: ""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 **on reporting of the product name (or INN and name of the marketing authorisation holder) and batch number(s)**."	
620-622		Comment: The requirement that marketing authorisation holders 'shall' report batch numbers may not be achievable as the responsibility for establishing a reliable system to capture	

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		batch numbers is a shared responsibility of the marketing authorisation holder and Member States as recognised in section P.II.C.1.2.2 Reporting of adverse reactions. Currently systems are not robust in this regard. Proposed change: "When reporting suspected adverse reactions, marketing authorisation holders shall provide all available information on each individual case, **which may include** ~~including~~, for biologicals, the name and batch number(s) of the administered product [IR Art 28(3)(h)]."	
623 - 627		Comment: Routinely including in the PSUR all batch related details such as "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" is a significant administrative burden for the marketing authorisation holder. This information should be held by the marketing authorisation holder and made available on request, where needed. Signalling processes should be able to sufficiently cover the evaluation of batch related events. Proposed change: "Marketing authorisation holders should ~~include in PSURs~~ **have available, on request,** the following information on the batches delivered during the PSUR-reporting period: batch	

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		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."	
646-650		Comment: It would be helpful to clarify what is meant "to provide the product name" to ensure adequate traceability and pharmacovigilance of biologicals. We also suggest adding the sentence below at line 650 to ensure clear identification of biologicals. Proposed change: "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 **(brand/invented name or, as appropriate, INN accompanied by the name of the marketing authorisation holder)** 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. **National competent authorities should consider adopting measures to encourage prescribing biological medicines by brand/invented name and preventing inappropriate**	

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		switches and/or substitution practices to occur."	
698-700		Comment: We suggest rewording this sentence to increase clarity. Proposed change: "provide advice on **the** RMP ~~subject to their review,~~. **I**n particular, for biosimilar **RMPs the PRAC** should ensure as appropriate that the pharmacovigilance plan and risk minimisation plan ~~of the RMP for a biosimilar~~ include similar activities as for the reference medicinal product."	
704-709		Comment: It is stated that benefit-risk perceptions of biologicals may vary between Member States. While the maturity and capacity of health systems may vary across the EU, it is not appropriate to include such a statement, especially for centrally authorised products where a benefit-risk assessment is included in the European Public Assessment Report (EPAR). Communication about benefit-risk assessment of biologicals should mainly be based on scientific evidence and not affected by other factors, e.g. national health systems. Proposed change: "Operational details of communication processes may differ according to different scenarios among Member States regarding the use of biologicals, in particular regarding	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		interchangeability and interchange practices of biosimilars. ~~Also, benefit-risk perceptions of biologicals may vary between Member States and cultures. Hence,~~ **T**hese differences should be accounted for during the EU-wide coordination of safety communication, while maintaining overall consistency on the **scientific benefit-risk** messages across the EU **Member States**.	
711-713		Comment: With regard to informing patients and supporting healthcare professionals it would be helpful to note the importance of traceability and tracking the product name and batch number for biological medicinal products. Proposed change: "and should support healthcare professionals **(incl. pharmacists and alternative drug dispensers)** with communication materials in order to facilitate **timely** communication with patients with a view to ensuring informed therapeutic choice, adequate risk minimisation and reporting of suspected adverse reactions **noting the importance of traceability of batch number and product name**."	

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<February 29th, 2016>

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
International Plasma Fractionation Association (IPFA) [redacted]

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*).*

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	It is agreed that due to their much more complex nature, biologicals pose a greater potential risk of immunogenicity compared to non-biologicals and require specific consideration. However, these GVPs are neither adapted nor proportionate to the risk, when asking that any manufacturing change require a change in the RMP, or a full batch listing in each PSUR. It is the assessment of the manufacturing change variation that leads or not to the decision of the need for an update of the RMP.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
P.II.A.1.2. Manufacturing variability Line 175		They need to be supported... Proposed change: "they <u>often</u> need to be supported	
Stability and cold chain Line 214 P.II.A.1.3.		Non-adherence to these processes and standards can affect... Proposed change: Non-adherence to these processes and standards <u>may</u> affect...	
P.II.B.1.1.3.2. RMP part III section "Additional pharmacovigilance activities" Lines 341-345 /348-349		Comment: This does not sound to be specific to biological products Proposed change: <u>Remove</u> any item not specific to biological products, since covered in other Good Pharmacovigilance Practices modules.	
Lines 346-346 / 377-381		Comment: MAH have access to very limited information collected in registries (ex : EUHASS)	
P.II.B.1.2. Updates to RMP due to manufacturing changes P.II.B.1.2.1. Potential impact of a manufacturing change Lines 412 to 416		If there is no impact identified by the comparability exercise, there is no need to submit a systematic updated RMP. Proposed change: Also the text: "*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*." is not clear, please clarify.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
P.II.B.1.2.3. Update of the RMP Lines 441-442		Comment: In which module/section of the RMP should the MAH address the way of ensuring batch-specific signal detection and surveillance?	
P.II.B.3.1. PSUR section "Estimated exposure and use patterns" / Lines 624-627 *P.II.C.1.1.3. Periodic safety update reports* Lines 483-487		Comment: It is not realistic to ask such information for all PSURs. Such information is not adapted to the PSUR format nor its objective. Off course the MAH has the information about all single batches and should be able to provide the data, but this is relevant only in case of any signal/issue. This could be useful in case of a signal detected for a specific batch. But if no signal aroused, the PSUR, in its current format, does not provide individual reports/batch number. Therefore, for the PSURs covering period when no significant changes of the marketing process occurred and /or no signal raised, all this amount of data concerning batch released will be useless. Moreover it is not clear if the batches are those delivered/ released/ sold during the period.	
P.II.C.1.2. Competent authorities in Member States *P.II.C.1.2.1. Risk management plan* Lines 633 to 639		In the case the authorities conclude on the need to update the RMP despite the risk analysis submitted by the MAH, this should be done as a commitment.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 January 2016

