Better regulation of medicinal products: The new legal framework for variations

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Keywords
Variations regulations; European Commission; Competent authorities; Directive 2009/53/EC; Regulation (EC) No 1234/2008; ‘Do and Tell’ procedure

Abstract
The European Commission’s variations initiative aims to improve the regulatory framework for variations by simplifying and clarifying the applications system and by building in greater flexibility. This article gives an overview of the new legislation and explains the changes relating to ‘purely national’ authorisations; revisions to the detailed rules applicable to handling variations; the ‘Do and Tell’ procedure; the establishment of coordination groups for mutual recognition and decentralised procedures involvement in disagreements regarding variations and the handling of unforeseen variations. It also looks at the increased flexibility in the classification of variations; the introduction of grouping of related variations into a single application and new procedures for worksharing among competent authorities.

Introduction
As most readers will be aware, the pharmaceutical industry in Europe is a highly regulated sector where the placing on the market and the subsequent monitoring of medicinal products are subject to detailed rules and administrative supervision. Regulation in the pharmaceutical field is essential for public and animal health and to ensure the availability of high-quality, safe and effective medicines. Medicines are regulated throughout their entire lifetime. Changes subsequent to their placing on the EU market are handled according to a specific Community legislative framework on so-called ‘variations’. The last round of revision of this framework occurred in 2003, and therefore did not incorporate general developments resulting from the global review of the Community pharmaceutical legislation (the ‘Pharma Review’) adopted in 2004.

The handling of variations requires significant administrative and regulatory resources, both for competent authorities and for the industry. If the regulatory requirements exceed what is necessary to the protection of human or animal health, they may lead to an administrative burden that constitutes a barrier to innovation and mobilises public resources unduly. Therefore, in 2006, the European Commission initiated an ambitious project to revise the overall framework for variations to make the whole system simpler, clearer and more flexible without compromising public health. The initiative aims at striking the right balance between protecting health, supporting innovation and enabling competent authorities to focus on substantial issues, related to the scientific monitoring of medicines and the protection of public health, rather than on paperwork.

The new regulatory framework on variations is the Commission’s main contribution to the ‘Better Regulation’ policy agenda in the field of pharmaceuticals. In the context of the renewed Lisbon Strategy, focused on growth and jobs, the Commission has taken a clear and strong position in favour of better regulation and committed to ensure that the regulatory framework in which businesses operate contributes to their competitiveness, growth and employment performance.

The variations initiative entails a major overhaul of the legislation governing this field, in two parts:

1. An amendment of the provisions empowering the Commission to adopt detailed rules on the handling of variations to include so-called ‘purely national authorisations’ within their scope, so that all authorised medicinal products are subject to the same criteria for the approval and administrative handling of changes, regardless of the procedure under which those medicines have been authorised.

2. A full revision of these detailed rules with a view, primarily, to their simplification.

Throughout the entire process extensive consultations with interested parties and the network of competent authorities have been carried out. ‘Having a say’ from stakeholders has permitted to give a direct response to their needs. As a result, the new set of rules for variations will be better adapted to the requirements that the various stakeholders and the protection of public and animal health demand.

‘Purely national’ authorisations
The current variations regulations adopted in 2003 apply to changes to marketing authorisations granted under the centralised procedure and the mutual recognition framework, but not to changes to national authorisations granted without any mutual recognition, so-called ‘purely national’ authorisations. This includes authorisations granted in the EU member states before application of the mutual recognition framework, as well as authorisations granted only in one member state. This situation is the result of the limited scope of the provisions in Directive 2001/83/EC and Directive 2001/82/EC entrusting the Commission with the adoption of rules on variations.

Changes affecting purely national authorisations are handled according to national rules, which can vary among member states. In fact, certain countries follow, by analogy, rules that are close to the variation regulations, but others apply divergent national rules. This means that critical changes such as the introduction of a new therapeutic indication may be handled differently in member states in terms of regulatory classification, administrative procedures and criteria for scientific assessment.

This non-harmonised situation has negative consequences in terms of public or animal health, administrative burden and overall
functioning of the internal market, in particular, because purely national marketing authorisations represent the vast majority of authorisations in the EU, both in the human and veterinary sector.

For national competent authorities, the direct implications of this situation are that depending on whether they are dealing with changes to a purely national authorisation or to an authorisation granted in the decentralised or mutual recognition procedure, the regulatory requirements are different.

