EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

PUBLIC CONSULTATION PAPER

BETTER REGULATION OF PHARMACEUTICALS:

TOWARDS A SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK ON VARIATIONS

Version: 24 October 2007

Deadline for Public Consultation: 4 January 2008

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

This document is to be read together with the Draft Commission Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (version: 24 October 2007).

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TABLE OF CONTENTS

1. ABOUT THE CONSULTATION

1.1. What is the purpose of this consultation?

The European Commission has announced its intention to make the regulatory framework on changes to medicinal products (the 'Variations Regulations') simpler, clearer and more flexible[1].

With this public consultation, the Commission intends to consult all stakeholders on a draft proposal to modify the content of the Variations Regulations. This draft proposal builds on previous discussions held with interested parties, in particular during the targeted consultation conducted in October-January 2007[2]. With this public consultation, the Commission is committed to ensure that all stakeholders can make their views known on this important issue.

1.2. Who is consulted?

Contributions are invited from all stakeholders dealing with medicines for human and/or veterinary use. Stakeholders who are not established within the European Union are equally invited to comment. Comments from Small and Medium-sized Enterprises (SMEs) involved in the pharmaceutical sector are especially welcomed.

1.3. How can I contribute?

Contributions should be sent by e-mail to nicolas.rossignol@ec.europa.eu, **before Friday 4 January 2008**. An acknowledgement of receipt will be issued for each contribution received, within five working days. Contributions will be made publicly available on the 'Pharmaceuticals' website of the Commission once the consultation period is over, unless a specific request for confidentiality is made, in which case only an indication of the contributor will be disclosed. If you do not wish your contribution to be made public, please clearly indicate so.

1.4. What will happen next?

All contributions will be carefully analysed. A summary of the outcome of the consultation will be published on the 'Pharmaceuticals' website of the European Commission and also sent directly to all contributors. Any future proposal on the revision of the Variations Regulations will build on this consultation and will outline how its outcome was taken into account.

1.5. Any questions?

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[1] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm
[2] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

2. INTRODUCTION

2.1. Background

Medicines are regulated throughout their entire lifetime. Changes subsequent to their placing on the EU market (*e.g.* change in the production process, change in the packaging, change in the address of the manufacturer etc.) are handled according to a specific Community legislative framework: the 'Variations Regulations'[3].

The handling of variations requires significant administrative and regulatory resources, both for competent authorities and for the industry. In 2006, the Commission announced its intention to make the Variations Regulations simpler, clearer and more flexible. This initiative is the main contribution of this Commission to the 'Better Regulation' policy agenda in the field of pharmaceuticals.

On 20 October 2006, the Commission released an Issue paper outlining key items for possible improvements of the regulatory framework on variations. This document, which is publicly available[4], was sent to all Member States, the European Medicines Agency, the Council of Europe's Directorate for the Quality of Medicines, as well as all major European industry associations. A series of workshops, roundtable and bilateral meetings with all interested parties was also held.

On the basis of the extensive comments provided by stakeholders on the Issue paper, a legal proposal for a revision of the Variations Regulations has been drafted. This Consultation paper describes the key policy items embedded in this draft proposal and outlines the reasoning behind. The draft legal proposal and this Consultation paper are therefore to be seen together, as one package. For the sake of clarity and consistency, the structure of this Consultation paper follows the one of the Issue paper released last year.

2.2. Structure of the proposal

The draft legal proposal is built as a single regulatory text, covering changes to all marketing authorisations (centralised, decentralised/mutual recognition, purely national).

A first draft detailed guideline on the conditions for classification of variations is also attached to the draft legal proposal (see Section 8.1). However, comments in the frame of this public consultation should be focused on the draft legal proposal rather than on the draft guideline, as this guideline will also be discussed after the period of public consultation (see Section 8.1).

An overview of the structure of the proposal is outlined in the Annex to this Consultation paper (see Section 9). A correlation table, outlining which Article(s) relate to what, is also provided.

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[3] Commission Regulation (EC) No 1084/2003, OJ L 159, 27.6.2003, p.1; Commission Regulation (EC) No 1085/2003 OJ L 159, 27.6.2003, p.24.