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
Irish Pharmaceutical Healthcare Association (IPHA)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	IPHA welcomes this guidance to support traceability of biologics in the context of pharmacovigilance. In that context, it would be helpful to state in the introduction that biosimilars are not generics and that this should be remembered when considering pharmacovigilance activities.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
141		Comment: delete the word 'rare' as immunogenicity may occur more frequently than rarely. Proposed change (if any): However, on ~~rare~~ occasions, immunogenicity could result in serious and life-threatening reactions.	
160		Comment: amend to read: '....demonstrated and accepted biosimilarity of quality...' Proposed change (if any): For biosimilars in particular, initial marketing authorisation is based on demonstrated and accepted ~~similarity~~ **biosimilarity** of quality, safety and efficacy	
170-171		Comment: discussion regarding the lack of clinical safety data, particularly in indication extrapolation should be included here. The only reference to 'extrapolation' in the document is on line 581. Proposed change (if any):	
193		Comment: replace do with 'should'. To read: 'Most manufacturing changes should result in a comparable product,...' Proposed change (if any): Most manufacturing changes ~~do~~ **should** result in a comparable product	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
232		Comment: Add the following at the end of the paragraph: Proposed change (if any): To enhance traceability, the product name, as per the EU Cross Border Directive (201/24/EU), should be used at the point of prescription.	
248-250		Comment: This sentence should be removed as beyond the scope of this guideline; also, in some countries e.g. Ireland, automatic substitution is not permitted. Proposed change (if any): ~~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.~~	
276		Comment: there should be a reference to the risks associated with the lack of clinical safety data where there has been indication extrapolation. Proposed change (if any): important potential risks and missing information e.g. clinical safety data where indications have been extrapolated.	
310		Comment: Amend 'comparability' to read 'biosimilarity' Proposed change (if any): outcome of the comprehensive ~~comparability~~ **biosimilarity** exercise	
396		Comment: recording the product name and batch number should be the default requirement, not just recommended. Proposed change (if any): should include a statement ~~strongly recommending~~ that the name and batch number of the administered product should be clearly recorded in the patient file.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
558-608		Comment: this section seems out of place and is written in a different style to the rest of the document.	
564-565		Comment: Not in scope for this GVP module Proposed change (if any): ~~Social risk amplification may also occur with other technologies used in biologicals like nanotechnology.~~	
567-569		Comment: Not in scope for this GVP module Proposed change (if any): ~~depriving them from therapeutic choice, non-adherence to prescribed therapy or inadequate compliance to risk minimisation measures.~~	
571		Comment: replace considered with 'well understood and the patient well informed.' Proposed change (if any): possible residues should be ~~considered~~ well understood and the patient well informed.	
578-579		Comment: This statement should be removed - what purpose does it serve but to heighten concerns. Proposed change (if any): ~~As regards blood- and plasma-derived products, patients may be concerned over transmission of infectious agents.~~	
592-593		Comment: Delete as not appropriate. Proposed change (if any): ~~Honest information over areas of scientific uncertainty may be required for building confidence.~~	
648		Comment: Amend to read: Proposed change (if any): ..product name (brand name or, as appropriate, INN accompanied by the name of the marketing authorisation holder).	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*

Please add more rows if needed.

29 February 2016

Submission of comments on GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014)

Comments from:

Name of organisation or individual
PHARMIG – Association of the Austrian pharmaceutical industry

