

Magistral preparations – Cosmetic and pharmaceutical combinations

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From time immemorial, the tinctures, ointments, creams and inunctions for dermatological applications were compounded by pharmacists on a small scale or individually prepared based on traditional folk medicine recipes. At the present time prefabricated compounds make up the majority of the products sold in pharmacies and in the cosmetic field. For different reasons though, the interest in personalized formulations has currently been increasing.

When proprietary medicinal products are not (no longer) available in pharmacies, the compounding of topical **individual formulations** can be an alternative solution. A variety of particular reasons as for instance a very rare indication, applications for toddlers or intolerance to certain ingredients can present specific challenges regarding the bases, the dosage of ingredients and their availability. Just as for the prefabricated compounds, quality criteria in terms of reproducibility, plausibility, effects and their evidence have been developed for individual formulations and found entry into standard formulations and standard manufacturing processes.

Medical drugs from pharmacies

Physician-directed **magistral preparations** or **small scale preparations** are compounded in pharmacies (**community pharmacy**) or by licensed service providers. The preparation of a single formulation is allowed once for up to 100 units per day **to be kept in stock** (rule of 100). Strict guidelines in terms of hygiene, preparation method, in-process-control, release and documentation apply to the preparation. It has to be mentioned, though, that according to the German Medicinal Products Act, pharmacies are not required to have a specific manufacturing authorisation or drug approval in contrast to the industrial production.

Examples for topical small scale preparations are capsaicin- and DMSO-creams. Information on the substances used as well as the basic regulations considering their verification and processing are found in the Pharmacopoeia Europaea (**Ph. Eur.**) in the form of monographs. The German Pharmacopoeia (Deutsches Arzneibuch – **DAB**), the Austrian Pharmacopoeia (Österreichisches Arzneibuch – **ÖAB**) and the Swiss Pharmacopoeia (Pharmacopoeia Helvetica – **Ph. Helv.**) have become less important in this regard and only list

complementary national regulations that are not contained in the Ph. Eur.

Plausibility and preparation

Precise instructions – particularly for pharmacies – as well as supplementary monographs regarding pharmaceutically used base substances, and above all, standard formulations as well as manufacturing methods are described in the German Drug Codex (Deutscher Arzneimittelcodex – **DAC**) and the affiliated New German Formulary (Neues Rezeptur-Formularium – **NRF**) both published by the Federal Union of German Associations of Pharmacists (Bundesvereinigung Deutscher Apothekerverbände e.V. – **ABDA**). The regulations listed in the DAC/NRF meanwhile also are applicable standard for the manufacturing of proprietary medicinal products and the test certificates required by the German Regulation on the Operation of Pharmacies (Apothekenbetriebsordnung – **ApBetrO**) concerning the identification, purity and content of starting material. Guidelines regarding the plausibility tests of individual formulations before their preparation also are contained.

The Dr. Lennartz laboratory programme for pharmacies is of more recent date; it is published by Deutscher Apotheker Verlag (**DAZ**). The digitalised edition is practice-oriented and contains the test recommendations regarding magistral substances and the identity tests of the DAC/NRF; it allows the download of test certificates and batches of manufactures including spectroscopic (NIR), chromatographic and microscopic data and figures.

The compiled manufacturing instructions allow access to the NRF but also to the Ziegler's library on formulations (**ZRB**) with more than 1000 formulations recorded and thus considerably reduce the documentation efforts as required by law. ZRB also contains topical formulas that are compounded without the conventional state-of-the-art emulsifiers and pre-

servatives. Tolerance and therapeutic synergy of the bases (base creams) thus come more to the fore.

Innovative products from the cosmetic field

As a consequence thereof, pharmacies also are receptive to innovative **base creams** as for instance lamellar skin-barrier-like creams that first have been developed in the cosmetic sector. Usually new systems are more rapidly implemented in the cosmetic skin care since the implementation of evaluations, evidence tests and registration of ingredients and cream bases in the form of monographs or Drug Master Files (**DMF**) can easily take several years until they are generally accepted. Moreover, particularly Drug Master Files (DMF) only are accessible for part of the public although their significance regarding the ingredients can be compared with the entry into one of the above-mentioned pharmacopoeias.

The manufacturer of the hydrogenated phosphatidylcholine used in lamellar base creams has recorded it with the American Food and Drug Administration (**FDA**) and with Canada Health as an ingredient for the use in pharmaceutical formulations.

The declaration of ingredients of a lamellar cream as a pharmaceutical variant is as follows:

Medium-chained triglycerides Ph. Eur. 9.0, Pentylene glycol DMF PH 250371 (EU), Hydrogenated phosphatidylcholine DMF 10991 (US) and DMF 9791 (Canada), Refined shea butter DAC 2017, Glycerin Ph. Eur. 9.0, Squalane Ph. Eur. 9.0, Purified water Ph. Eur. 9.0.

By way of comparison, the INCI declaration in cosmetic applications: Aqua, Caprylic/Capric Triglyceride, Pentylene Glycol, Hydrogenated Lecithin, Butyrospermum Parkii Butter, Glycerin, Squalane.