[4] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

3. KEY ITEM 1: PURELY NATIONAL AUTHORISATIONS

It has been proposed to amend the legal basis of the Variations Regulations in order to include purely national authorisations within the scope of the revised Variations legislative framework. Thus, all authorised medicinal products would be subject to the same rules for the approval and administrative handling of changes, regardless of the procedure under which those medicines have been authorised (purely national, mutual recognition/decentralised, centralised).

This suggestion has been welcomed by the vast majority of stakeholders. Because it requires a 'co-decision' proposal to amend the legal basis of the Variations Regulations, this key item has been dealt with separately. Public consultation on the topic has already been conducted and completed[5]. It is therefore not addressed in the present Consultation paper and draft legal proposal.

Some stakeholders have requested clarification on the timing and conduct of the two strands of the project ('co-decision' and 'comitology'). The intention is to proceed in three steps (Figure 1):

(1) Review of the content of the Variations Regulations ('comitology');

(2) Extension of the legal basis of the Variations Regulations ('co-decision');

(3) Update of the Variations Regulations to include the necessary provisions regarding purely national authorisations, once steps (1) and (2) have been completed ('comitology').

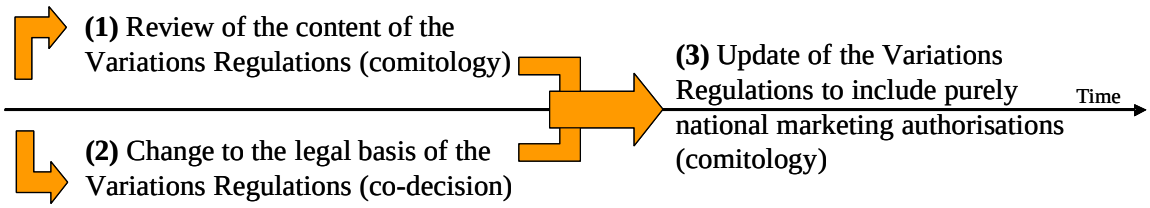

Figure 1: Review of the regulatory framework on variations: a 3-steps approach.

In order to save time, step (2) -which is expected to take the longest time- is carried out in parallel with step (1).

Formally, step (3) can be carried out only once steps (1) and (2) have been completed. Nevertheless, the draft legal proposal attached to this Consultation paper already includes the legislative provisions concerning variations to purely national authorisations (see in particular Chapter II of the draft proposal). Although these provisions will be formally adopted during step (3), this enables stakeholders to have the whole picture of the entire regulatory framework within one document, already at this stage.

Provisions to be adopted during step (3) only are highlighted in italics in the draft legal proposal.

[5] http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm

4. KEY ITEM 2: ICH

4.1. Design space

In the Issue paper released in October 2006, it was suggested to formally introduce in the Variations Regulations certain notions developed at the level of the International Conference on Harmonisation (ICH), namely the notion of 'design space'. The introduction of the 'design space' creates the 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.

The use of the 'design space' notion remains optional for the marketing authorisation holder. The design space is established and reviewed either (i) as part of the initial marketing authorisation application, or (ii) later, independently. Introduction of a new design space or changes to an approved design space is evaluated as a Type II variation.

In the light of stakeholders' comments, the initial proposal that changes within an approved design space should be notified through an annual reporting system has been dropped. Nevertheless, competent authorities still have the right to request, at anytime, data demonstrating that the risk-benefit balance for the concerned medicinal product remains favourable[6].

4.2. Continuous improvement of manufacture

Beyond the notion of 'design space', ICH developments -namely the Q8, Q9 and Q10 guidelines- introduce modern tools (risk management, quality systems) that could facilitate continuous improvement of the manufacture over the products' life cycle, while maintaining a state of control that ensures high standards of quality.

At the moment, ICH work on these tools is still ongoing. How to implement them, in practice, in the EU regulatory system may also not appear fully clear at this preliminary stage.

Nevertheless, continuous improvement of manufacture should be supported, *e.g.* by providing further flexibility to manufacturers who have undertaken the efforts to put in place modern quality tools.

