
**Position Paper
on
Variation Regulations**

**APIC Position on Change Authorisation Procedures
EC Regulations nr 1084/2003 and nr 1085/2003
relating to the manufacture of APIs**

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1. EXECUTIVE SUMMARY

1.1 Introduction

The Active Pharmaceuticals Industry Committee (APIC) welcomes the opportunity offered by the authorities to involve the industry in the update of the European Variation Regulations. APIC recognises the importance of this initiative as the current Variation system is no longer adequate. The current system implies that the authorities have full control over the approval and implementation of changes. However, the lack of workability of this system is in fact causing widespread non-compliance. Therefore, APIC, along with other industry parties, wishes to collaborate with the authorities to create an efficient and effective system for the future that is beneficial to the patient, the authorities and the API industry.

Change is a vital element of life and is therefore unavoidable. The manufacture of APIs is no exception to this. Change is the most important tool for industry to create sustainable growth and to remain competitive in continuously changing circumstances. Drivers for these changes are:

- Improvement of the quality of the API and hence the Medicinal Product
- Introduction of new and/or improved technologies
- Further upgrading of the chemical industry in optimal harmony with the environment
- Use of new scientific knowledge
- Rapidly emerging API manufacturers in the developing world

For many API manufacturers, making a change under the current system is impossible. The 37-page document prepared in February 2005 entitled “Additional Rationale and Examples for ICH Q10 – Quality Systems for Continuous Improvement” illustrates the alarming extent to which changes are being blocked because of the current Regulations (see Annex 1).

1.2 Key Expectations

It is imperative that, instead of blocking progress, the revised Variation Regulations allow industry to improve while continuing to protect patient safety. APIC’s main expectations are as follows:

- The new system should put the responsibility for managing change back into the hands of industry. In doing so, significant harmonisation with the rapid developments taking place regarding the “Pharmaceutical GMP for the 21st Century – a Risk-Based Approach” Program will be achieved.
- The new system should be supported by a verification system through inspections by the authorities.
- The new system should allow the optional replacement of existing regulatory information in the dossier with an evaluation in accordance with ICH Q8, Q9 and Q10 when supported by a regulatory agreement between manufacturer(s) and authorities.

These proposals are described in more detail in section 2.

1.3 Suggestions for Interim Improvements

APIC appreciates that such a system will take time and effort to establish. APIC would therefore like to put forward suggestions as to how the current system could be improved in the interim. Please note that these proposals represent APIC's "minimum option" and are seen as a temporary fix to allow time to implement the preferred system outlined above.

- Exclusion of the majority of API changes from the requirement to submit by the MA holder. Changes involving the API should be submitted by the API manufacturer. Only changes with an impact on the safety / efficacy of the Medicinal Product should require a supplementary submission by the MA holder.
- For APIs, a distinction should be made between changes impacting on the API itself and changes impacting on intermediates / starting materials / raw materials.
- Replacement of the current Type I Variations list with a limited list of major Type II Variations. In addition, it should be possible to incorporate multiple changes within one submission.
- Establishment of a fast track approval system for changes with clear quality, environmental or safety benefits.
- Creation of a single EU (or ideally World Wide...) change authorisation system that is accepted by the whole of the EU to ensure that a change is assessed in the same way by all EU authorities.
- In the absence of a single system, establishment of common, enforceable approval times between the different authorisation systems (National, MRP, Decentralised, Centralised).
- Introduction of an annual payment per MAA instead of a payment per Variation to avoid the blocking of progress in the API industry by the MA holder.

These proposals are described in more detail in section 3.

2. THE PREFERRED SYSTEM

The responsibility for managing change should be put back into the hands of industry, supported by a measuring system to verify reliability through inspections.

- Variations currently constitute a huge burden for industry in terms of time, effort, cost and workability. For this reason, changes, in particular those proposed by the dedicated API industry, are often blocked by MA holders (see Annex I for examples). For the MA holders, the filing of Variations in different countries, for different formulations, via different procedures with different approval times, means that full approval for implementation may only be obtained after several or even many years. Under these difficult circumstances, it's easy to understand why MA holders have developed a very negative attitude towards changes proposed by their API suppliers.

The dedicated API industry is closely related to and interacts intensively with the Medicinal Product industry (MA holders). APIC strongly recommends the adoption of a regulatory approach that will put much of the responsibility for change implementation back into the hands of these industries. APIC's view is that co-operation at the interface between API manufacturer and API user should be the primary means of handling and managing change. The more the authorities assume to take over the role of this interface (but by assessing paperwork only), the poorer it will function.

APIC also considers it necessary to move away from developing lists of minor/major changes and instead to move towards an assessment system based on performance (a "trust and verify" system). This system should allow companies to demonstrate the good performance of their established cGMP systems, including change management, in line with the principles laid down in ICH Q8, Q9 and Q10. This requires the upgrading of the current inspection system to incorporate these aspects as key elements and to develop a concrete performance scale. Take, for example, changes in suppliers of raw materials and starting materials. These changes should be covered solely by the GMP system of the company. Verification by the authorities should focus on performance assessment and inspection of that company.

The risk-based characteristics of such an approach would fit perfectly within the new "21st Century paradigm".

