ECHAMP
European Coalition on
Homeopathic & Anthroposophic
Medicinal Products

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ECHAMP welcomes this Commission initiative to revise the variation framework for medicinal products acknowledging the request from industry and regulatory authorities for improvement to be made to the current variation framework in terms of efficiency and flexibility. Today a disproportionate amount of resources are required to maintain marketing authorisations. We appreciate that the Commission sees the necessity for a short term solution under the existing legislation.

While it is stated in EC regulation No. 1234/2008 [1] on variations to the terms of marketing authorisation that:*"…For reasons of proportionality, homoeopathic and traditional herbal medicinal products which have not been granted a marketing authorisation but are subject to a simplified registration procedure should remain excluded from the scope of the Regulation", the variations regulation is also referenced by many member states for simplified registrations. This revision is therefore of high interest not only for the marketing authorisation product category but also for the simplified registration category, which we* hope will be of significant benefit to our industry.

The specific challenges for the maintenance of authorized homeopathic medicinal product dossiers lies in

- The wide variety of materials required – up to 3000 raw materials of botanical, zoological, human, mineral, chemical or biological origin
- On average more than 50% of raw materials are of botanical origin
- Small batch sizes
- Large number of suppliers needed
- Increasing administrative effort

We would like to take this opportunity to create awareness and mutual understanding of these specific challenges and to make constructive proposals without reducing data transparency or impairing any current quality and safety standards.

The attached table 1, followed by a detailed substantiation, shows an overview of the most important variations together with the current classification according to the Guideline and our proposed new classification reflecting the nature of homoeopathic medicinal products without reducing information on the product quality [2].

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Table 1: Proposed classification concerning quality changes for homoeopathic medicinal products

	Classification according to guideline	Description of change	Current Classification	Proposed classification
	Active substance B.I.a)	Control of active substance: 1. manufacturer 2. geographical source		
1	B.I.a.1.z.	Change in the **manufacturer of a starting material**/reagent/intermediate used in the manufacturing process of the active substance	Type IB or II	No variation or type IA depending on type of starting material
2	B.I.a.2.d	The change relates to a herbal medicinal product and there is a change to any of the following**: geographical source**, manufacturing route or production	Type II	No variation or type IA
	Active substance B.I.b)	Control of active substance: change in the 1. specification parameters and/or limits 2. test procedure		
3	B.I.b.1.f	Change outside the approved specifications limits range for the active substance	Type II	max. type IB
4	B.I.b.1.g	Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product	Type II	max. type IB
5	B.I.b.2.e	Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	Type IB	Type IA (B.I.b.2.a)

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	Finished Product B.II.d)	Control of the finished product: change in the test procedure		
6	B.II.d.2.d	Other changes to a test procedure (including replacement or addition)	Type IB	Type IA (B.II.d.2.a)
	Monographs B.III.	Comply with monographs		
7	B.III.2.b	Change to comply with an update of the relevant monograph of the Ph.Eur. or national pharmacopoeia of a Member State	Type IA	Grouping of changes under this category

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Change in the manufacturer (supplier) of starting material (B.I.a.1.z.)

The names of the manufacturers or suppliers of the raw material are requested in the application form of a dossier (Module 1.2) and in the quality part (3.S.2.1). From a formal point of view, it should be sufficient to restrict this kind of information to the application form, since it is a matter of principle of the CTD to avoid doubling of information. Furthermore, in the view of digitalisation (IDMP/SPOR), transparency and efficiency, this type of information will in future be included in the European data base and could therefore be left out of the dossier. This represents a model of the complete quality-defining processes of the medicinal product. Since various manufacturing steps take place between raw material and homoeopathic active substance, the name of the supplier of the raw material should in principle only be part of the registration dossier if this information is relevant for the quality of the active substance.

Listing only exemplary suppliers in the registration dossier should guarantee flexibility in the production process, in order to avoid out-of-stock situations when the manufacturer has to switch to another qualified supplier. In this context a substance type-specific approach is adequate which results in the respective variation type: no variation, variation type IA.

Raw material of chemical origin

A change in a manufacturer of raw material of chemical origin has only limited influence whereas a change in the supplier has no influence on the quality of the homoeopathic stock prepared thereof, especially in cases where compliance to a pharmacopoeial substance monograph is given, and can be considered as a minor change. Based on the fact that the substance specifications must be fulfilled without exception during incoming good control and manufacturers have additionally to comply with ICH Q3C and Q3D guidelines [16,17], it is adequate to indicate the raw starting material suppliers for material of chemical origin only exemplarily in the application form of the dossier. For this reason, a variation is not required.

Raw material of mineral origin

A change of the supplier of raw material of mineral origin has no influence on the quality of the homoeopathic stock prepared thereof. The only method for getting a quality statement of the mineral consists in its mineralogical and analytical testing, which is always performed under the responsibility of the manufacturer of the homoeopathic stocks of mineral origin. Thus, the naming of the raw material supplier would only be a formality without pharmaceutical relevance and is therefore not appropriate. For this reason, a variation should not be required.