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	PHARMIG, the association of the Austrian pharmaceutical industry welcomes the opportunity to comment on the draft GVP Considerations – Product- or Population-Specific Considerations II: Biological medicinal products.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
140 and throughout the document		Comment: please use benefit-risk (balance) in a consistent way (sometimes it's risk-benefit, then benefit-risk) Proposed change (if any):	
246-248		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.). Comment: This is not strong enough just by mentioning 'best clinical practice dictates'.... Documentation of product name and batch number shall be a MUST to physicians, HCPs or whoever is administering etc. a product. Moreover the traceability of biological products is a legal requirement of the new EU PHV legislation (Art. 102e Dir. 2001/83) Proposed change (if any): ~~Best clinical practice~~ Art. 102e Dir. 2001/83 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.).	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
323		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). Comment: We would rather appreciate the word 'ensure' instead of 'support' to emphasize relevance Proposed change (if any): … may be required to ~~support~~ ensure product traceability (e.g. provision of ‘sticky’ labels, bar coding).	
621		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)]. Comment: Please use either 'product name' or 'brand name' to have a clear differentiation from INN / substance name	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
644		… with due regard to the name of the medicinal product Comment: Please use either 'product name' or 'brand name' to have a clear differentiation from INN / substance name Proposed change (if any):	
698-700		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 Comment: The wording of this paragraph is confusing. Please consider rewording. Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<29/02/2016>

Submission of comments on 'Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations II: Biological medicinal products'

(EMA/168402/2014)

Comments from:

Name of organisation or individual
[redacted] REGenableMED consortium

Please find below the answer to the 'Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products' by the REGenableMED consortium.

[redacted]

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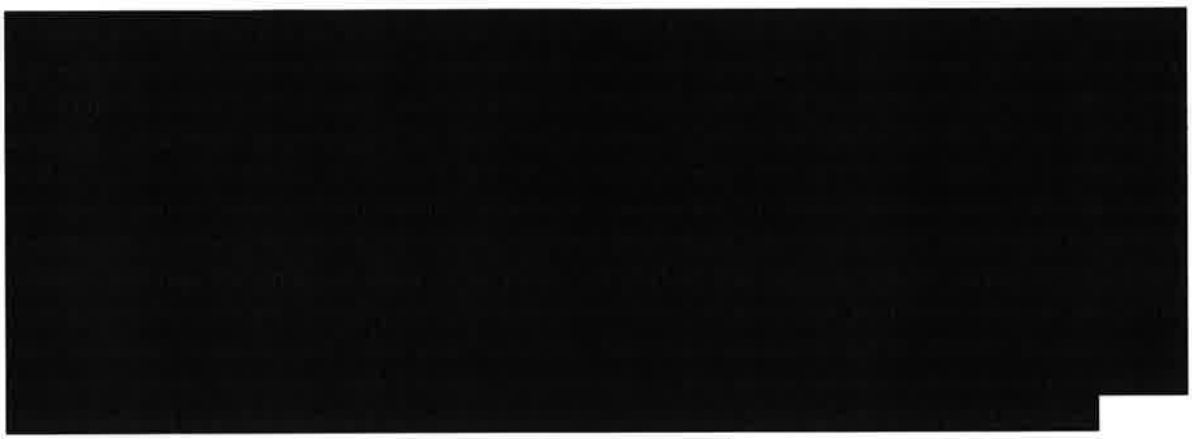

The REGenableMED consortium is grateful to the European Medicines Agency to have been given the opportunity to contribute to this consultation.

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	All the partners of the REGenableMED project are aware of the existence of this draft Guidance. We welcome the opportunity to review this 'Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products'. It has been chosen to exclude Advanced Therapy Medicinal Products from the scope of this guideline because of the existence of previous separate specific guidance (lines 65- 68). However, as long as Advanced Therapy Medicinal Products are biological medicinal products it should be more relevant to consider the general principles of pharmacovigilance and patient traceability in this Module also apply to Advanced Therapy Medicinal Products. Such approach would also be more logical from a global point of view regarding the guidelines on biological medicinal products as long as it would be the same as the one provided for plasma- derived medicinal products. Indeed, it has been chosen that the general principles of pharmacovigilance and patient traceability in this Module also apply to plasma- derived medicinal products even though separate guidance exists on donor traceability of medicinal substances derived from blood and plasma	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	(lines 89- 91).	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 65- 68		Comment: As long as Advanced Therapy Medicinal Products are biological medicinal products it should be more relevant to consider the general principles of pharmacovigilance and patient traceability in this Module also apply to Advanced Therapy Medicinal Products even though separate guidance exists. Proposed change (if any): "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~~). Although separate guidance exists on Safety and Efficacy Follow up of Advanced Therapy Medicinal Products (see ☐Guideline on Safety and Efficacy Follow up- Risk Management of Advanced Therapy Medicinal Products), the general principles of pharmacovigilance and patient traceability in this Module also apply to such products."	
Line 112- 113		Comment: To be the clearest as possible in the definitions, it should be specified that the Agency stand for the European Medicines Agency. Proposed change (if any): "Member States and the European Medicines Agency (here after the Agency)."	
Line 444		Comment: PSURs should be written entirely the first time it is used in the text. Proposed change (if any): "Following an update to the RMP,	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		subsequent Periodic Safety Update Reports (PSURs)"	
Lines 697		Comment: EURD should be written entirely the first time it is used in the text. Moreover, the agreed abbreviation generally used by EMA is EURDs instead of EURD. Proposed change (if any): "products as identified in the EU Reference Dates (EURDs) list;"	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.