ECHAMP
European Coalition on
Homeopathic & Anthroposophic
Medicinal Products

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Ministry of Health and Care Services in Norway
Mr. Jan Berg
Mrs. Katrine S. Edvardsen Espantaleón
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Norway

Brussels, 20 October 2016

ECHAMP comments on the consultation paper "Proposed amendments to Regulations relating to medicines: Registration system for homeopathic medicines"

Dear Mr. Jan Berg, dear Mrs. Katrine S. Edvardsen Espantaleón,

ECHAMP, the European Coalition on Homeopathic & Anthroposophic Medicinal Products, is the European association of companies that work closely together to ensure that its members can meet the demand from users and prescribers across Europe for these products. It advocates in favour of an appropriate regulatory environment in the EU. It has about 45 members from 18 Member States.

ECHAMP highly welcomes the recent consultation paper on proposals for amendments of the registration system for homeopathic medicinal products. The consultation paper seriously takes into account the situation of homeopathic medicinal products in Norway and the EU Directive 2001/83/EC.
Especially the following proposals are very valuable to overcome the actual transition period with the aim of product registrations and towards a harmonized EU market:

- The implementation of a registration system for new registration of homeopathic medicinal products in accordance with Art.14 in the spirit of the legislation:
  - Introduction of a true simplified registration for these products by following expressly Art. 15 without requesting more documentation.
  - Acceptance of the 1:10000 dilution (equivalent to D4) as main rule, requiring further safety data or higher dilutions only in case of extremely toxic substances.

- The implementation of a registration system for homeopathic medicinal products which are already registered in an EU country in accordance with Art.14 of Directive 2001/83/EC as amended
  - Requirement of submission of the EU homeopathic application form including its annexes, which gives the core data and responsibilities without requesting a complete registration dossier;

  - Taking fully into account existing assessments on product quality and safety carried out by EU competent agencies;
  - Fulfilment of the intention of the EU legislator towards harmonisation of requirements and free movement of goods in the EU / EEA market.
- The introduction of a temporary exemption from the Norwegian language requirement during which Swedish / Danish / English packaging is accepted.
- The reduction of the registration fee to NOK 1000.
- The decision that registered homeopathic medicinal products are non-prescription products.

Nevertheless, we would like to draw your attention on the following points of the consultation letter:

- Definition of the term "external" for homeopathic medicinal products in Directive 2001/83/EC:
  According to the Norwegian Medicines Agency eye drops do not fall under the definition “external”. We kindly ask you to reconsider this interpretation and to take into account the considerations of the HMPC in the “Public Statement on the interpretation of the term “external use” for use in the field of traditional herbal medicinal products” which states the following:
  “*For the purpose of traditional use registration, the term “external use” shall be interpreted as “application to the skin”, however if the traditional u se of a herbal substance, preparation or medicinal product refers to the delivery to the oral, nasal, rectal, vaginal mucosae or to ocular or auricular use, such use may be acceptable if no safety concerns exist and if local action is intended*”. We think that the same approach is true for the registration of homeopathic medicinal products according to Art. 14, even more considering the fact that these homeopathic dosage forms do exist in the EU since many years. Please see also page 10 of the attached ECHAMP position paper on the meaning of “administered orally and externally”.

- Approval exemption
  The possibility to import medicinal products without a marketing authorisation with a special permit from the Norwegian Agency called approval exemption is essential for doctors and patients to choose the therapy they consider the adequate. The Ministry proposes for homeopathic medicinal products, which are approved in another country in the EEA, that they should be covered by this approval exemption. We welcome this decision. What is not acceptable is that the Ministry wants to establish a negative list for the products that cannot be notified in this way including injections, which have been under this exemption for the last thirty years. This leads to a very time consuming procedure in which doctors have to explain the reasons for their prescription. This procedure leads to a delay for delivering the medicinal product to the patient. Considering that these medicinal products have been imported with the approval exemption without any special declaration of the doctors till now and there is no incident to assume a higher risk we advocate no to change the procedure for homeopathic injections.

