The New European variations system: An industry perspective

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Abstract
This article provides an industry perspective on recent changes to the European regulatory framework for marketing authorisation variations (post-approval changes). Within the context of the principal features of the new system, views on key aspects of its operation are offered, broadly categorised into successes and challenges, and exemplified by practical experience in 2010. Constructive proposals are made for potential next steps in the development of the system to the anticipated benefit of patients, regulators and industry.

Key aspects of the New EU variations system
New elements: New elements of the revised variations system include the concepts of Type IA “do and tell” variations, grouping of variations, worksharing, the facility for scientific recommendations for “unforeseen variations” (ie, those variations not readily classified by reference to the existing guidance) and the recognition of the ICH science- and risk-management based approach (Quality by Design and resulting control and change management strategies).

Type IA (minor) variations, now known as “do and tell”, are defined within Annex II of the variations regulation as those which have minimal or no impact on the quality, safety or efficacy of the medicinal product(s) concerned. Such changes may be implemented by the marketing authorisation holder (MAH) without prior approval, and must be notified to the competent authority (CA) within 12 months of implementation or, in certain cases requiring early notification in order that the CA may discharge their supervisory duties (eg, certain site changes), immediately upon implementation. An exclusive list, delineated by description, conditions and data availability, is provided in the European Commission (EC) classification guidance.

Examples of Type IA “do and tell” variations include: purely administrative changes; deletion of a manufacturing site; tightening of specification limits under defined circumstances.

Grouping: It is possible to group variations of different categories for the same marketing authorisation (MA) and submit them in one submission, under a single application form, to the same relevant authority. This is permissible where variations are covered under the cases listed in Annex III to the variations regulation. Examples are any group of IA changes, a group comprising a Type IB or Type II change plus one or more of the same or lower category which are consequential to the first, and a group of administrative changes to labelling. If a projected group is not listed in Annex III, the regulation and supporting guidelines permit the MAH to request agreement of the relevant authority(ies) to grouping of related changes where a single data package and evaluation are meaningful. Generally excluded is grouping of changes to drug substance and drug product, unless very closely connected.

For the purpose of the variations regulation, a single MA has been defined as covering all pharmaceutical forms and strengths of a given pharmaceutical product.

For Type IA variations, it is additionally possible to group the same variation, or set of variations, in a single submission covering multiple MAs.

Evaluation of groups of different types of variation is conducted in line with the procedure of the highest category included within the group. For example, an extension plus a Type II variation would be assessed as an extension application, and a Type IB variation plus a Type IA variation would be assessed as a Type IB.

Worksharing: Article 20 of the regulation provides for an optional worksharing procedure, where an MAH may elect to submit one or more changes to several MAs under a single application. Eligible variations for initiating the procedure are Type IB or II, and the procedure is currently applicable to Centralised Procedure (CP), Mutual Recognition Procedure (MRP) and Decentralised authorisations; purely national authorisations will be included once they are brought within the remit of the Regulation. A group of variations may not include a line extension, but pending IA changes may be incorporated. A single evaluation is conducted (by a single reference authority where multiple CAs are involved), resulting in issue of a scientific opinion.

Recommendations on unforeseen variations: The variations regulation describes a facility for MAH or CA to request pre-submission advice on classification of a variation where this is not clear from the regulation or current guidance (Article 5(1)). Advice may be sought from the Co-ordination Group for Mutual Recognition and Decentralised Procedures–Human (CMD(h)) or, for centrally authorised products, the European Medicines Agency (EMA).

Since implementation of the regulation, experience has been gathered regarding classification of unforeseen variations and information on Article 5 outcomes is publicly available via the CMD(h) website. It is understood that this information will be considered during future revisions of the regulation and supporting guidance.

Science and risk-management based approach: The Classification Guidance acknowledges the principles of risk-based quality management, identifying introduction of or extension to a Design Space as a Type II variation and introducing the concept of a Change Management Protocol.

ICH guidance clarifies that movement within an approved Design Space is not subject to submission of a post-approval change, but would be managed internally within the company’s Quality System.

Filed within a new MAA, or as a Type II variation, a Change...
Management Protocol enables the MAH to propose a post-approval change management plan describing specific changes they would like to implement during the lifecycle of the product, and how these would be prepared and verified. For each proposed change, a detailed protocol is required. In this way sponsor and regulator can reach prior agreement on the strategy (data and acceptance criteria) to be used to support foreseen changes, and later submission of the agreed data package may be facilitated under a lower change category than would otherwise be the case.

