EuropaBio submission to the
EUROPEAN COMMISSION PUBLIC CONSULTATION ON THE COMITOLOGY PART OF THE REVISION OF THE VARIATIONS REGULATIONS
JANUARY 2008

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I. About EuropaBio

EuropaBio, the European Association for Bioindustries, was created in 1996 and is solely and uniquely bringing together bioscience companies from all fields of research and development, testing, manufacturing and distribution of biotechnology products. It has 84 corporate members operating worldwide, 8 associate members, 6 BioRegions and 25 national biotechnology associations. Through its associations EuropaBio is also the voice of over 1800 small and medium-sized enterprises involved in research, development, testing, manufacturing and commercialisation of biotechnology applications.

EuropaBio's mission is to promote an innovative and dynamic biotechnology-based industry in Europe. We advocate free and open markets and the removal of barriers to competitiveness with other areas of the world. We are committed to an open, informed dialogue with all stakeholders about the ethical, social and economic aspects of biotechnology and its applications. We champion the responsible use of biotechnology to ensure that its potential is fully used to the benefit of people and their environment.

II. Introduction

EuropaBio welcomes the opportunity to comment on DG Enterprise and Industry's review of the current regulatory framework on changes to medicinal products ("Variations Regulations") in the EU.

Significant advances in biosciences and in manufacturing technologies have led to a steady increase of bio-pharmaceuticals and advanced bio-therapies that are depending on a regulatory framework that supports innovation and continual improvements to manufacturing processes without causing unnecessary delay in supplying these innovative products to the market.

The vast majority of changes to the manufacture and control of a biological medicinal product are excluded from usage of the Type IA/IB notification submission route which requires significant administrative and regulatory resources, both for competent authorities and for the industry. EuropaBio considers that many of the changes outlined in Annex I of the current Regulations could be processed for biological products as a Type IA or IB notification, with no negative implications to quality, efficacy or patient safety.

We believe that there is opportunity to maintain or even increase the level of public health protection in simplifying the system without compromising human and animal health by allowing more human and fiscal resources be focused by the industry on greater innovation and efficiency in development of high quality, safe and effective medicinal products.

By minimizing unnecessary burdens of administrative practices and keeping the right balance between protecting health and supporting innovation such regulation should not hinder but rather stimulate the introduction of changes that are beneficial to patients and to society in general.

EuropaBio very much appreciates the consultation documents of the Commissions regarding the comitology aspects of the Review of the Variations Regulations, issued on 24th of October 2007, taking EuropaBio comments on the Issue Paper from 20th October 2006 into consideration. The approach of continued efforts to simplify the current Variation Regulations in making it simpler, clearer and more flexible and to reduce the administrative burden within agencies and industries as well as adapt to ICH Q8, Q9 and Q10 concepts and further alignment with US supplements setup without compromising human and animal health are highly welcomed.

EuropaBio very much appreciate the structure of the following "comitology documents":

- Public Consultation paper of 24th of October 2007 building on the same structure as the Commission "Issue paper" from 20th October 2006 and additional clarification figures/tables included
- Draft Commission Regulation of 24th October 2007 covering all EU regulatory procedures, i.e. CP, MRP/DCP and NP in one document with:
  - Annex I (list of Extensions),
  - Annex II (list of grouping of variations)
  - Annex III (elements to be included in the various types of variation applications (Type IA/IA_{IN}, IB, II and Extension)

- Draft detailed guideline referred to in the Variation regulation covering the conditions for classifications of variations.

The “comitology documents” intended for consultation of all stakeholders give a very good overview of the entire process and we welcome the proposals of the Commission within the various items, although knowing that finalisation of the Variation regulation will depend on the outcome of the “co-decision” part (Extension of the legal basis of the scope of the Variation regulation also to cover purely national authorisations).

The Commission has asked stakeholders in their feedback on the “comitology documents” to focus on the Public consultation paper and the draft Variation regulation and on the preliminary draft detailed guideline with categorisation conditions. We understood that this last preliminary document will not be finalized with this public consultation phase, but afterwards, in parallel with the regulatory procedure for the adoption of the legal proposal reviewing the Variations Regulations.

EuropaBio has in this position paper given its comments to all the three “comitology documents” as follow:

1. Key items in the order given in the Public consultation paper, but also covering the parallel items in the draft Variation regulation. The positions are divided in what we support and concerns “of high importance” and “for considerations”.
2. Comments to the detailed preliminary draft guideline for conditions of categorisation of variations (text part and Enclosure 1 focusing on biologicals).
3. Comment template with all specific suggestions for improvements indicated under the below Items, but also additional ones following the structure of the Commission draft regulation (all in Enclosure 2).

III. Abbreviations used in this document

- AR Annual Report
- CA Competent Authority/ies
- ChE Chemical Entity/ies
- CP Centralised Procedure
- DCP Decentralised Procedure
- DP Drug Product
- DS Drug Substance
- EP European Parliament
- EPh European Pharmacopoeia
- HRT Hormone Replacement Therapy
- IN Immediate Notification
- M Month(s)
- MA Marketing Authorisation
- MAH Marketing Authorisation Holder
- MRP Mutual Recognition Procedure
- MS Member State
- Nos. Numbers
- NP National Procedures

VI. EuropaBio position on specific key items

Key Item 1: Purely national authorisations:

Medicinal products for human use derived from biotechnology and other high-technology processes must be approved via the centralised procedure at the EMEA. EuropaBio nonetheless would like to express its support for the parallel running of the consultation on the "co-decision" and the "comitology" processes enabling improvements of the variation regulation system in EU in a timely and efficient manner. Further EuropaBio is thankful for a draft legal proposal that already includes the legislative provisions concerning variations to purely national authorizations to enable having the whole picture of the entire regulatory framework within one document from an early stage.

Key Item 2: ICH:

EuropaBio supports the introduction of the 'Design Space' as a basis for a less prescriptive, more flexible regulatory approach, whereby changes within an approved 'Design Space' would not be considered to require any variation application. Further we acknowledge the fact that discussions around 'Design Space' are still ongoing at the level of the International Conference on Harmonisation (ICH) Q8 and any further proposals will have to be considered in the light of its latest developments.