As for companies, which often operate globally, the non-harmonised procedures for purely national authorisations means that they might be confronted with different rules in different countries as regards the same variation for the same product. In addition, the result after assessment could be different for the same variation. This legal uncertainty may delay, impair or even prevent the introduction of certain changes.

From a public health perspective, this dis harmonised situation does not appear in any way justified.

To address this situation, on 4 March 2008, the Commission adopted a legal proposal for a Directive of the European Parliament and of the Council intended to amend Directive 2001/82/EC and Directive 2001/83/EC in order to empower the Commission to adopt rules on the handling of variations to the terms of marketing authorisation which would also include purely national authorisations within their scope, thus allowing harmonisation of the variations’ rules for all authorised medicines within the EU.


This Directive, to be transposed by the member states within 18 months, allows variations to all types of marketing authorisations to be subject to harmonised rules for their evaluation, approval and administrative handling within the EU. There is only one exception to this harmonisation permitted by the Directive. In the area of medicinal products for human use, member states may continue to apply existing national rules on variations to medicinal products fulfilling several conditions: the marketing authorisation has been granted before January 1998; the product is only authorised in one single member state; and the conditions: the marketing authorisation has been granted before January 2001/82/EC and Directive 2001/83/EC was adopted on 18 June 2009.4

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Revision of the detailed rules applicable to handling variations

In addition to the further harmonisation that Directive 2009/53/EC provides for, the Commission has undertaken a global revision of the specific rules on variations, adopted through Commission regulations, with a view to rendering them simpler, clearer and more flexible. As a result, Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medical products for human use and veterinary medicinal products was adopted on 24 November 2008 and will be applicable from 1 January 2010. It replaces, in one single text, the two variations regulations of 2003.

In a first step, Regulation (EC) No 1234/2008 will apply to the variations of the marketing authorisations granted centrally or through the mutual recognition framework. This has allowed its adoption without awaiting the finalisation and transposition of Directive 2009/53/EC, which would have otherwise delayed implementation of the new rules. In the future, the scope of this new regulation will be extended to include variations for purely national marketing authorisations, once the transposition deadline of Directive 2009/53/EC has expired and some experience with the implementation of Regulation (EC) No 1234/2008 has been gained, thus facilitating, for competent authorities and industry, a step-wise transition from the 2003 variations regulations to the new rules.

The new regulation is based on the same high-level principles for the handling of variations as the current system: types of variations are classified according to their impact on quality, safety and efficacy (Types IA, IB, II, extensions) and the regulatory approval procedure is adapted to the level of risk. It nevertheless contains the following significant novelties:

Variations not requiring prior approval (‘Do and Tell’ procedure): In the current system, the simplest variation follows a ‘Tell and Do’ procedure: only after the notification is made (‘Tell’), the change may be implemented (‘Do’). In order to reduce the overall number of variation 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 so-called minor variations of Type IA is now introduced. These are variations with only a minimal impact, or not impact at all, on the quality, safety and efficacy of the product.

The new regulation does not require any prior approval for minor variations of Type IA. Type IA variations can be implemented anytime before notifying to the competent authorities.

Moreover, the reporting of Type IA variations may be done on the occasion of an annual report compiling all ‘Do and Tell’ changes made in the last twelve months; or forthwith in the case of certain Type IA which are considered to require immediate notification.

It is important to note that the new regulation does not impose any specific date for the annual reporting, as long as all 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 agreement with the relevant competent authority.

Handling of unforeseen variations (Type IB by ‘default’): It is usually not possible to anticipate all specific variations to the terms of a marketing authorisation, in view of the technical and scientific progress in the area of pharmaceuticals, and therefore the regulatory framework for variations usually identifies a variation type as the default classification in the case of unforeseen variations.

At present, the default category is the Type II variation. In practice, this means that certain changes which may not raise any major health issue and could be handled in a simple manner are subject to the lengthiest and most complex variation procedure, solely because they were not foreseen in the variations regulations.

In the new regulation, it is proposed that variations which are not explicitly recognised as Type IA, Type II or line extensions are handled, by default, as Type IB variations. In this way, unforeseen variations are dealt with though a lighter procedure with a shorter assessment period. A safeguard mechanism is however introduced: if, within the initial validation period of the Type IB procedure, the relevant competent authority considers that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned, the variation is then reclassified and evaluated according to the Type II procedure.
**Increased flexibility in the system of classification of variations:** The actual classification of concrete variations demands regular adaptation to technical and scientific progress and to experience acquired in the field, to incorporate new variations, reclassify variations or revise the conditions to which variations are made subject, as appropriate.