It is therefore proposed to take the opportunity of the drafting of the detailed guideline referred to in Section 8.1 to discuss case-by-case with Member States, the EMEA and interested parties, where and how these ICH quality tools could be implemented (*e.g.* in which cases the fact that a manufacturer is in compliance with ICH Q9-Q10 could be sufficient to consider a given variation less risky for public or animal health and to validate it through a more flexible procedure).

The fact that the conditions for classification of variations would be laid down in a guideline (and not anymore in an Annex to the Variations Regulations) should also help to review implementation of these quality tools as regulatory experience with their application is gained, or in the light of new ICH developments.

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[6] Article 23 of Directive 2001/83/EC, Article 27(3) of Directive 2001/82/EC and Article 16(2) of Regulation (EC) No 726/2004. See also Article 27 of the draft legal proposal.

5. KEY ITEM 3: "DO AND TELL" PROCEDURE

In order to further reduce the overall number of variations procedures and to enable competent authorities to focus on those changes that have a genuine impact on quality, safety or efficacy, a "Do and Tell" procedure for Type IA variations is introduced. Such variations do not require any prior approval and can be implemented anytime *before* notifying the competent authorities.

Reporting of Type IA variations can be done:

– on the occasion of an annual report compiling all "Do and Tell" changes made in the last twelve months. If no such changes have been made, no annual report needs to be submitted;

– forthwith in the case of certain Type IA which, mainly for administrative reasons, require immediate notification to the authorities.

With this system, Type IA variations would hence fall within two categories: those subject to the annual reporting system, and those subject to immediate notification.

The proposal also enables the holder:

– to combine the submission of a Type IA variation requiring immediate notification with the submission of the annual report, provided the 12-months deadline is respected;

– to group several Type IA variations to the terms of one or several marketing authorisations, which are notified simultaneously to the same relevant authority, within one single notification (Figure 2).

It is important to note that the proposal does not impose any specific date for the annual reporting. The only constraint is that all annually-reportable Type IA variations are reported *within* 12 months. A holder may choose to submit the report at anytime during this period. This choice may be made in concertation with the relevant competent authority.

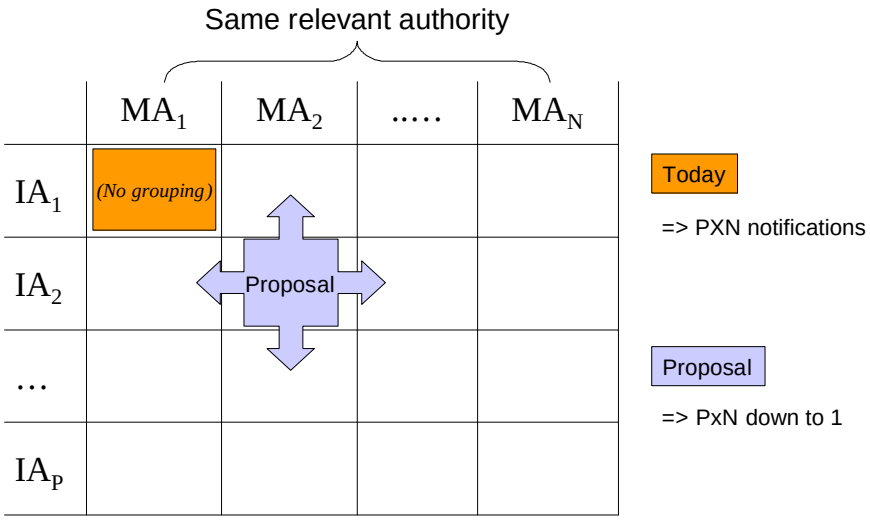

Figure 2: Annual reporting system for Type IA variations. IA_X refers to a Type IA variation X subject to annual reporting. MA_Y refers to a marketing authorisation Y affected by the variation(s).

As shown in Figure 2, the annual reporting system could reduce the number of notifications dramatically. For example, a company making 2 Type IA changes on average per year, affecting 6 products all authorised in 10 Member States at purely national level, has to submit 2*6*10=120 notifications (and wait for the approval of all notifications before actually implementing the changes) under the current system. With the "Do and Tell", annual reporting system, the number of notifications would be reduced up to 12-fold.

