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Position Paper

Justification for the practice of not fixing the supplier of certain raw materials in the homeopathic medicinal product dossier

SCOPE

Recently, manufacturers of homeopathic medicinal products were asked by a national drug agency to indicate each supplier of raw materials in the quality dossier. This requirement contradicts the current practice of these companies in referring to the suppliers of raw materials in an exemplary way, only. The manufacturers of homeopathic medicinal products represented by the ECHAMP need to maintain this approach and have summarised the arguments and justified the approach.

DEFINITIONS

In this paper the term "raw material" is employed to denote a material in the way the term is used in the document *Guidance on Module 3 of the Homeopathic Medicinal Products Dossier* (HMPWG, Nov 2007).

SCIENTIFIC DISCUSSION AND JUSTIFICATION

Situation of the manufacturers of homeopathic medicinal products

Most of the manufacturers of homeopathic medicinal products offer a wide range of medicinal products whose ingredients are derived from more than 1,000 different raw materials. Some of those raw materials are fairly uncommon and are only used irregularly and in small quantities. It can be difficult for suppliers of those raw materials to offer the material in the required quality. Therefore, in order to ensure the quality of the homeopathic product and the availability of the product on the market, flexibility is needed to be able to change to a different supplier at short notice.

The quality and availability of natural products like plants cannot always be guaranteed over time even by an established supplier, as these materials strongly depend on natural variables such as the climate, pests, harvests, etc. Crop failure or very slow plant growth may e.g. occur. Even the quality of a material from the same supplier may differ too much in two subsequent seasons, which requires a change in the supplier to ensure compliance with the respective requirements of the pharmacopoeia and other relevant regulations. Due to the low demand on the market for some plants, for a number of suppliers it is not feasible to establish a continuous cultivation programme. This can lead to problems for the homeopathic product or the homeopathic active substance manufacturer. Supplier changes may even be necessary to maintain the quality (e.g. purity) as a measure of quality management.

Not having the flexibility to quickly change the supplier endangers the availability of the homeopathic medicinal product.

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The procedural manner of the members of the ECHAMP is in compliance with the *Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin* (EMEA/HMPC/246816/2005). Section 11 "Harvest" states: "Medicinal plants/herbal drugs should be harvested when they are at the best possible quality for the proposed use." In order to achieve the "best possible quality" it is advantageous to be able to change the supplier at short notice. Compliance to GACP recommendations guarantees reproducible quality of herbal raw materials and provides a high level of safety (Lipinsky et al., 2014).

The quality of the used raw material is ensured and guaranteed by the manufacturer of the homeopathic active substance. Generally, suppliers of the raw material or of a mother tincture thereof would deliver a certificate of analysis covering the raw material (the plants) in question, but in certain cases the raw material is bought directly from the collector of a plant, or from the (certified) breeder of an animal. Of course, also in those cases detailed information according to GACP (such as cultivation, harvesting, drying, cutting and primary processing of plants) or comparable data for raw material of animal origin (e.g. breeding conditions) are provided. If the collector or breeder himself is not able to test the material according to the relevant specifications or pharmacopoeial monograph because the equipment for quality control (e.g. chromatographic device) is not available, it is the manufacturer of the active substance who will ensure and guarantee the quality of the raw material by supplier qualification and by testing according to the specifications.

In some cases e.g. if the homeopathic stock is bought from a supplier, the supplier of the raw material might not be known, because the supplier of the homeopathic stock does not provide this information. Since some materials are very rare, the finished product manufacturer has very limited choice and in some cases there is no alternative supplier.

Regulatory background

The production of the homeopathic active substance starts with the most concentrated homeopathic preparation which can be manufactured (e.g. the mother tincture).

According to the HMPWG Guidance on Module 3 (*Guidance on Module 3 of the homeopathic medicinal products dossier*, adopted by the HMA in Nov 2007) information on raw material data and data on the control of raw material have to be provided in section 3.2.S.2.3 "Control of materials" (nomenclature, description, and supportive data) and section 3.2.S.4.1 "Specifications". Section 3.2.S.4.1 states "*The specifications for raw materials, the homeopathic stock(s) and final dilutions should be provided.*" Section 3.2.S.2.1 "Manufacturers" reads "*The name, address, and responsibility of each manufacturer, including manufacturer of stock, dilutions and/or triturations as well as, contractors, and each proposed production site or facility involved in manufacturing/collection and testing should be provided."* This means that raw materials have to be controlled and in line with the specifications for raw materials which have to be provided. In section 3.2.S.2.1 mentioning of the manufacturers of the stock i.e. the mother tincture, the dilution, or the trituration does fulfil the requirements of this section and the distinct and exhaustive mentioning of each possible raw material supplier is not required.