We understand that the approval of a new or a not purely administrative updated 'Design Space' requires a Type II variation before it can be implemented in accordance with ICH Q8 (new variation item Nos. 5 and 6 in the detailed guideline).

Related to these aspects EuropaBio proposes the following improvements as high importance

- Use latest knowledge of biological compared to Chemical Entity (ChE) products (Enclosure 1)
- Minor change to an approved Design Space protocol of purely administrative nature and not on critical parameters should be handled as a Type IB and not a Type II variation

Key Item 3: "Do ands Tell" procedure (Type IA and Type IA_{IN}):

Regarding those changes that have a genuine impact on quality, safety or efficacy of a medicinal product EuropaBio supports in particular:

- The concept of the Type IA and Type IA_{IN}, i.e. implementation can take place before notifying the Competent Authority (CA) and notification in an Annual Report (AR) can take place within 12 months (M) of implementation;
- The concrete proposal of downgrading several current variation items from category IA or IB to IA_{IN} and from category IB to IA in the draft detailed guideline;
- Possibility of grouping within Type IA and Type IA_{IN}, respectively and across these for one or more MAs to the same CA, at the same time and by the same applicant (one notification) as long as the 12 M deadline is respected

For further improvement of the procedure EuropaBio proposes the following next important steps:

- Development of detailed guidance for clarification on how to group variations. Currently it is not always clear on how to group e.g. in regard to handling of e-CTD with different version numbers
- Although the impact of fees handling is out of the scope of this regulation we consider industry as important stakeholder in the review of the system that should also be consulted before finalisation
- Reviewed fees should not be higher than within the existing variation system

Further EuropaBio proposes as for consideration to include into the scope of grouping also products from one MAH that are registered via purely national procedures in some Member States (MSs) and MRP in other MSs.

Key Item 4: "Worksharing":

EuropaBio supports the "Worksharing procedure" among CAs with the EMEA as body in charge of the evaluation to ensure that all MSs are properly involved and to facilitate pooling of expertise. The request for "Worksharing" is optional and the MAH decides if taken place.

Further EuropaBio supports the following aspects with regard to "Worksharing":

- Applicable to Type IB, II and Extension
- Grouping possibilities across categorisations and across MAs – assessment after highest risk category
- MAH can request an EMEA assessment (within 60 days) causing downgrading at national levels, i.e. IB to IA_{IN} and Extension or Type II to Type IB
- Procedure description in case of "Worksharing"

EuropaBio propose as high importance:

- EMEA assessment recommendations should be binding for all CAs
- EMEA assessment recommendation for Type IB variations to be issued in 30 and not 60 days
- If applicant disagrees to EMEA assessment a formal procedure of objection to be established in a guidance (applicant to object within max 15 days from EMEA assessment)
- Maximum time for clock-stop in case of CA requested information to Type II variations/"Worksharing" to be indicated
- Guidance needed for applicants on concrete steps after receiving a positive or a negative recommendation. For NP one CA should take the lead
- Entire timelines should not be increased
- For an upgrading from Type IB to Type II see comments provided below (key item 5)

EuropaBio propose for consideration:

- Scope also to include products from same MAH approved in some MSs through NP and MRP or DCP in other MSs
- Ensure that the EMEA has sufficient resources for taking on this additional task
- Fees should not be higher than within the existing variation system

Key Item 5: Type IB (Tell, wait 30 days and do if no objections) **by default:**

EuropaBio supports the approach taking in the consultation paper that:

- Variations which are not explicitly recognised as Type IA, II or Extensions and do not have a substantial potential to have a negative impact on Quality, Safety and Efficacy are handled, by default, as Type IB variations (and no longer as Type II)
- To define foreseen Type IB changes including conditions to be fulfilled in a detailed guideline
- Timelines of clock stop (30 days) and repeat of 30 days if answers to questions requested and additional 30 days for CA counted from receipt of the answer (max 90 days)

- **In addition EuropaBio proposes the following as high importance:**

- The current draft regulation foresees a resubmission in case of an unforeseen Type IB variation is reclassified as a Type II variation. This procedure is not in line with the "Switch" as described in Figure 4 of the Consultation Paper, and would entail significant delays and possibly duplicate fee payments for the applicant. Therefore, we propose that a true "Switch" within the procedures should be foreseen. This could be achieved by not requesting a new submission but rather having the procedure continued as a Type II variation after day 30.
- For an upgrading from Type IB to Type II guidance is needed if additional information has to be provided to the EMEA/CA to enable efficient adaptation of the procedure without major delays. We propose that additional documentation, such as quality or clinical overviews, can be submitted as response to a request for additional information.
- EMEA recommended classification should take place within 30 days and not 60 days as stated
- Timelines for validation period for (CP), MRP, DCP or NP to be kept at two weeks if no objections and not possible to extend by CA case by case depending of their workload (as currently taken place in practise).
- If a CA classifies a change more restrictive than the submitted application e.g. as Type II instead of a Type IB, the impact on timelines to reduce "lost time" should be minimized in collaboration of applicant/CA.
- If a CA cannot accept the application/does not agree with the proposed classification, the CA has to justify their decision on grounds stated in the regulation related to a potential serious risk to public health concern as defined by the Commission guideline 2006/C 133/05 document.
- If an applicant disagrees with the EMEA assessment a formal procedure of objection should be established in a guidance (applicant to object within max 15 days from EMEA assessment).

Other proposals

EuropaBio overall supports the following additional proposals:

- Harmonized definitions in Art 3 of the draft regulation for all procedures
- Replace the current legal Annexes by a detailed guideline on the conditions for classification of variations (except Annex 1: List of Extensions).
- The opportunity to include EMEA for centralised scientific assessment/opinion of classifications (proposed 30 days and not 60 days) or assessment of Type IB, II and Extension applications (60 days).
- For Type II changes a timeline to be divided in 30 days (urgency matters), 60 days, and 90 days (new therapeutic indication).