In the 2003 variation regulations, the classification is laid down in the annexes to the regulations themselves, and any change in classification demands a legislative amendment. To introduce more flexibility in the system, the new regulation contains high-level rules on the classification of variations, but foresees that the details of the various categories of variations are to be laid down in guidelines drawn up by the Commission.

In addition, where an unclassified variation is concerned, a new option is introduced for a marketing authorisation holder or a member state to request 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. The recommendations will moreover be relied on for the regular update of the guidelines.

**Grouping of related variations:** Currently, different variations cannot be grouped within one single submission unless they were all consequential to one given change. The new regulation foresees a series of cases where grouping of variations into one single application, handled in a single regulatory procedure, is allowed:

- Grouping of several Type IA variations to the terms of one or several marketing authorisations from the same marketing authorisation holder, provided the exact same group of Type IA variations affects all concerned marketing authorisations and they are notified simultaneously to the same relevant authority, within one single notification.
- Grouping of several variations to the terms of one marketing authorisation provided the variations are submitted at the same time and fall within one of the cases listed in the new regulation or agreed with the competent authority.

In this way, the new regulation makes possible the joint evaluation of different but interrelated changes to one medicinal product, as well as the single evaluation of certain changes which are common to more than one marketing authorisation. This may significantly reduce workload both for competent authorities and industry and avoid unnecessary administrative burden, through the overall reduction in the number of procedures.

**Worksharing among competent authorities:** In order to avoid duplication of work in the evaluation of variations and to further increase consistency and efficiency in the network of competent authorities, the new regulation introduces a worksharing procedure so that one authority, chosen among the competent authorities of the members states and the Agency, examines the variations on behalf of the other concerned authorities. Worksharing should not only reduce the burden imposed on competent authorities’ assessors by avoiding redundant evaluations, but also promote the availability of expertise in case of changes of major and innovative nature.

A minor variation of Type IB, a major variation of Type II, or a group of variations in the cases foreseen in the regulation or agreed with the competent authority which does not contain any extensions, may be submitted under a worksharing procedure.

It should be highlighted that worksharing in the new regulation is also possible where a group of marketing authorisations includes both centrally and nationally authorised products; in this case the authority assessing the application will be the Agency. This is the first time in the pharmaceutical acquis where issues common to products authorised under each of these procedural routes may be handled jointly in a single assessment and procedure.

**Coordination groups for mutual recognition and decentralised procedures (CMD):** The establishment of the coordination groups (CMD, human and veterinary) in the 'Pharma Review' and the related procedures for addressing disagreements between member states are at present not reflected in the 2003 variations regulations, but have been introduced in the new regulation. Moreover, the CMD is entrusted with additional tasks to further strengthen the coordination of member states’ in the area of variations, in areas such as grouping, worksharing and the classification of guidelines.

**The way ahead**

With the tabling of proposals allowing the full harmonisation of variations’ rules for all medicinal products placed on the EU market, leading to the adoption by the European Parliament and the Council of Directive 2009/53/EC, and the adoption of a new set of rules on the handling of variations (Regulation (EC) No 1234/2008), the Commission has delivered key elements of its ambitious ‘Better Regulation’ package in the area of variations to marketing authorisations. These new pieces of legislation have been very much welcomed by stakeholders. However, important challenges still lay ahead for the new system to be fully operational.

Regulation (EC) No 1234/2008 will apply from the beginning of next year. Currently, Commission guidelines are being prepared to facilitate the interpretation and application of this new regulation to authorities and industry alike.

The new regulation foresees the adoption of guidelines by the Commission as regards the details of the various categories of variations, as well as on the procedures for the handling of variations. When preparing these guidelines, it must be borne in mind that the detailed classification of variations to be provided for in the guidelines should further contribute to the objectives of simplification of the overall system, while maintaining a high level of protection of public and animal health. In turn, the procedural guidelines should be an instrument for the smooth transition to the novelties in the variations’ procedures and for the consistent application of the new regulation across the Community.

The final step to conclude the adoption of the variations’ initiative announced by the Commission in 2006 will be the future amendment of Regulation (EC) No 1234/2008 to enlarge its scope to include purely national authorisations, in accordance with the mandate given by Directive 2009/53/EC. In this way, the new legal framework for variations will be complete and provide for a set of clearer, simpler and more flexible rules applied in a harmonised manner to all medicinal products authorised in the EU.

**Notes and references**

3. Information on the whole process is available at: http://ec.europa.eu/enterprise/legislation/vacre/vareg/vareg_key.htm