6. KEY ITEM 4: "WORKSHARING"

In the light of the comments received on the Issue paper, it is proposed to introduce a 'worksharing' procedure in the following two cases:

(a) where the change concerns one given medicinal product that is authorised at purely national level in several Member States;

(b) where the change is common to several, distinct medicinal products.

The procedure is optional; the choice is for the holder. It is applicable to variations of Type IB, Type II, line extensions and grouped variations (see Section 8.2).

A voluntary worksharing pilot project is already ongoing at the level of the European Medicines Agency (EMEA)[7]. The centralised evaluation of plasma master files has also proven to be successful in reducing the administrative burden and redundancy of evaluations. In the light of this positive experience, it is proposed that the body in charge of the evaluation under the 'worksharing' procedure is the EMEA. This should ensure that all Member States are properly involved, facilitate pooling of expertise, and keep the overall procedure simple.

The EMEA assessment results in a scientific opinion. If positive, this opinion triggers a 'downgrading' of the classification of the change (Figure 3):

- where the 'worksharing' relates to a change affecting one medicinal product authorised at purely national level (case (a) above), the positive opinion downgrades the variation to a Type IA (requiring immediate notification);
- in the other case (case (b) above), the positive opinion downgrades the variation:
  - from Type IB to IA (immediate notification);
  - from Type II or line extension to IB.

Hence, the benefits of this proposal do not come from a reduction of the number of variation procedures, but rather from the lightening of the procedures themselves, through downgrading.

It is important to stress that the 'worksharing' procedure does not affect the final responsibility of Member States competent authorities as regards medicinal products

[7] http://www.emea.europa.eu/Inspections/docs/12045706en.pdf

authorised at national level. It does not impose any sort of mutual recognition. However, the procedure is built in such a way that it should facilitate the decision making of the competent authorities. By minimising the redundancy of evaluations, the 'worksharing' procedure should also enable authorities to focus more resources on serious public or animal health-related issues.

It is recognised that evaluation of variations through the 'worksharing' procedure may entail a significant workload for the EMEA. Although details of the EMEA internal working procedures and organisation are beyond the scope of this legal proposal, it is important that the evaluation of 'worksharing' submissions is carried out in the most flexible way using existing working parties, advisory groups and other EMEA expert networks, so as to avoid overburdening the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Veterinary Medicinal Products (CVMP). The current EMEA fee structure would also need to be amended in order to introduce this new type of service.

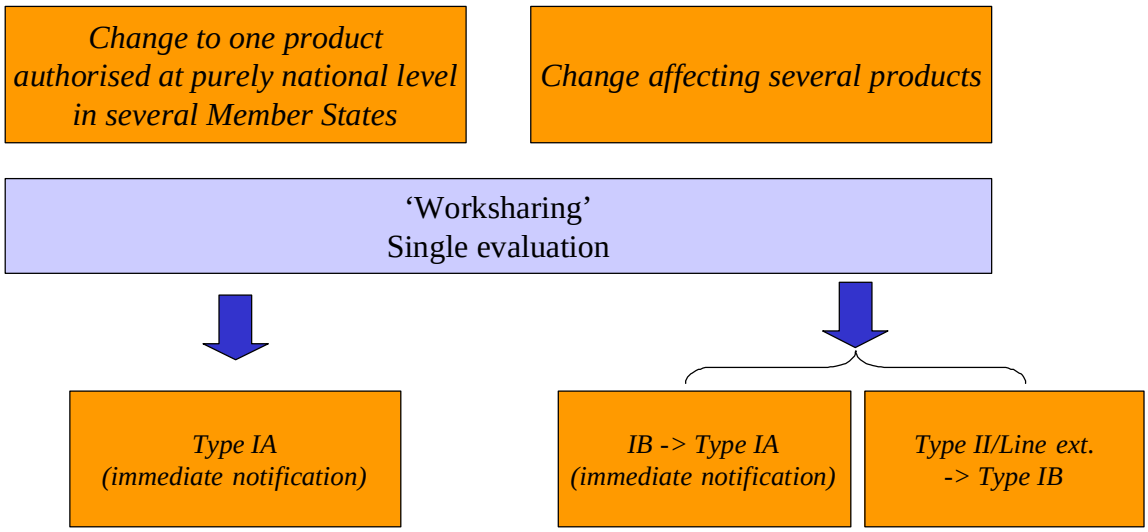

Figure 3: 'Worksharing' procedure.