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- Timelines
  We understand the intention of the Norwegian Medicines Agency to finalize the transitional situation of homeopathic medicinal products as soon as possible. Nevertheless, we see that it could be a problem to for many companies to produce the mock-ups within a few months left until January 12 because not all companies do have labelling in Swedish and/or Danish and/or English. We would appreciate to have an extended period of transition for this topic, e.g. until end of 2017.

- Marketing authorization
  Unfortunately, the consultation paper does not mention the possibility of marketing authorization according to Art. 16.2. of the Directive 2001/83 as amended. For the homeopathic industry, doctors and patients, it is of high importance to have this possibility in Norway as well. There are several countries, which implemented Art. 16.2 with specific requirements adapted to the tradition of homeopathic and anthroposophic medicinal products. The proposed Norwegian system of acceptance of registrations existing in EU countries could also be applied for marketing authorizations granted in accordance with Art. 16.2.

- Anthroposophic medicinal products
  In our last communication we addressed the topic recognition of the general monograph "Anthroposophic preparations" and "Manufacturing methods for anthroposophic preparations" of the Swiss Pharmacopoeia and the Anthroposophic Pharmaceutical Codex (APC) (www.iaap.org.uk). As a member of EFTA, Norway could adopt this decision like Switzerland or to accept the APC as supportive reference for the manufacturing methods. We also would like to encourage you to include the definition of anthroposophic medicinal products into the Norwegian law (see German Drug Law, APC, or Swiss Pharmacopoeia Ph. Helv 11.1.)
  Again, we would like to point out that these monographs would be the basis for an equivalent simplified registration for those products which are not produced exactly according to a homeopathic manufacturing method but have similar safety profiles like homeopathic medicinal products and are registered in another European country.

ECHAMP welcomes the constructive proposal for amendments and would very much appreciate if you could take these comments into your consideration

We are looking forward to your reply.

Yours sincerely,

Dr. Gesine Klein
President of ECHAMP

Dr Mónica Mennet-von Eiff
Deputy Board Member of ECHAMP

Annex: ECHAMP position paper on oral and external use

What is the meaning of "administered orally or externally" as given in Art. 14 of Directive 2001/83/EC for simplified registration of homeopathic medicinal products?

Contents

1. Background

The Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 states in Article 14(1). "Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:
- they are **administered orally or externally**,
- ….."
The same directive amended in 2004 by Directive 2004/24/EC states in Art 16a an amendment which led in 2004 to the Directive 2004/24/EC, in Article 16a(1). "A simplified registration procedure (hereinafter "traditional- use registration") is hereby established for herbal medicinal products which fulfil all of the following criteria:
…
(c) they are an **oral, external and/or inhalation preparation;**
…"

For assignment of terminology, as German literature has been used for compiling this discussion, the text from the directive is also given here in German:

"Die Richtlinie 2001/83/EG des europäischen Rates und des Rates vom 6. Nov. 2001 legt in Artikel 14 (1) fest "Einem besonderen Registrierungsverfahren können nur homöopathische Arzneimittel unterliegen, die alle nachstehend aufgeführten Bedingungen erfüllen:
- **orale und äußerliche Anwendung;**
- ….."

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Diese Richtlinie aus der durch eine Änderung im Jahr 2004 die Richtlinie 2004/24/EG hervor ging, legt hinsichtlich traditioneller pflanzlicher Arzneimittel in Artikel 16a(1) folgendes fest. "Hiermit wird ein vereinfachtes Registrierungsverfahren (nachfolgend "Registrierung als traditionelles Arzneimittel" genannt) für pflanzliche Arzneimittel festgelegt, die allen nach stehenden Anforderungen genügen:
…
c) Sie sind eine Zubereitung, die zur **oralen, äußerlichen Anwendung und/oder zur Inhalation** bestimmt ist."

It is worth mentioning that also the precursor directive, Council Directive 92/73/EEC, gives no further information. The text given in Article 7 "they are administered orally or externally" is identical to the text in Article 14(1) of Directive 2001/83/EC as quoted above.