- APIC fully supports the intention of the EU Commission to build the new Variations system upon the principles of ICH Q8, Q9 and Q10. The inclusion of already marketed products (in addition to New Chemical Entities) within the scope of a system based on these guidelines should be an option. It should, for example, be possible to use either retrospective data, or to generate new data, to update the product knowledge information in existing dossiers. This replacement of existing regulatory information with an evaluation in accordance with ICH Q8, Q9 and Q10 could be supported by a regulatory agreement between manufacturer(s) and authorities.

3. MINIMUM OPTION

Principles to be adopted in order to "fix" the current, malfunctioning system.

Should the EU conclude that the adoption of a system as outlined above would not (yet) be feasible – a conclusion that APIC would regret – then it is APIC's view that at least the following principles should be adopted in order to move as quickly as possible from an inefficient system to a system that provides significant relief for both the authorities and the industry in at least some of the situations involving changes to API manufacture.

- A practical option to resolve the blocking of progress, that would still provide for extensive authority oversight, would be to create a system for approval of APIs that includes its own approval procedures for changes to processes, specifications, analytical methods etc. Under this system, it is envisaged that the majority of changes would be submitted by the API manufacturer and would not require a supplementary submission by the MA holder. This would especially apply to changes that do not have an impact on the safety / efficacy of the Medicinal Product. In order for such a system to function properly, a strong relationship / partnership between the API manufacturer and the MA holder is vital in order to assess the impact of the API change on the Medicinal Product. This should be enforced through inspection by the authorities.

A system similar to this has, to a certain extent, already been in place in the EU and has proved to work well. We refer to the CEP system as it was operated before the introduction of the revised Variation Regulations in 2003. Under this system, minor changes did not result in a variation to the MA which meant that the system was effectively functioning as an API-dedicated approval system. It is APIC's view that changes to CEPs are amongst the most plausible examples of changes that should not require a supplementary submission by the MA holder.

Note

Until 1997, a successful, dedicated API approval system was also in place in the USA – the so-called “Abbreviated Antibiotics Drug Applications for bulk” system (“bulk AADAs”). Its deletion in 1997 was an unintended “side-effect” of the adoption of the FDA Modernization Act that removed the special status of antibiotic APIs versus other APIs.

- For APIs, a distinction should be made between changes impacting on the API itself and changes impacting on intermediates / starting materials / raw materials when it can be scientifically demonstrated that such changes have no impact on the quality of the API. In the current EU system, changes concerning raw materials, starting materials and intermediates are often classified in the same categories as similar ones applying to the API itself. It would be reasonable practice to classify such changes into categories that allow for easier and quicker assessment and approval.
- The current list of Type I Variations creates an enormous administrative burden both for the authorities and the industry and may even preclude a scientific assessment of the fundamental nature of a change. For example, currently, if not all the conditions required by the Regulations are fulfilled, the change must be submitted as a Type II Variation, even if a good, scientific reason exists why a particular condition is not valid. Another example would be the submission of changes that are interrelated because they form part of one project. These cannot be included in a single submission but must be submitted as individual Type I Variations. This prevents the presentation of the overall scope of the project to the authorities. In addition, changes not listed as Type I are automatically and often unscientifically classed as Type II.

To address this, APIC proposes the replacement of the current Type I Variations list with a limited list of major Type II Variations. Also, it should be possible to include interrelated changes within one submission. This will significantly increase the focus on the essence of the change and, importantly, reduce the workload for both industry and the authorities. This will create a situation in which “non-Type II” Variations really will cover all non-major changes and will, of course, include all administrative changes. We propose that non-Type II changes are notified through biennial reporting.

- A fast track approval system for changes with clear quality, environmental or safety benefits should be established in order to promote the implementation of such improvements.
- The various national systems should be replaced by a single EU (or ideally World Wide...) change authorisation system that is accepted by the whole of the EU. This would ensure that a change is assessed in the same way by all EU authorities. Currently, there is a lack of consistency – situations frequently arise in which a variation is classified as Type I by EU Member State X but as Type II by Member State Y.

- In the absence of a single system, the establishment of common and visible approval times between the different authorisation systems (National, MRP, Decentralised, Centralised) would be an important step forward. These approval times should be legally binding.
- Under the current system, due to the high costs involved, MA holders can refuse to co-operate in the submission of API changes, even when the changes concerned have a positive impact on the Medicinal Product. Removing the Variation fees and replacing them with a single annual payment per MAA would remove this barrier.

4. GENERAL CONCLUSION

APIC recommends a change control system that allows the Medicinal Product industry and the API industry to fulfil their responsibility to the patient. It should be GMP-based, supported by a verification system, through inspections by the authorities, to guarantee equal performance of all manufacturers. Such a system should focus on the scientific evaluation and risk assessment of the change, reduce the administrative burden for both authorities and industry and ensure fast approval of changes beneficial to the patient, environment and competitiveness of the industry.

5. REFERENCES

Annex 1

Document on the need for revision of the current - often unworkable - Variations Regulations, submitted to the EU authorities in May 2005 by the unified EU pharma-related industry:



"FINAL DRAFT
RATIONALE AND EX/

Annex 2

Recent presentation given by the US/FDA that reflects and summarises current "21st Century thinking":



"FDA Yu QbR DIA
18-22 June 2006.pdf"