EuropaBio propose as high importance:

- To downgrade certain changes to biological products to be handled like changes to Chemical Entities (ChE) if different handling is not scientifically justified (Enclosure 1).
- To change in Annex 1, Extensions, Item 2, c (new strength) d (new form) or e (new route of administration) to follow an abbreviated 90 days procedure similar to Type II variations, but handled as an Extension with new MA No., as an assessment of these changes is not foreseen to be greater than the assessment of a new or updated indication, which are classified as Type II variations following a 90 days procedure. The following conditions must be fulfilled:
    - No change in bioavailability or pharmacokinetic (PK) (new form or route of administration) and
    - Linear dose-PK-response in investigated dose range (additional strength).
- Impact of implementation of a Type IB or Type II variation (except Paediatrics indications and extensions) compared to CA amending the MA within 6 months is unclear.
- Further clarification is needed on why the implementation of an Extension can take up to 6 months versus an entire new application which can be implemented immediately after the approval
- Implementation of Type IB or II variations dealing exclusively with quality changes but with no SPC, PI or labelling impact should be possible independent of procedure when a positive opinion or agreement has been obtained
- The definition of major variation/Type II should be adjusted as changes which have a substantial impact on quality, safety and efficacy, e.g. the introduction of a new indication can not be considered as having a **negative** impact
- Request for any additional information during a Type II should not increase the entire foreseen timelines
- Technical changes that only require assessment through inspections without significant change in the dossier should be classified as IB and not Type II variations
- EMEA recommended classification should take place within 30 days and not 60 days as stated
- EMEA classification must be binding for all CAs
- If applicant disagrees with EMEA classification a formal procedure of objection to be established in a guidance (applicant to object within max 15 days from EMEA classification).
- Timelines for validation period of EMEA as well as the MRP, DCP or NP validation period to be kept at two weeks and not possible to extend by CA case by case depending of their workload.

EuropaBio proposes the following for considerations:

- EMEA should annually publish the list of examples of EMEA recommendations for variations with substantial potential (negative) impact on Quality, Safety and Efficacy.
- Allow for a new medicinal product, which is going through an extension application, to add a modifier/additional term to the name indicating the respective modification
- Add headings to Annex II and Annex III like heading of Annex I describing the content, e.g. Annex II: *Examples* of grouping of variations; Annex III: Elements to be included in the various types of variation applications
- Annex II: Not to be a complete list but examples. Applicant to justify if other types of grouping are chosen
- The detailed guideline to categorise the variation classification numbers should be reordered in a more logical way, e.g. DS, DP and misc. items.

EuropaBio has the following additional proposals

Regulatory agreement:

EuropaBio proposes as high importance a regulatory agreement that covers low risk quality changes other than related to 'Design Space' or/and the production process and that:

- Is justified by applicant and approved by CA
- Maintains the high level of Quality with no impact on Efficacy and Safety
- Reduces overall administrative workload for authorities and companies
- Is part of a MA or a Type II variation after MA
- Changes to an approved Regulatory Agreement are handled either as a Type IB (minor administrative changes) or Type II (major changes) variations
- Examples in the Regulatory Agreement depend on outcome of regulatory flexibility (what is up for review and what is for inspection)

If the concept of a Regulatory Agreement is not introduced as such, we suggest adding the following examples to a detailed guideline for changes similar to the 'Design Space' Numbers instead

Examples of a Regulatory agreement:

A. Compliance commitments:

Use the CP template for the Letter of undertaking to what agreed upon within each case and to be used for all procedures, i.e. not only CP, but also MRP, DCP and NP e.g. extension of shelf life fulfilling compliance conditions.

http://www.emea.europa.eu/htms/human/postguidance/Form%20letter%20of%20undertaking.doc

B. Pre-approval/Comparability protocols:

- Reduce workload by reviewing and approving the original data for the change and acceptance criteria only once in a pre-approved protocol without compromising quality, safety and efficacy
- Pre-approved protocols describe the change(s) prospectively and
  - a.) Specify the studies and tests that will be performed
  - b.) Include analytical procedures that will be used and
  - c.) State acceptance criteria that will be achieved to demonstrate that a certain quality related change does not adversely affect the product regarding Quality, Efficacy and Safety
- Must differentiate what is within (binding details) and what is outside (supportive details) the Regulatory Agreement
- Ensure sufficient supply to the market with no delays and increase applicant supply flexibility

Current examples of Pre-approval/Comparability protocols which EMEA has approved case by case covering a range of products within the same product family (e.g. different strengths and administrative forms):

- Changes within an approved protocol do not need to be submitted as variations each time, but Documentation can be obtained through inspection or if not through an Annual Reporting Principle in accordance with the approved protocol, e.g.:
  - Changes between different approved manufacturing sites,
  - Changes between different approved analytical sites
  - Changes within an approved batch size range
- Changes where a Pre-approval/Comparability protocol is not appropriate:
  - For a manufacturing site where a cGMP inspection is warranted
  - Changes requiring clinical or non-clinical data
  - Changes of specifications
  - Non-specified plans for Chemical and Manufacturing changes

Enclosure 1

Treatment of biological compared to Chemical Entity (ChE) products.

EuropaBio supports the downgrade of certain changes to biological products to be handled like changes to Chemical Entities (ChE) for Nos. 12, 13, 17, 19, 20, 37, 38, and 42.

Below EuropaBio position on biologicals that are handled differently from ChEs: current situation, EuropaBio suggestion and justification

Change No.	Commission classification	EuropaBio classification	Justification for EuropaBio classification
7. DP: Replacement or addition of a manuf. site for part or all of the manufacturing process of the DP b. Primary packaging site: b.2 Semisolid pharmaceutical forms , b.3 Liquid pharmaceutical forms (e.g. suspensions, emulsions) c. All other manuf. operations except batch release	 II II	Condition 3 sterile and 5. biologicals to be deleted from b.2 and b.3. . b.2: Semisolid or solution pharmaceutical forms: IB (as ChE) b.3 Liquid pharmaceutical forms (e.g. suspensions, emulsions): IB (as ChE)	Required documents available on GMP inspections The only way to increase flexibility here may be to add conditions for sterile and biologicals e.g. more batch data and that the site must be GMP certified to manufacture sterile products so that dossier information is less significant.
New change: Add new Type IB (30 days) for replacement or addition of manufacturing site for drug substance	-	IB	Conditions: Protocol for adding a new site has previously been approved by the Competent Authority by Type II variation or in the original dossier. The data is then presented as a Type 1A. This saves 3-4 M and is similar to the US situation where a protocol is submitted and approved and the company is able to proceed with the site transfer.