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Raw material of herbal origin

In contrast to herbal medicinal products, most herbal raw materials used for homoeopathic medicinal products are used in the fresh state for further processing of the homoeopathic active homoeopathic substance, that is the mother tincture or further dilutions. Moreover, some special plants used in homoeopathy are fairly uncommon and have only a very limited availability on the market as they grow exclusively in a special geographic region or do not have any importance on the international markets for herbal products. If there is a supply bottleneck e.g. a crop failure due to adverse weather conditions, immediate action has to be taken, since the harvesting period is restricted, and the herbal material has to be processed within hours. An approach is needed which guarantees the consistency of the raw material quality and which technically enables the manufacturer to maintain the production process.

Therefore, indication of the names of the suppliers for raw materials of herbal origin can only be done exemplarily, confirming that the quality management system in place guarantees consistent product quality independently from the supplier. Any incoming new batch of a specific raw material must fulfil GACP and the same raw material specification, anyway.

As a consequence, in case of changes of the supplier, a variation should not be required or a variation type IA should suffice. A variation type IB for a change of a supplier does not seem scientifically justified and is technically not feasible in practice, since as a worst case this might result in a loss of a whole production year of the active substance in question. This would have an impact on the availability of the product derived from an out-of-stock situation. Thus, the variation system should be suitable for homoeopathic medicinal products.

Change of geographical source (B.I.a.2.d)

According to the classification guidance [14] for a herbal medicinal product the change of the geographical source is a type II variation and in practice results of two batches have to be delivered in the dossier. Since for homoeopathic medicinal products, plants are usually collected once a year, the submission of results of two new batches of collected plant material would result in a waiting period of two years at least to get a new supplier approved. This prevents the manufacturer of medicinal products from reacting to market needs, either for climatic variations or other reasons. However, the term “geographical source” is not further defined. Although a broad interpretation of the term seems to be intended, some regulatory authorities restrict it to a small area. The more restricted the interpretation the more probable is a variation in case of change of the origin of a plant. In the view of regulatory optimization and harmonization there should be a generally applicable definition of “geographical

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source", e.g. based on existing definitions of geographical regions, such as e.g. the agro-ecological zones of the FAO.

Taking into consideration the pharmacopoeia monographs of herbal materials, it is noticeable that quality requirements are defined independently of cultivation sites and countries of origin. The quality of the herbal raw material is proven by GACP and GMP confirmation and by compliance with the specification, e.g. the requirements of the homoeopathic or Ph.Eur. monographs.

Consequently, this means to accept a change of the cultivation site or geographical origin, which does not affect the requirements of the pharmacopoeia monograph, without prior approval of a variation application as type IA or without variation application. In this case it should be acceptable to list potential geographical sources in the dossier.

Change in specification parameters and/or limits (B.I.b.1.f and B.I.b.1.g)

The optimisation of analytical methods can lead to changes in the approved specification of a starting material (raw material or homoeopathic stock (mother tincture)) or an active substance. As an example, the implementation of an analytical device such as a new TLC photographic documentation system can lead to subsequent changes in the colour and/or number of detected zones in the chromatographic fingerprint. Nevertheless, the specificity and hence suitability for identity testing is still maintained. It would therefore be inappropriate to classify this as change outside the approved specification of the starting material type II B.I.b.1.f regardless whether this affects a stock constituting the active substance (type II B.I.b.1.g) or not. Although the variation regulation defines the identity test as critical parameter, in such justified cases a type IA should be appropriate, especially when the active substance in the finished product has a higher potency.

Change of a testing procedure (B.I.b.2.e and B.II.d.2.d)

Thin layer chromatography is increasingly performed by HPTLC. Since TLC and HPTLC are both covered by Ph.Eur. monograph 2.2.27 [19], a replacement by or addition of HPTLC as an option is to be considered as a minor change to an approved testing procedure and therefore to be classified as type IA, whenever the used HPTLC method is not covered by another monograph, e.g. Ph.Eur. 2.8.25 [20].

Change to comply with an update of Pharmacopoeia monographs (B.III.2.b)

In many cases, changes of specification parameters and/or limits as well as test procedures are result of an update of the relevant monograph of the Ph.Eur. or national pharmacopoeia of a Member State. Although the classification guideline allows

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categorising such changes as type IA (B.III.2.b), the authorities can request a variation for the specific change under the corresponding variation number. This could result in a higher classification, for example if there is a change outside the approved specifications limits (type II) or an addition/deletion of a test procedure (type IB). The classification guide should clearly state that variation category B.III.2.b is superordinate regarding to the individual variation categories.

Conclusion

We are asking for predictable and contextual application of standards without impairing quality and safety standards. A higher degree of flexibility is essential to allow our sector to manage a number of specific challenges as outlined above.

We highly appreciate your serious consideration of our proposals.

References

[1] European Commission. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures. Official Journal of the European Union C 223 of 2 August 2013.
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013XC0802(04)&from=EN

[2] Estibaliz Larrucea et al “Lean application “ for homeopathic and anthroposphic medicinal products. A proposal from industry for application and variation dossiers.
https://www.ecv.de/beitrag/pharmind/Lean_application_for_homoeopathic_and_anthroposophic_medicinal_products