7. KEY ITEM 5: TYPE IB BY DEFAULT

It is proposed that variations which are not explicitly recognised as Type IA, II or line extensions are handled, by default, as Type IB variations (and no longer as Type II).

A safeguard clause is however introduced: if, within the initial 30-days period of the Type IB procedure, the relevant competent authority considers that the variation has a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product concerned, the variation must be evaluated according to the Type II procedure (Figure 4).

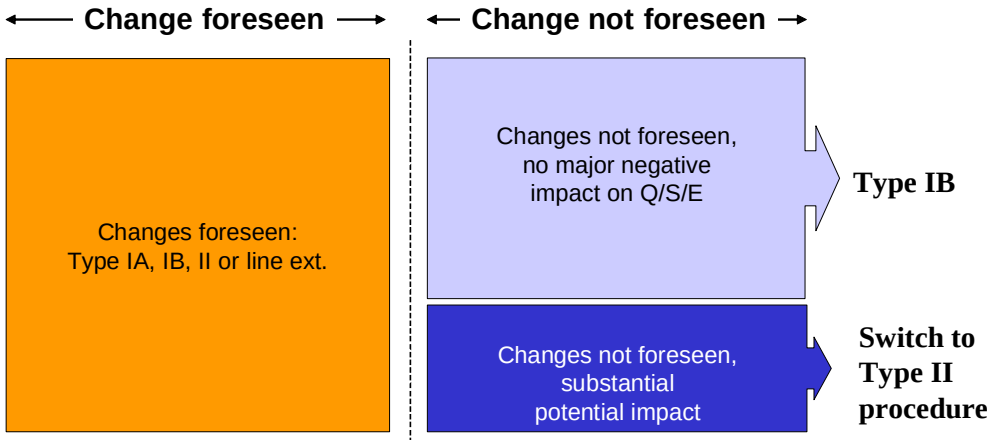

Figure 4: Type IB procedure by default, with safeguard clause.

In addition, where an unclassified variation is concerned, a new option is introduced for the marketing authorisation holder to request the EMEA to provide a scientific recommendation, with a view to determining the potential impact on the quality, safety or efficacy of the referred variation. Publication of these recommendations, after deletion of confidential information, should help to bring further predictability to the system.

8. OTHER PROPOSALS

8.1. Classification of variations

At the moment, variations conditions are listed in the Annexes to the Commission Regulations. In order to bring further flexibility, it is proposed:

– To introduce generic definitions of variations (Type IA, IB, II, line extensions) in the legal text;

– To replace the current Annexes by detailed guidelines on the conditions for classification of variations (except for line extensions), to be drawn up by the Commission in consultation with the Member States, the EMEA and interested parties;

– To introduce a mechanism of scientific recommendation regarding unclassified variations (see Section 7).

A first draft detailed guideline on the conditions for classification of variations is attached to the draft legal proposal. In the light of the comments received on the Issue paper, it appears reasonable to reclassify certain cases of changes affecting chemical and biological medicinal products, both in the human and veterinary sector, and to introduce new categories of changes.

The detailed guideline is of scientific and technical nature. Finalisation of this guideline requires gathering of all available expertise in the various fields concerned. The draft provided in the frame of this public consultation is therefore preliminary only and not definitive. It is only intended to be used as a starting point for technical discussions with Member States, the EMEA and interested parties. These discussions will take place not only during this public consultation phase, but also afterwards, in parallel with the regulatory procedure for the adoption of the legal proposal reviewing the Variations Regulations. The fact that the conditions for classification of variations would be laid down in a guideline (and not anymore in an Annex to the Variations Regulations) should also provide greater flexibility to swiftly review those conditions in the future.