Change No.	Commission classification	EuropaBio classification	Justification for EuropaBio classification
8. DP: Change in batch release arrangements and quality control testing of DP a. Replace/add. of batch control site b. Replacement/add of manufacturer resp. batch release 1. Excl. batch control test 2. Incl. batch control test	 IB (ChE= IA) IA_{IN} (=ChE) IB (ChE= IA_{IN})	 As commission As commission As commission	 Biological handled different from ChE for 8a, b2. and similar for 8b.1 in accordance with proposal from Commission -
10. Minor change in the manufacturing process of the DS DP a biological	II (ChE=IB)	IB (as ChE) or II	Some IB or II depend. on product (product complexity and related to type of change. <u>Example Biol.DS: Type IB and II incl. conditions for IB or II:</u> Examples will be delivered if requested by the Commission *Examples of IB:* 1. Exchange of some less critical culture components (like salts) with equivalent materials (like Na3PO4 to Na2HPO4) (if no change in cell growth characteristics and in process controls); 2. Addition of duplicate unit process, like extra columns (if no change in process parameters). *Example of Type II:* Use of alternative sugar carbon source in cell culture.
11. Change in batch size of DS or intermediate. DP a biological	II (ChE=IA≦ 10 & IB>10)	Certain IB otherwise II (fermenting).	Some Type IB or II depending on product (product complexity and related to type of change. *Example biol.DS: Type IB and II incl. conditions for IB or II:* *Example of IB:* Double batch size in same

Change No.	Commission classification	EuropaBio classification	Justification for EuropaBio classification
			equipment: IB , *Example of II:* Double batch size in different equipment. *Example for biol. intermediate: IB and II incl. conditions for IB or II:* *Example of IB*: Increase in batch size of intermediate as consequence of duplication of preceding process *Example of II:* Increase in batch size of intermediate as consequence of doubling of capacity of individual fermentation tanks and downstream processes
13. Change in the test procedure for DS, starting matr., intermediate or reagents used in the manuf. of DS	IB (as ChE)	As ChE; IB Condition 5 to 13.a and 13.b to be deleted. IA, if EPh compliance	No difference biological/ChE, but if EPh compliance, assessment already taken place then downgrade to IA)
14. Change in the manufacturer of DS, starting matr., intermediate or reagents used in the manuf. of DS	II (ChE=IB)	II except non-biological reagents: IB cond.4 “not a biological” to be deleted if only change of non-biolog. reagents.	Reagents are accepted by MAH based on specifications. If condition 1. applies: IB even for biological reagent. Condition 2 should not trigger a Type II variation, when adequate documentation available for new assessment of viral and TSE safety – therefore reword condition 2
18. Replacement of an excipient with a comparable excipient DP a biological	II	As ChE: IA: no SPC change IB: SPC change	Change of a non-biological excipient to another non-biological excipient as e.g. glycerol 85 to glycerol 100.
20. Change on test procedure for an excipient	IA/IB	As commission, but for 20 a condition. 5 re. Biol. to be deleted	
29. Change in the qualitative and/or quantitative composition of the immediate pack. material		As ChE:	Examples will be delivered if requested by the Commission

Change No.	Commission classification	EuropaBio classification	Justification for EuropaBio classification
a. Semi-solid and liquid b. All other pharm forms	II II	IB IA_{IN}	Suggest add conditions 2, 3, 4 to the response.
32. Change in batch size of DP a Up to 10 fold b. Down to 10-fold c Other situations DP a biological	 II II II	As ChE: IA IA IB	Examples will be delivered if requested by the Commission Change can be implemented as Type I if validated according to a protocol. Simple steps are applied: DS thaw, dilute, mix, sterile filtered and fill and test. Justification is that this involves sterile formulation and filling – it is the process and facility that is important and not the scale. The site (same) is inspected over 2-3 years.
33. Minor change in the manufacture of the DP	II	IA (as ChE)	Examples will be delivered if requested by the Commission Current conditions allow for minor changes in manufacture of a sterile product provided Sterile General Chapter Ph.Eur. is followed. Examples include a change in order excipients added to formulation buffer, new mixing time or speed providing it has been validated.
36. Change in shape or dimension of the container or closure a. Sterile pharm. form or biological DP.	IB (biological add. data)	IB (biological no add. data)	Examples will be delivered if requested by the Commission
38. Change in test procedure of the finished product	IA/IB .	As commission. but for 38a cond. 5 re. Biol. to be deleted.	
Additional No.: Adoption of EU core SPC, e.g. HRT Not part of Commission proposal of New Nos. 7 and 8.	-	IB	Examples will be delivered if requested by the Commission

Change No.	Commission classification	EuropaBio classification	Justification for EuropaBio classification
Additional No: Minor administrative/GMP facility update.		For already approved products due to an approval of a new product to be produced in that facility: IA (all)	For an approved multi-purpose factory: In case of GMP related update and not product related update a Type IA notification can be used. *Examples:* * Introduction of new product(s) into a facility already approved for multi-purpose manufacture (DP) IA for DS if no change in approved and validated cleaning and changeover procedures and no additional containments required * Moving of activities leading to change of floor plans in Facility document 3.A.1 Reallocation of analytical tests within site. Addition of equipment (e.g. freezer) not leading to a change in manufacturing procedure.
Add. No.: *Administrative update of Module 3*	-	IA_{IN}	As Commission proposal for New No. 7. Condition: the change is purely administrative nature and does not require to be substantiated by any sort of scientific data e.g. change in equipment.
Add. No. *Annex I, Item 2, c, d, e*	-	Annex 1, Extensions, Item 2. c (new strength) d (new form) or e (new route of administration) to follow a 90 D procedure as Type *variation, bu obtaining a*	Assessments of these changes are not foreseen to be greater than assessment of a new or updated indication, which require a 90 days Type II procedure. The timetable could be less than 210 days as currently applies for new strengths, new pharmaceutical form and new routes of administration.