**Experience with new elements of the system**

**Benefits/fulfilled expectations:** The introduction of the “do and tell” IA change in conjunction with the facility to group IA changes within one MA has brought about a considerable simplification for the MAH, and we hope also for the responsible authorities. This is especially so for those changes with a 12-month reporting period. Grouping of associated changes of categories higher than IA within a single MA is also of major benefit from a resource and administrative perspective. Recent suggestions by the EMA to simplify further by combining very closely related changes, e.g., within a specification, into a single variation are highly welcome.

Much appreciated by industry is the publication by the CMD(h) of a list of proposed groupings (not already covered by Annex III) found to be acceptable and for which in future no prior acceptance need be sought; one example very welcome in the Quality arena is the clarification that changes related to a manufacturing site change are considered to fall under the Annex III category “project intended to improve the manufacturing process”. The list usefully includes some proposals not found acceptable, giving MAHs an enhanced framework for future planning. Industry looks forward to expansion of this list as more experience is accumulated, and hopes it will be incorporated into future review of regulation and guidance documents. MAHs would also welcome ratification from the EMA that the agency is aligned with the framework laid out by CMD(h).

The facility to group IA changes across MAs is seen as an additional potential simplification, especially for administrative or site changes which may impact multiple licences, whereby it must be said that a company’s internal organisation may place hurdles in the way of maximising the benefits if responsibilities for products are split between discrete groups with little synergy in working procedures.

When combined with forward-thinking planning, the advent of the Change Management Protocol offers significant opportunities both for optimal preparation of data packages for changes, and for facilitating smooth and rapid approval once the foreseen variation (or group) is submitted.

**Challenges/disappointments/open issues:** There is still discussion on the interpretation of “consequential” changes for grouping. Initial regulator presentations during the development phase of regulation and guidances indicated a relaxed approach aligned with practical circumstances, but more recently there have been some indications that the older definition of an “unavoidable consequence” is being rejuvenated. Pragmatism in this complex arena would be appreciated, for the necessity to approach authorities for agreement for every new grouping scenario involves considerable time and resource on all sides, and this will be magnified substantially when purely national licences come under the scope of the regulation.

The initial euphoria at the prospect of using the worksharing procedure is being diluted by the long timelines involved – a pre-notification period which has increased to up to six months, plus the extra delay which can be incurred when a specified submission date is just missed. The negative impact is magnified if the subject of the procedure is a group of changes including simple IBs where a more rapid resolution would historically be established in planning schedules. Also, the proviso introduced into guidances that eligible changes should require no or only limited product-specific assessment restricts the applicability of the procedure and makes for discussion regarding selection; there is a school of thought that where multiple CAs are involved, the more data assessment required, the more synergies could be achieved.

In those circumstances where the timelines can be accommodated by sound planning, the worksharing procedure does at least bring benefits not only in terms of simplification of documentation (a feature of all the new elements), but also a reduction in fees. With the exception of this procedure, however, an unfortunate consequence of the introduction of Annex III grouping, accompanied as it is by individual listing of (and with some authorities full payment for) all changes covered, is an increase in the fees being paid which is becoming more evident as practical experience accumulates. It may be that during preparation of the revision and accompanying fee structures, there was an underestimation of the extent to which it was already possible to negotiate for logical groups of associated changes to be submitted as a single Type II variation to facilitate the work of industry and assessor alike. An illustrative example would be a site transfer of a biologic, where each associated change, regardless of how minor, is likely to fall under the Type II umbrella. This increase in fees has imposed a substantial extra strain on industry budgets. This, plus the resource-intensive coordination of changes across MAs in a complex organisation and the challenges of managing changes worldwide across countries with different approaches (see below), is leading to a rethink about the overall financial impact of the new EU system. It is hoped that further opportunities for synergies will be identified as experience accumulates, accompanied by a reconsideration of fee structures where currently no concessions are made.

Not unexpected are the problems which arise for a global organisation with a worldwide market. The opportunities of “do and tell” cannot be fully implemented in practice because of the need for prior notification/approval in some ex-EU countries. This currently applies equally to purely national licences in EU countries not yet having adopted the principles of the new regulation for these. Global dossiers must therefore continue to be updated on every occasion of change, multiple regulatory activities continue to be necessary, and careful steering of implementation of changes remains an essential facet. Less frequent, but nevertheless a hurdle to full adoption, is the situation for those few IA changes where support is required for some ex-EU countries in the form of an updated Certificate of Pharmaceutical Product (CPP) because particulars in either the certificate itself or the appended product information must be amended. Here it becomes necessary to obtain approval in the certifying country prior to being able to progress the change in the dependent territory.

