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Public Consultation Paper
Better regulations of Pharmaceuticals

About PCAS:

PCAS is a French medium size fine chemicals manufacturing company, 4 sites among 8 are dedicated to the manufacture of APIs (60% of our activity).

We supply APIs to over 400 pharmaceutical companies around the world about half of them are located in Europe and as most of such independent European APIs manufacturers we have often several customers for a same API. Each of those customers can have various applications again with a same API, which means multiplicity of MAAs and (as an introduction to the following comments) quite **impossible to get the agreement of all of the customers on a same change (variation) related to any of our APIs with the current variations regulations which means any evolution is blocked.**

Our comments on the Variations Draft Guideline dated 24 October 2007

The draft document dated 24 October 2007 intended to amend the legal basis of the Variations regulation constitutes a real progress compared to the previous versions. Unfortunately the progress and the intended flexibility is quite exclusively extended to the Drug Products Manufacturers and only few flexibility is given to APIs manufacturers on some limited points such as administrative information (variations 3, 4 and 9) or points which were already somewhat covered through European Pharmacopoeia guidance (variations 13 and 25).

The only noticeable progress is noted on variation 11 (Batch size)
Unfortunately, with the implementation of the current draft, the situation still remains unworkable and even blocked when the APIs of a manufacturer are delivered to different customers, as it is the drug product manufacturer responsibility to file the variation and some of them refuse or delay systematically any variation).

The main points and proposals are listed here bellow:

10. (1B) Minor change in the manufacturing process of the active substance

The 1B classification adds no flexibility at all but blocks any improvement or progress, in some situations it will even stop some productions e.g.: within the frame of the implementation of REACH some processes will require a better containment (which is also an improvement in terms of contamination prevention), to achieve that, some adjustments / minor process changes are requested but cannot be implemented because of the refusal of some drug product manufacturers to file any variation on which they do not find a direct interest.

The suggestion would be to reclassify some minor changes 1A if those fulfil the following conditions:

- analytical profile / impurities profile / physical properties remain unchanged
- no change in the route of synthesis
- same raw material
- …

12. (1B if wider specification) Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance

This is understandable for API, intermediates and API starting material, but often not applicable to other raw material, e.g. a manufacturer stops and we have to switch to another one, change of a specification for safety reasons (recent decrease in NH_3 concentration in transported ammonia).

This variation shall only consider API, intermediates and API starting material under 1B (raw material, reactives: 1A if no incidence on the impurities profiles)

14. Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph. Eur. Certificate of Suitability is available

Same problem as for variation 12, for some reactives and solvents, even in Europe, it goes through distributors and is not even controllable, and again, it happens that suppliers / manufacturers disappear or stop productions which makes unworkable the current and anticipated variation filing system.

As for GMPs, the stringency of control shall increase from Reactives / Raw material (1A provided there is no incidence on the quality of the API manufactured) to intermediate / final intermediate (1B).

17. Change in

a. The re-test period of the active substance

Initially at the time of the filing only limited experience is available and the retest period is the minimum. With the years, as experience and data get available there shall be the possibility to extend the retest period under ***1A if it fulfils the following conditions:***

- *Natural ageing (25°C / 60% RH) stability data available for the suggested retest period.*
- *no change in impurities profile*
- *in agreement with specification*

Note: the purpose of stability studies on APIs is the assessment of packaging and storage conditions.

b. The storage conditions for the active substance

This is even incomprehensible e.g.: if we switch from a cardboard drum to a high density PE drum in order to preserve the product in difficult shipment conditions to foreign countries we shall ask our customers to file 1B variations!

It shall be 1B only if packaging is less protective than in previous situation, could be understandable if there is a substantial change in primary packaging material.

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