Change No.	Commission classification	EuropaBio classification	Justification for EuropaBio classification
		new MA, if following conditions are fulfilled: : (PK) (new form or route of administration) and - linear dose-PK-response in investigated dose range (additional strength).	These can be assessed in 90 days. The following conditions must be fulfilled: - no change in bioavailability, pharmacokinetics or linear dose-response in investigated dose range (additional strength). *Examples:* * A new device or a new strength in an unchanged device and a within linear dose-response area for a parenteral disposable dosage form fulfilling above conditions.

ENCLOSURE 2

EUROPEAN COMMISSION PUBLIC CONSULTATION
ON THE COMITOLOGY PART OF THE REVISION OF THE VARIATIONS REGULATIONS
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GENERAL COMMENTS
The move towards simplified processes, grouping, Worksharing, submission of changes with no impact on efficacy, safety or quality by an annual report mechanism, etc is greatly appreciated and the majority of the changes are well thought-out and transparently presented. Notwithstanding these congratulations, there are a few points which we feel require further attention and/or a rethinking on details. In particular, we are concerned that ▪ Biologicals have not been downgraded to the extent of latest well-known knowledge. ▪ The new variation regulations system could potentially improve the current regulatory framework and well–established administrative practices whereby sponsors have the right to file an application for a new MA instead of applying for a variation or an extension of an existing authorisation. ▪ A Regulatory Agreement should be included covering e.g. pre-approval/comparability protocols and compliance commitments ▪ Simple Extensions with no change of bioavailability and PK should be handled as a 90 and not 210 D procedure as the assessment work load is not foreseen to be greater than (entire) new indications which are handled as a (Type II) 90 D procedure). ▪ The principles and processes of work sharing are inadequately described. Also, some of the proposed timelines are unnecessarily lengthy and will lead to further delays compared to the situation of today. These points are addressed more fully in the EuropaBio position paper and in the comments below. ▪ The EMEA (the Agency) is involved in the scientific recommendation for a classification of a variation (Art 5) and in the work sharing procedure (Art 24). ▪ A close collaboration of national CA and EMEA regarding fee setting is needed in order not to increase the fees compared to the current system.
The scope of the legislation apart from products registered via centralised, mutual recognition or purely national procedures, should also cover those products of one MAH approved through NP in some MSs and through MRP or DCP in other MSs.
It has to be acknowledged that the EMEA will face a big workload. Therefore, the agency needs to clarify if it has sufficient resources within current setup before the variation regulation is finalised.

Page, Section title, article	**Relative Importance**	**COMMENT AND RATIONALE**	**PROPOSED CHANGES**
Variation regulation, page 2, recitals, starting by "*Having regard to….*"	High	It is necessary to add to the recitals of the proposed variations regulations a new recital, which would have similar wordings that recital 6 of Regulation 1085/2003 and/or recital 8 of Regulation 1084/2003, in order to clarify that the EU variations regulations system does not prevent a sponsor from filing an application for marketing authorisation, instead of applying for a variation or an extension of an existing authorisation.	Add a new recital in the Regulations on variations which would read as follows: **"It is necessary to clarify the definition of a variation to the terms of a marketing authorization and to specify the changes to a marketing authorisation leading to an extension application, although it should still be possible to submit a separate, full application for a marketing authorisation for a medicinal product which has already been authorised, but under a different name.**
p. 4, Article 3, point 6	high	Major variation of Type II means …, which has a substantial potential to have a negative impact on…. Not only those changes, which have a negative impact but also positive impact (e.g. new indication) will be classified as Type II variations.	Change sentence to: Major variation of Type II means …, which has a substantial potential to have an ~~**negative**~~ impact on…. In addition the detailed guideline on Type II variations should define "substantial potential"
p.5, Article 4, point 2	medium	It is **highly** appreciated that changes unforeseen by the guideline may be submitted as Type IB by default, and it would be expected that the majority of unforeseen changes would fall into this category. In addition we welcome the increased flexibility achieved by the replacement of the current Annex 1 by a guideline. A switch to Type II, if deemed necessary, would invoke an added dimension of complexity involving further activity (submission of extra fees, update of Expert Report/Summaries etc), and it is unclear at this stage how this would be handled. In order to avoid this added complexity and potential	….shall be considered a minor variation of Type IB, **unless the applicant judges the change to meet the criteria of Type II and chooses to submit it as such**.

		delay arising unnecessarily owing to submission as IB of changes which are expected to be judged to have a substantial potential for impact (perhaps because of the nature of the product, or previous history), we suggest that the applicant may himself decide to classify a change as Type II and submit is as such.	
p.5, Article 5.1, 1st paragraph	high	The facility to obtain an agency opinion on the classification of a change unforeseen by the guideline is a welcome option and is an excellent route for bringing a change initially unforeseen, but likely to recur in the future, into the public domain in a consistent fashion. We propose that a holder wishing to approach the Agency with an unforeseen change would *propose* a classification for confirmation, rather than make a neutral request for a judgement.	Add the following text: … potential impact on the quality, safety or efficacy of the referred variation on the medicinal products concerned. **The marketing authorisation holder may also request the Agency to confirm a classification of a variation proposed by the holder.** The Agency shall deliver this recommendation **or confirmation within 30 day….**
p.5, Article 5.1, 1st paragraph	high	To strengthen the opinion made by the agency on the classification of the variation as well as to prevent a prolongation of the overall timelines (comprised by scientific recommendation plus assessment of the variation) the opinion shall be considered binding to the NCA.	Add the following text: Prior to submission of a variation whose classification is not laid …. A holder may request the Agency to provide a scientific recommendation …. on the medicinal products concerned, **which is binding to the national competent authorities.**
p. 5, Article 5.1, 2nd paragraph	high	Having in mind that the assessment of minor variations and many type II variations need 60 days or less, 60 days for delivering a recommendation on the type of the variation appears to be excessively long.	The agency shall deliver this recommendation within **3**0 days following receipt of the request,…
p. 5, Article 5.1, new additional 2nd paragraph	medium	The recommendation delivered in accordance with the first subparagraph shall be sent to the holder and to the competent authorities of all Member States. In case the applicant does not agree with the recommendation, there should be a formal process to object in order to achieve a revision.	Add the following text: Prior to submission of a variation … on the medicinal products concerned. **The Agency shall provide the applicant with the draft recommendation on the request of the applicant referred to in paragraph 1. If the applicant does not**