8.2. Grouping variations

Today, variations cannot be grouped within one single submission unless they are all consequential to one given change. However, a number of stakeholders requested, during the consultation phase held in 2006-2007, to introduce the notion of grouped variations *i.e.* to allow several variations to be submitted together, at once.

On this basis, the draft proposal outlines a series of cases where grouping of variations could be allowed (see Annex II to the proposal). Those 'grouped variations' are evaluated in accordance with the procedure of the 'highest-risk' variation included in the group (Figure 5). Importantly, grouped variations are also eligible to the 'worksharing' procedure (see Section 6).

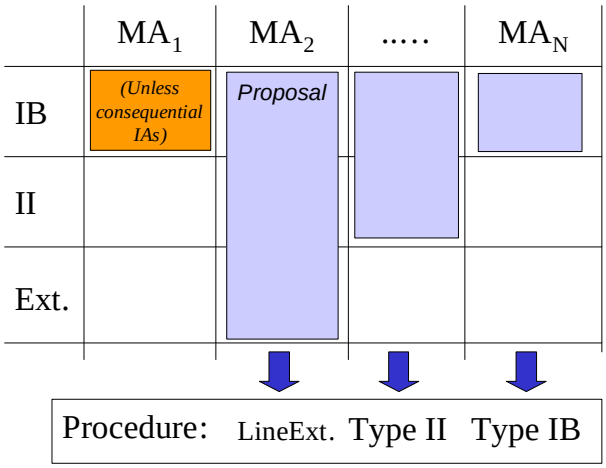

Figure 5: Grouping variations. MA_N refers to a marketing authorisation N affected by the variation(s).

8.3. Clarification of deadlines

An article is introduced to clarify when exactly a holder is allowed to implement a given variation.

Additionally, a fixed time period is established for competent authorities to amend, where necessary due to an approved variation, the terms of a marketing authorisation. A delay of six months is introduced (so-called 'sweep' mechanism), which provides further flexibility for authorities to group various amendments to the terms of the same marketing authorisation within one single decision.

9. ANNEX

Overview of the draft legal proposal

Chapter I General Provisions	**Chapter II** Purely National	**Chapter III** MRP	**Chapter IV** Centralised
Art. 1: Subject Matter Art. 2: Scope Art. 3: Definitions Art. 4: Classification Art. 5: Scientific recom. Art. 6: Guidelines Art. 7: Grouping	Art. 8: Type IA Art. 9: Type IB Art. 10: Type II Art. 11: Human flu	Art. 12: Type IA Art. 13: Type IB Art. 14: Type II Art. 15: Human flu Art. 16: coordination and arbitration	Art. 17: Type IA Art. 18: Type IB Art. 19: Type II Art. 20: Human flu

Chapter V Section 1 Closure & Implem.	**Chapter V** Section 2 Special procedures	**Chapter VI** Final provisions	**Annexes**
Art. 21: Closure of procedures Art. 22: Implementation by operators	Art. 23: Extensions Art. 24: Worksharing Art. 25: Pandemic flu Art. 26: USR	Art. 27: Monitoring Art. 28: Reporting Art. 29: Pending applic. Art. 30: Repeal Art. 31: Entry into force	Annex I: extensions Annex II: cases for grouping Annex III: documentation

Correlation Table

Topic	**Section in the Consultation paper**	**Article(s) of the draft legal proposal**
Key Item 1: application to purely national authorisations	Section 3	Addressed in a separate 'co-decision' proposal See Chapter II
Key Item 2: ICH	Section 4	No specific article; see the draft detailed guidelines on the conditions for classification of variations
Key Item 3: "Do and Tell" procedure	Section 5	Articles 8, 12 and 17. Point 1 of Annex III
Key Item 4: "Worksharing"	Section 6	Article 24
Key Item 5: Type IB by default	Section 7	Article 4. See also Article 9(5), 13(5) and 18(5)
Definitions and classifications of variations	Section 8.1	Articles 3 to 6. See also the draft detailed guideline attached to the draft legal proposal.
Clarification of deadlines	Section 8.3	Articles 21 and 22
Grouping variations	Section 8.2	Article 7 and Annex II