Dermatological cosmetics

Lamellar base creams show how magistral preparations for dermatological purposes and modular cosmetics can perfectly intertwine and how skin problems can thus be resolved in a sustained manner. Medical drugs are integrated into a base cream for the dermatological therapy and thus allow for a fast relief in the case of indication-induced medical conditions (e.g. anti-inflammatory effects). After the acute crisis is over, the cosmetic prevention phase can begin while continuing with the same lamellar base creams however with effective cosmetic agents added. The benefits for patients are obvious:

- The base, or more precisely, base cream, for therapy, prevention and skin care remains the same.
- Thus there is no need to change from one base cream product to another, a fact which usually is accompanied with a change in functionality and a transition phase for the skin. At this point, it should be mentioned that not every base cream is suitable for individual skin care.
- The same base supports the acceptance and consequent follow-up care on the part of the patient.
- A significant issue in this context is that already during the medical therapy the skin barrier is repaired and maintained with physiologically useful components so that it is guarded against potential relapses caused by external germ-induced-, allergic- and chemical stress.

This is not a recent concept though. Albert A. Kligman, dermatologist, could show in the nineties that the care of the skin barrier (without medical drugs) is a significant clinical issue. In this context, he coined the term “corneotherapy”. It will probably still take decades until the pharmaceutical formulations that predominantly use conventional bases which basically focus on their function as a medical drug carrier will be exchanged into skin-barrier-affine, or in other words, corneotherapeutic bases.

Good manufacturing practice

From time immemorial the bases have played a predominant role in the cosmetic field as it basically focuses on skin care and skin protection. In the field of modular (“individualized”) cosmetic care, the first step after implementing an analysis of the skin is to select the individually optimal base creams and only then, in a second step, choose the formulation with the adequate cosmetic active agents that, i.e. can smooth erythema or wrinkles or improve the skin hydration.

Pharmacy however usually has focused on the medical drug and then chosen the base (carrier substance) that can incorporate the drug and release it in the desired form. Today dermatology increasingly takes recourse to particularly well tolerable and barrier-supporting cosmetic bases. The Regulation on the Operation of Pharmacies (Apothekenbetriebsordnung – ApBetrO) is taking this into account by stipulating the certificate for Good Manufacturing Practice (**GMP**) for pharmaceutical active agents, but also by excluding the active agent free bases in its § 11. “The test certificate shall inform on the GMP-compliant manufacturing of

a starting material as far as it is an active agent". It can be expected, that this restriction will fall when compiling future versions of the Regulation on the Operation of Pharmacies, for the following reasons:

- The unequal treatment of different components of a pharmaceutical formulation does not make any sense. Already today the health authority pharmacist in charge, contrary to the statement listed in the Regulation on the Operation of Pharmacies asks for the GMP certificate for cosmetic bases in the respective pharmacies.
- It also is quite illogical when the components of formulations to be applied onto the skin of patients or consumers are examined and tested on the basis of different guidelines.
- The **cosmetics GMP** that has been introduced several years ago is brought more and more into line with the GMP for topical-pharmaceutical preparations.
- More and more frequently pharmaceutical active agents are integrated into cosmetic preparations, as e.g. in anti-dandruff preparations.

Profitable secondary business

Other than that, the manufacturing of cosmetic preparations in pharmacies has developed into a profitable secondary business. It should however be mentioned that many of the pharmacists are ignorant as to the fact that such manufacturing is subject to the guidelines of the European Cosmetic Directive (**EG Nr. 1223/2009**) respectively the identical German Cosmetic Directive (**KVO**) and the above mentioned Rule of 100 for small scale production according to § 1 a (9) Regulation on the Operation of Pharmacies hence is not applicable in this case. Since we are dealing here with a production in terms of the law, the pharmacies are controlled by the responsible official veterinary and food control authorities in accordance with the Foodstuffs and Consumer Goods Law (Lebensmittel- und Bedarfsgegenständegesetz (**LMBG**)).

German Cosmetic Directive (KVO) and the daily practice in cosmetic institutes

In the cosmetic institutes finished products usually are individually adapted before their use, either by mixing different finished products or by addition of water, perfumes or also harmless chemicals such as salt (peeling), sugar (peeling), healing earth (masks) and herbal oils (skin care, massages).

As far as such adapted preparations are sold over the counter, the institutes, just as the pharmacists, legally are regarded as cosmetic manufacturers and hence are subject to all respective requirements stipulated in the German Cosmetic Directive (KVO), in other words, requirements that the institutes usually cannot abide by. This applies to modular, individualised cosmetic preparations but also to the bottling of salon products in smaller-sized and labelled dispensers or jars. Also an automated dispenser in shopping malls which, after analysing the skin, can mix a ready-made and labelled cosmetic compound from a limited amount of components is regarded as a manufacturer involving all requirements stipulated by the German Cosmetic Directive.

Cosmetic institutes only have two alternatives for selling modular, or in other words, hand-made cosmetic preparations to their customers:

- Selling bases (base creams, base gels, foundations, lotions) and active agents in the form of aqueous or oil-containing sera with all components being registered in the European Cosmetic Products Notification Portal (**CPNP**) as finished products. The customers then mix the products at home according to the formulation provided with the components.
- Mixing of components of the individual formulation in the institute on behalf of the client and then billing it as a service.

Adjustment of regulations expected

It can be assumed that the regulations for pharmaceutical-topical- and cosmetic finished compounds and individual formulations and their manufacturing will be adjusted in future.

Moreover it can be assumed that the special status of topical **medical products** will change, since quality requirements and the thus related compositions often do not even correspond with the basic standards of the German Cosmetic Directive. In spite of the above-mentioned progress in corneotherapy it remains to be seen how the restrictive handling of health **claims** will develop in the future.

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Dr Hans Lautenschläger