			object within 15 days after receiving the draft recommendation, the recommendation shall be considered final. The Agency shall deliver this final recommendation ….
p. 7, Article 8.1b and p. 10, Article 12.1	For considerati on	Grouping of variations: detailed guidance needed incl. if product approved through different procedures as e.g. NP and MRP. Fees, format and other handling to be specified in guidance.	Guidance is needed for the steps to be taken to group variations as well as concerning fees, format and other handlings of grouping.
p 7, Art 9.2, 2nd paragraph p 8, Art 10.2, 2nd paragraph p 9, Art 11.2, 2nd paragraph p 10, Art 13.2, 2nd paragraph p 11, Art 14.2, 2nd paragraph p 12, Art 15.2, 2nd paragraph p 14, Art 18.2, 2nd paragraph p 15, Art 19.2, 2nd paragraph p 16, Art 20.2, 2nd paragraph	high	There should be a timeline for the validation of a variation ("acknowledge receipt of a valid notification") of 14 days in order to allow a timely start of the procedure.	For Art. 9 and 10: If the notification fulfils the requirement laid down in the first subparagraph the relevant authority shall acknowledge receipt of a valid notification **within 14 days**. For Art. 11: If the notification fulfils the requirement laid down in the first subparagraph the relevant authority shall acknowledge receipt of a valid notification **within 14 days** and inform the holder… For Art. 13: If the notification fulfils the requirement laid down in the first subparagraph the competent authority of the reference Member State shall acknowledge receipt of a valid notification **within 14 days**. For Art 14 and 15: If the notification fulfils the requirement laid down in the first subparagraph the competent authority of the reference Member State shall acknowledge receipt of a valid notification **within 14 days** and inform the holder… For Art 18 and 19: If the notification fulfils the requirement laid down in the first subparagraph the Agency shall acknowledge receipt of a valid notification **within 14 days**.

			For Art 20: If the notification fulfils the requirement laid down in the first subparagraph the Agency shall acknowledge receipt of a valid notification **within 14 days** and inform the holder…
p. 8, Article 9.5 p. 11, Article 13.5 p. 15, Article 18.5	High	When the reference Member State comes to the conclusion that the classification of the variation needs to be changed from Type IB to Type II a) this should be only possible if there is a defined reason, such as a potential serious risk to public health connected with the variation in question as defined by the Commission guideline 2006/C 133/05 b) it shall be clarified in a guidance what additional documentation will be required for the upgraded variation and timelines for its submission need to be defined. We propose that a new submission should not be made and the procedure should continue as a Type II variation after Day 30. It should be foreseen that additional documentation, such as quality or clinical overviews, can be submitted as response to a request for additional information within foreseen timelines. c) The assessment time for upgrading the variation type from IB to II should be taken into account in the overall assessment timeline in order not to prolong the entire process compared to the current procedures.	Add the following text to Article 9.5, 13.5 and 18.5: ..., the variation shall be evaluated in accordance with the procedure laid down in paragraphs **3** to 6 of Article 10/14/19 **after notifying the applicant**. **A guideline will specify, in agreement with the Commission guidance on the Definition of a potential serious risk to public health, the grounds on which a re-classification of a Type IB variation to a Type II variation is justified.** **If, consequential to the decision of the Member State/RMS/Agency, additional information is required to be submitted by the holder, it shall be provided as a response to a request for supplementary information.**
p. 8, Article 10.4 and page 12, Article 14.4 and p. 15, Article 19.4	High	A suspension of the procedure is foreseen in case of questions. However, it is not mentioned how long this clock stop may be. A definition of a window for questions and a time frame for the clock stop period is necessary similar to as it is now in the current system. In national, MRP/DCP and CP Type II	Add the following text: ... the procedure shall be suspended until such supplementary information has been provided. In this case the period laid down in paragraph 3 may be extended ~~for a further period to be determined by the~~

		procedures it is foreseen that the CA may request for additional documentation at any time during the 60 days period.	~~relevant authority~~ **by maximum 60 days.**
p. 10, Article 13.2, new third paragraph	high	In case the applicant does not agree with the recommendation, there should be a formal process to object in order to achieve a revision.	Add the following text: **The reference Member State shall provide the applicant with the draft opinion on the application referred to in paragraph 2. If the applicant does not object within 15 days after receiving the draft opinion, the opinion shall be considered final.**
p. 10, Article 13.3	low	If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph 13,	If within 30 days following the acknowledgement of receipt of a valid notification referred to in paragraph **2**,
p. 10, Article 13.4	low	Where the competent authority of the reference Member State is of the opinion that the notification referred to in paragraph 13 cannot be accepted,	Where the competent authority of the reference Member State is of the opinion that the notification referred to in paragraph **2** cannot be accepted,
p. 13, Article 16.1	High	In case not all CAs support the conclusion of the RMS it should be foreseen to bring the matter to the CMD. An attempt should be made first to solve the issue between RMS and CMSs during the procedure before involving the CMD. In case of involvement of the CMD there is a need to define details and time lines of the procedure, which may be done as a reference to Article 29 of Directive 2001/83/EC.	Add the following text: … Within the coordination group, all Member States shall use their best endeavour to reach agreement on the action to be taken **according to the procedure and timelines laid down in Article 29 of Directive 2001/83/EC**.
p. 17, Article 21.1b	high	The amendment of marketing authorisations regarding the addition of a new paediatric indication via Type II variation should be amended within 30 days after sending the information referred in point (a) in order to enable the fast application for the 6-month SPC extension according to the paediatric regulation. Therefore, a new paragraph should be added.	Where necessary, the relevant authority shall amend the marketing authorisation in accordance with the accepted variation or notification: – within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification; - within 6 months after sending the information referred to in point (a) in the other cases. - **within 30 days after sending the information referred to in point (a) in case of major Variations**