An issue still arising is the interpretation of whether or not a Type IA change may be submitted prior to implementation. EMA procedural guidance5 and note for guidance on completing the application form indicate that pre-submission is permissible where synergies can be achieved, but companies have reported non-acceptances. Furthermore, at least one national CA guidance explicitly forbids submission prior to implementation, and this authority has recently cited this as a reason for refusal of variations. There are, however, circumstances where it is counterproductive to chronologically separate implementation or submission of related changes. For example when a product specification is being substantially overhauled, a two-stage implementation would have to be employed to include all changes in one submission, or a
Focus – Variations

Evolution of the new European variations system

During the period 2003–2009, the European Commission recognised a number of areas where the EU variations system would benefit from improvement. These included the need for an aligned approach to data requirements and procedures for variations to national marketing authorisations (it was noted that ~80% of European authorisations fell into this category); incorporation of evolving science and risk based concepts into post-approval change management; enhancement of the existing “tell and do” variations approach and improved facility for grouping of related post-approval changes.

The following high level objectives for variations system improvement were identified, without compromising human health:
- A simpler, clearer and more flexible regulatory framework
- Reduction in administrative burden
- Harmonisation of procedures and requirements for national authorities
- Accommodation of science and risk management based approaches (ICH Q8, 9 and 10).

Following a number of stakeholder consultations, the new European variations system was implemented in January 2010* for marketing authorisations issued via the CP and MRP/DCP procedures.

Purely national MAs will be brought formally within the scope of the variations regulation by means of Directive 2009/53/EC**. This will only be possible from early 2011 at the earliest, but a number of MS have elected to apply some of the regulation’s principles in advance, although unified evaluation timelines have not been adopted throughout and “early adopter” MS are not eligible to participate in the new worksharing procedure. Further information on MS adoption for purely national authorisations may be found via the CMD(h) website.

Implementing texts and guidelines

The principal implementing text is Commission Regulation EC/1234/2008 (“the variations regulation”), which provides a high-level framework for the new system and makes provision for subordinate regulatory guidance to provide detail on procedural and submission data requirements.

In this category the European Commission has published two principal guidelines, one on categories of variation and document requirements (the “Classification guideline”), and one explaining how the new procedures laid down in Chapters II, III and IV of 1234/2008 will work (the “Procedures guideline”).

Further detailed guidance is available via the CMD(h) website, including a Best-Practice Guide for the submission and processing of variations in the MRP, recommendations on acceptable groupings of MRP/DCP products and outcomes from Article 5 (unforeseen variations) referrals. The EMA has also posted extensive procedural guidance on post-approval changes.

* The Article 5 provision of the regulation, relating to unforeseen variations, applied from January 2009.
** Directive 2009/53/EC contains an exemption permitting the national law on variations in a Member State to continue to apply to products approved before 1998, in that Member State only. However, the Commission must be notified by the National CA before 20 January 2011, otherwise the provisions of the new Directive will apply.

two-stage submission if the wish was for simultaneous implementation. Equally, where a IA change is consequential to one of a higher category and in practical terms cannot be implemented until the leading change is approved, it is unhelpful to withhold submission of the IA change until approval and implementation of that of the higher category – the data package will anyway almost certainly cover all proposed changes. Finally, if a CPP is needed in order to submit in dependent countries it may be necessary to obtain the EU approval early if approval is to be obtained worldwide prior to implementation.

Although the adoption of a heightened risk-based approach has opened several doors, there are at present also disappointments. Currently, biologics are outside the scope of the Change Management Protocol approach, which industry has challenged. Also, any small adjustment to a Design Space is automatically classified as a Type II change. The Quality Working Party has acknowledged that this is an evolving area of regulatory science, and it is hoped that the full potential of a science- and risk-based approach may be realised as industry proposals around the post-approval management plan progress.

Classes of variation

The key changes compared to the current system are the transformation of Type IA “tell and do” changes into “do and tell” as already described above, and introduction of the concept of Type IB by default rather than the Type II default of the previous regulations. The established concepts of classification based on risk have been carried through, as has the need for prior submission and review of Type IB and Type II changes. Extensive information on classification of variations may be found within the Classification Guideline. As well as providing an exclusive list of Type IA variations and a comprehensive set of Type II changes, this guideline also provides illustrative examples of Type IB variations. These are helpful to the applicant in determining the careful delineation between variations of Type II and Type IB.