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This happens to be in line with the details laid down in the information sheet of the SWISSMEDIC *Details regarding manufacturers of herbal active substances*, August 2010 (Enclosure 1) where this issue is covered in more detail than in the guidelines of the European Union. In chapter 5 "Details to be provided in the form *Manufacturer Information* with regard to manufacturers of herbal active substances" it is stated that the information to be provided is in alignment with the GMP regulations. In the table on page 2 the "Herbal substances" are listed in "Category I" meaning that both "Test laboratory" and "Batch point release" are "mandatory in GMP rules" and have "to be included on the form", whereas "Manufacturer *(e.g. cultivator)*" is not "mandatory in GMP rules" and does not have "to be included on the form". The accompanying text states:

"Swissmedic considers that full compliance with GMP requirements for manufacturers of i) herbal substances (Category I) […] is compulsory only for the manufacturing steps associated with testing and batch release, as the manufacturers concerned do not usually serve the pharmaceutical market alone, but also supply herbal substances to other markets such as the food, flavourings and cosmetics markets. In this regard, Swissmedic is of the opinion that the authorisation holder or manufacturer of the medicinal product must remain flexible with regard to the purchasing of these products, and will only be able to adequately verify the quality of the herbal substance after carrying out the appropriate analytical tests.

It is essential that the company responsible does not release a medicinal product for the market which contains herbal active substances, which have been released without a GMP compliant quality control performed under the terms of an appropriate licence."

Congruence of the opinion of the SWISSMEDIC with the opinion of the member states of the European Union is demonstrated in *Note for Guidance on Good Manufacturing Practice for Active Pharmaceutical Ingredients* (CPMP/ICH/4106/00; EMEA 2006); "table 1: Application of this Guide to API manufacturing" (Enclosure 2) where the necessity of full compliance with GMP requirements is compulsory only for the manufacturing steps associated with testing and batch release. In the case of homeopathic stocks GMP does not earlier apply than for the first homeopathic production step, e.g. the production of the most concentrated homeopathic preparation (e.g. the mother tincture) (Lipinsky et al., 2014).

Scheme for ensuring quality

All manufacturers of homeopathic medicinal products represented by the ECHAMP are Good Manufacturing Practice (GMP) certified companies. The quality of each raw material, homeopathic stock(s), and intermediates up to the final dilution(s) or trituration(s) to be incorporated into the finished product has to be and is ensured by internal quality control and by qualifying the supplier. In all cases an alternative supplier has to fulfil the same requirements as the original supplier and is evaluated according to the same standard qualification procedure. For all materials only qualified suppliers are accepted and in particular for plant material only qualified suppliers are accepted where compliance with Good Agricultural and Collection Practice (GACP) is confirmed.

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Quality and safety of raw material from animal parts is ensured by complete documentation within a consistent Quality Assurance system of animal origin / breeding, slaughtering, control by a veterinary surgeon, and viral safety assessment.

The requirements laid down in "Points to consider on safety of homeopathic medicinal products from biological origin" (HMPWG, July 2007) are therefore fulfilled for material from animal origin.
All materials introduced in the production process comply with the current versions of the pharmacopoeial monographs or the respective in-house monographs. The specifications for raw materials and for the most concentrated homeopathic preparations together with corresponding certificates of analysis are supplied in the registration dossiers.

Concepts for supplier audits and supplier qualification are employed. The extent of the raw material evaluation is established for each material individually. Monitoring and testing concepts are in place to control the potential impurity levels (e.g. aflatoxins, heavy metals, or pesticides in plant material). By this, possible contamination due to different geographical locations, agricultural cultivation practices, industrial contaminations, storage and shipping conditions are taken into account.

Periodic audits are performed at the homeopathic product manufacturer by the respective authority of each state, investigating and checking the quality control system and the compliance with the requirements.

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OVERALL CONCLUSION

The difficulties of complying with the request to indicate and restrict the manufacturers of homeopathic and anthroposophic medicinal products to a defined selection of suppliers of a raw material in the dossier have been explained. Time constraints, time and cost expenditures, regulatory burdens (variations) together with the risk of not being able to deliver the homeopathic product are high.

Through the quality ensuring procedures within the homeopathic companies the required high quality standard for raw materials, homeopathic stock(s), and intermediates up to the final dilution(s) or trituration(s) to be incorporated into the finished product is guaranteed, and with this efficacy and safety of the homeopathic medicinal product. Therefore, the current practice of mentioning a supplier of certain raw materials in the dossier in an exemplary way only, could and should be kept.

LITERATURE REFERENCES

EMEA, 2006: CPMP/ICH/4106/00: ICH Topic Q 7, Good Manufacturing Practice for Active Pharmaceutical Ingredients, Table 1: Application of this Guide to API Manufacturing

HMPWG, Jul 2007: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2007_07_safety_MP_BO.pdf

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Lipinski A., Beck-Dreschel A., Wellhausen R., Hering J., Orth H., Striebel P., Steinhoff B., Manufacture of Homoeopathic Preparations. Pharmazeutische Industrie 2014;76(3), 388–394

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