			of Type II according to Article 8 of Regulation (EC) No 1901/2006.
p. 17/18, Article 21.2b	high	The amendment of marketing authorisations regarding the addition of a new paediatric indication via Type II variation should be amended within 30 days after sending the information referred in point (a) in order to enable the fast application for the 6-month SPC extension according to the paediatric regulation. Therefore, a new paragraph should be added.	Without prejudice to Article 16, each relevant authority shall, where necessary, amend the marketing authorisation in accordance with the accepted variation or notification: – within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification; - within 6 months after sending the information referred to in point (a) in the other cases. - **within 30 days after sending the information referred to in point (a) in case of major Variations of Type II according to Article 8 of Regulation (EC) No 1901/2006.**
p. 18, Article 21.3c	high	The amendment of marketing authorisations regarding the addition of a new paediatric indication via Type II variation should be amended within 30 days after sending the information referred in point (a) in order to enable the fast application for the 6-month SPC extension according to the paediatric regulation. Therefore, a new paragraph should be added	The amendment of the marketing authorisation referred to in point (b) shall be made: - within two months after sending the information referred to in point (a) in the case of minor variations of Type IA which do not require immediate notification; - within 6 months after sending the information referred to in point (a) in the other cases. - **- within 30 days after sending the information referred to in point (a) in case of major Variations of Type II according to Article 8 of Regulation (EC) No 1901/2006.**
P.19., Article 23 add new paragraph refer also to: p. 23, Annex I items 2 c, d, and e	medium	The assessment time for extensions (new strength, dosage form or route of administration) shall be reduced to 90 days under certain conditions, which are: • no change in bioavailability or pharmacokinetic (PK) (new dosage form or route of administration) • linear dose-PK-response in investigated dose ranged (additional strength)	Add the following text: **1.** An application for an extension of a marketing authorisation shall be evaluated **in accordance with the same procedure as for the granting of the marketing authorisation to which** it relates. **2. An Extension to a marketing authorisation should be assessed within 90 days, if the following conditions apply:**

			• **The Extension has no impact on bioavailability or pharmacokinetics of the product (in case of a new dosage form or route of administration).** • **The marketing authorisation is extended by an additional dosage strength, which demonstrates a linear dose-pharmacokinetic response within the used dose range.**
p. 19, Article 24.1	high	Where a minor variation of Type IB, a major variation of Type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations, the holder of such authorisations may follow the procedure laid down in paragraphs 2 to 6. Further clarification is needed.	Where a minor variation of Type IB, a major variation of Type II, an extension or a group of variations falling within one of the categories listed in Annex II relates to changes that concerns several marketing authorisations, the holder of such authorisations may follow the **'work sharing'** procedure laid down in paragraphs 2 to 6. **The work sharing applies in the following two cases:** **(a) where the change concerns one given medicinal product that is authorised at purely national level or a mixed registration status, i.e. registered via national and mutual recognition procedure in several Member States;** **(b) where the change is common to several, distinct medicinal products, which are registered via purely national, mutual recognition or decentralised or centralised procedures.**
p. 20, Article 24.3	high	An introduction of a fixed validation period is needed in order to ensure a timely start of the procedure.	Add the following text: The Agency shall **validate the application referred to in paragraph 2 within 14 days and shall** issue an opinion ….
p.20, Article 24.3	High	In the Consultation Paper a positive Agency opinion leads to a downgrading of the variation. This is in principle an acceptable approach, which should be included into the Regulation. However, the current timeline proposals would lead in most scenarios to delays in approval (60-day EMEA assessment plus resubmission by traditional route represents a doubling for Type IB and an increase from 60+ to 90+ days for a standard Type	Add the following text: 3. The Agency shall issue an opinion…. **(a) 30 days following receipt… Type IB** (b) 60 days…….. Type II (c) 210 days……. extensions

		II). In case (a), single product with "purely" national licences, the increased timelines are offset only by reduction in fees payable (assuming that an appropriate change to fee structures is achieved), the administrative workload not being reduced at all (EMEA submission in addition to individual CMS submissions). Real gains to offset the increased timelines are only to be seen in case (b), change affecting multiple products – assuming that the subsequent submission to CMS may also be made as a single application akin to the preceding EMEA submission. This last point should be clarified. It is suggested that a Type IB change can be assessed in 30 days, as is currently the case, which would somewhat reduce the "penalty" to industry.. A further reduction in workload for all concerned could be achieved if an Agency-approved Type IB could be downgraded to a Type IA without Immediate Notification as long as there were no aspect involved (e.g. a site change) which would otherwise fall into the "IN" category.	
p. 20, Article 24.6	high	Before a final opinion is reached the applicant should be informed about the draft opinion and should have the chance to formally object it in order to achieve a revision.	Add a new second paragraph: **The Agency shall provide the applicant with the draft opinion on the application referred to in paragraph 2. If the applicant does not object within 15 days after receiving the draft opinion, the opinion shall be considered final.** Where it reaches a final opinion on the application ….
p. 20, Article 24 new sub-paragraphs 8 and 9	high	The proposal for worksharing, with the enormous potential for efficiency gain, is laudable. The draft Regulation, however, *omits to address the immediate subsequent steps*, and additionally, some of the timelines are questionable.	Guidance needed for the next steps in case of a positive or negative opinion, respectively.