A key outcome of stakeholder consultations during development of the new system has been the agreement that changes which are not listed in the Classification Guideline and are not extensions, nor whose classification has been decided via an Article 5 (unforeseen variation) procedure, default in first line to a Type IB. These may be minor changes which do not fulfil all the conditions of a listed IA, or a change the nature of which is not addressed at all in the guidance. A “safeguard clause” in the regulation confers the ability to change the categorisation of such a potential Type IB change to a Type II, if the scope of the change is such as to not fit into the IB risk category. The MAH may already propose this when submitting the variation, or the CA may require it if it concludes that the change may have significant impact upon the quality, safety or efficacy of the medicinal product.

Experience with variations classification system

Filled expectations: The default of changes not listed in the classifications guidance to Type IB is viewed by industry as a positive and pragmatic development, avoiding the illogical situation where any minor but unforeseen change automatically had to undergo the full Type II evaluation.

The review of the risk framework and consequential downgrading of some variations, especially of some changes previously classified as Type II for biological products purely on the basis that the product was a biologic without taking into full account the relationship between biological risk aspects and the proposed change, is highly welcome. The pragmatic approach taken in classification and definition of conditions and requirements is appreciated by industry and is felt to demonstrate the value of the close and cooperative stakeholder consultation process.
which took place during the review period. Furthermore, recent experience indicates that classification of some variations may be rationalised and down-regulated by informal negotiation.

**Challenges/disappointments/open issues:** There is still feeling in some quarters that a number of changes remain classified in a higher risk category than is appropriate, and stakeholders are encouraged to continue working on opportunities for down-classification.

The published list of Article 5 recommendations provides extra guidance on classification, some of which is easy to understand and can be usefully applied to future decisions. There are, however, concerns that for some of the examples listed the context is not transparent, and it is hoped that before any of these examples may be added into a guideline update, the text will undergo the same depth and quality of consideration which was applied during generation of the first version of the guidances. It is assumed that draft guideline revisions will also be shared with stakeholders for review and comment. It is also noted that there isn’t always agreement between the CMD(h) and the EMA on classification. For simplicity’s sake it is hoped that divergence will not be too frequent, and it is of course essential that the growing list continues to indicate where such divergence exists. Disagreement is not restricted to Article 5 decisions; some companies have reported submitting IB (by default) changes to nationally-licensed products and having them accepted in one country but escalated to Type II by another.

Terminology for Type IB variations is variable (IB, IB by default, IB foreseen and IB unforeseen) and not always used consistently by all stakeholders, leading to a danger of misunderstandings arising. The differences can be seen when one looks at different sections of the application form, and into the list of Article 5 decisions. It is recommended that every effort be made by all stakeholders to reach alignment; a good starting point may be a glossary jointly published by the EMA and the CMD(h), indicating not only meaning but also where use of each term is expected.

Despite the clarification that date of implementation of a change is the date on which it is implemented in the company’s Quality System, there continue to be discussions on what this really means for different types of change. Assurance from the CAs that interpretation is regarded pragmatically and with primary regard to protection of the patient from unauthorised changes would go a long way to reassuring MAHs who find themselves facing a dilemma when a strict definition fails to match a logical interpretation or business need. A simple example would be the difference between approving an updated batch record and permitting production of drug substance using a revised process versus release of dosage form manufactured from that drug substance onto the market. Many operations are performed “at risk” prior to approval having been obtained, the key compliance factor being final release of product.

**Conclusion**

In conclusion, revision of the European variations system, though still evolving, has yielded some notable benefits from industry’s perspective. Introduction of the concepts of Type IA “do and tell” variations, grouping, worksharing and Change Management Protocols has opened the door to more effective management of change. The stakeholder consultations which have taken place throughout development of the new system have provided an opportunity for constructive dialogue which has led to more pragmatic positions on, for example, the classification of certain variations and the facility for Type IB, rather than Type II, by default changes.

It is appreciated that the system is still developing, partly due to the ongoing inclusion of national authorisations, and partly due to experience being gathered with the elements of the system now in place. It is hoped that the good practices of consultation and dialogue adopted for the early stages of system development will continue to be utilised as formal adoption reaches its conclusion and opportunities for system refinement are identified. It is understood that both Annexes I, II and V to EC/1234/2008, and the Commission guidelines themselves will be subject to review by January 2012, and that industry, as a stakeholder, will contribute to this process. Industry’s objective remains the realisation of a pragmatic way forward built on sound principles of science and risk management to the mutual benefit of patients, regulators and industry.

**References**

3. CMD(h) – Article 5 Recommendations (Unforeseen Variations). http://www.hma.eu/293.html

**Additional information**


**Glossary of abbreviations**

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<th>CA</th>
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<td>CMD(h)</td>
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<td>CP</td>
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<td>CPP</td>
<td>Certificate of Pharmaceutical Product</td>
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