		a) Further guidance is needed on what are the next steps in the case the Agency issues a positive opinion. Will the closing procedure automatically be done by the relevant Competent Authorities or has the marketing authorisation holder to take the necessary next steps? b) It is unclear what steps need to be done in the case of a negative opinion. Does it mean that the product is non-approvable or can it just not be down-graded? Further clarification is needed.	The addition of the following text may clarify as well: **8. Where the EMEA assessment results in a positive opinion, this results in a downgrading of the classification of the change at the national level. Where the change affects one medicinal product authorised at a purely national level, the positive opinion downgrades a variation of Type IB or an Extension to a Type IA_{IN}. A variation of Type IB is downgraded to Type IA unless containing a component requiring immediate notification (IA_{IN}). Where the change is common to several distinct products the positive opinion downgrades a Type IB change to IA (unless containing a component requiring immediate notification (IA_{IN})), a Type II or an Extension to Type IB.** **9. The results of the EMEA assessment are considered binding for the relevant national competent authorities. The subsequent submission of the change to the relevant competent authority will be as a single application.**
p. 23, Annex I	high	Add text before "1. Changes to the active substances", according to the text of Annex II of the former Variation Regulations 1084/2003 and 1085/2003.	Annex I: Extensions of marketing authorizations **These changes, listed below, will be regarded as an 'Extension' application.** **The MA holder has the option to propose a new invented name consisting of the original name and an additional term .** Changes to the active substance(s): (a) replacement of a chemical active substance by a different slat/ester complex/derivative, with …. (b) replacement of a different isomer, a different ….
p. 24, Annex II	low	Annex II *The addition may make the purpose of this Annex clearer.*	Annex II: **Examples for grouping of variations**

p. 24, Annex II	high	It is not completely clear how to group different variations for one product, in particular in the case when a product is purely nationally registered in some member states and at the same time registered via mutual recognition procedure in some other member states.	Detailed guidance on grouping is needed.
p. 24, Annex II	medium	In the context of simplification and enhancement of flexibility, we suggest additional possibilities for grouping in certain cases: - Combination of points 8 and 9. - Combination of points 10 and 11.	The following points should be added: **14. All variations in the group are consequential to a given urgent safety restriction, which relate to the implementation of a given class labelling and submitted in accordance with paragraph 3 of Article 26.** **15. All variations in the group are consequential to the assessment of a given periodic safety update report as well as to a given post-authorisation study conducted under the supervision of the holder.**
p.24, Annex II	High	The opportunities for grouping of variations are welcomed. For changes to chemistry, manufacturing and controls, however, these opportunities are restricted to consequential variations or to changes within a process/quality improvement project. It should be clear that other changes made (as required by European Directives) in order to maintain processes and controls within "state of the art" can also be included, even if no measurable "improvement in quality" can be demonstrated, and other projects, for example site changes, should also be within scope as long as there is no deterioration in product quality.	6. All variations in the group relate to one of the following: • a project intended to improve or update manufacturing process, controls or quality • a project to transfer manufacture or controls to a new or additional site, where no negative change in quality or performance is demonstrated
p. 25, Annex III	low	Annex III The addition may make the purpose of this Annex clearer.	Annex III: **Elements to be included in the variation applications (Type IA, IB, II and Extension)**

p.25, Annex III, 1(d)	High	This item requires the date of implementation of Type IA variations to be given. This should be accepted in general terms, with sufficient flexibility that country-specific reports or lists need not be generated.	Point 1(d) needs to be modified as follows: (d) the **approximate** date of implementation for each variation described;
p. 27, Detailed guideline of categorisation	High	The latest knowledge regarding biologicals compared to chemical entities (CE) shall be applied and should lead to a similar handling of biological products. Nos. 7 Sterile and biol. conditions to be deleted 8 If EPh Eur compliance down graded for CE and Biol. to IA_{IN} 10. IB or II depending on product (product complexity and related to type of change. 11. IB or II 13. Condition 5 to 13.b to be deleted. if EPh compliance down graded for CE and Biol. to IA_{IN} 14. II except non-biological reagents. Condition 4 to be deleted. 18. As CE: IA: no SPC change; IB: SPC change 20. As commission, but for 20 a Cond. 5 re. Biol. to be deleted.. 29. As CE: IB/IA_{IN} 32. As CE: IA/IA/IB 33. IA (as CE) 36. IB (biological no add. data) 38. As commission. but for 38a cond. 5 re. Biol. to be deleted. Additional Nos. Adoption of EU core SPC, e.g. HRT Not part of Commission proposal of New Nos. 7 and 8. Minor facility update A (all)	Please refer to EuropaBio position paper for more details: 13b. If EPh compliance downgraded for CE and Biol. to IA_{IN}.

		e.g. approved multi-purpose factory with fulfilled cleaning and validation incl. a new development product (not covering DS where traces can cause safety problems as e.g. hormones and penicillin) Admin. update of Module 3: A (all) : Type IA_{IN}. Annex I, Item 2 c, d and e: downgraded to II The latest knowledge regarding biologicals compared to chemical entities (ChE) shall be applied and should lead to a similar handling of biological products.	Biol./ChE: Even classified Biol= ChE, not all related conditions adjusted accordingly
p. 27, detailed guideline additional proposal	high	Admin. Update of Module 3: Type IA_{IN}. Annex I Extensions No. 2c, d, e products. Include a regulatory agreement covering other issues than related to Design Space, (production process control), i.e. * Part of MA or a post-marketing approval and if changed a Type IB or Type II variation * Differentiate what is within (binding details) and what is outside (supportive details) * Depends on outcome of regulatory flexibility (what is up for review and what is for inspection) * E.g.: - Preapproval/Comparability protocols - Compliance commitments. Letter of undertaken template already used in CP to cover all procedures http://www.emea.europa.eu/htms/human/postguidance/Form%20letter%20of%20undertaking.doc	Regulatory agreement: Examples: * Preapproval/Comparability protocols: Optional, requested by the applicant and if not approved within an MA through a Type II variation. * Compliance commitments. Final to be agreed with CA in a “Letter of undertaken”