Different opinions regarding the definition of "oral application" [in German: "orale Anwendung"] and "external application" [in German: "äußerliche Anwendung"] exist, and this is obviously the reason why the HMPWG in their 20th meeting on 4-5 December 2014 in Rome, Italy, dealt with the definition of "administered orally or externally". The member states were asked to express their point of view and cast their vote on one of the proposals:

"*Three different proposals were put forward:*
(I) Considering the interpretation of the term "administered orally or externally" by excluding all the routes of administration but cutaneous use, or
(II) delete any reference to the routes of administrations in the Notice to Applicants or
(III) whether the requirement "administrated orally or externally" mentioned in article 14 in the Directive 2001/83/EC, where appropriate could include routes of administration other than cutaneous use such as "nasal, rectal, vaginal, ocular or auricular use" on a case by case basis provided that the safety of the application is ensured. Injectables are excluded.

A new letter to the European Commission will be drafted taking into account all the different positions expressed by the MSs."

In the meantime the HMPWG has informed in a public report about the outcome of their 21th meeting held on 28-29 May 2015 in Strasbourg, France:
"*The contents of an official letter to the European Commission regarding the interpretation of "homeopathic medicinal products administered orally or externally", as it was discussed in Rome, were agreed. The document is going to be handed over directly to the European Commission*"

It is noted, that it remains unclear what the intention was, when choosing the terms "orally" and "externally" in Article 14 (Directive 2001/83/EC). Were the application forms restricted because of safety concerns or was it writing down, what was commonly used in homeopathy?

The following compilation and discussion of different statements from the text of regulatory directives, guidelines and guidance, as well as pharmaceutical, pharmacological, clinical and medical literature is meant to illuminate the question of which application forms are included in the term "administered orally or externally", or "oral and external application". For the consulted references see chapter "5. Literature".

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2. European Guidelines and Guidance - external use and local use

Firstly, definitions and statements given in directives, guidelines and guidance are looked at.

Notes are given in ***"Public statement on the interpretation of the term "external use" for use in the field of traditional herbal medicinal products" from 12 May 2006*** of the HMPC (Committee on Herbal Medicinal Products):

Although the HMPC clearly states that the term "external use" should be interpreted as "application to the skin", in the same sentence it also allows other application forms for the traditional use registration if there are no safety concerns and if local action is intended:

"For the purpose of traditional use registration, the term 'external use' shall be interpreted as "application to the skin"; however if the traditional use of a herbal substance, preparation or medicinal product refers to the delivery to the oral, nasal, rectal, vaginal mucosae or to ocular or auricular use, such use may be acceptable if no safety concerns exist and if local action is intended."

In order to describe more exactly the term "local action" (see above), the following definition is given in the ***"Note for guidance on the clinical requirement for locally applied, locally acting products containing known constituents" from November 1995 (CPMP/EWP/239/95)*** of the CPMP (Committee for Proprietary Medicinal Products): "*Locally acting products are products which are applied locally and are assumed to exert their effect at the site of application; systemic action, if any, would be considered as an undesired effect. Examples are dermatological products (e.g. creams, ointments), inhalatory products like powders or aerosols for inhalation, eye drops, ear drops, nasal products but also orally, vaginally, or rectally applied products which act locally (see also: Note for Guidance CPMP list for allowed terms III/3593/91)*".

Also the more recent "***Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**)" from 20 January 2010*** confirms this definition (on page 24 of 27) below the heading *"Locally acting locally applied products":*
"For products for local use (after oral, nasal, pulmonary, ocular, dermal, rectal, vaginal etc. administration) intended to act at the site of application, recommendations can be found in other guidelines (CPMP/EWP/4151/00 rev 1, CPMP/EWP/239/95)." […]
"Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured."

The recently published ***"Concept paper on the development of a guideline on quality and equivalence of topical products (EMA/CHMP/QWP/558185/2014)" from 2 December 2014,*** gives on page 2 the following "Problem Statement":
"Topical products are exemplified by medicines for cutaneous use; but in broadest scope, they are locally applied, locally acting products. They can be applied to any of the diverse external surfaces of the body that may present a physiological barrier to drug absorption e.g. skin, eye, ear.
The site of local action for topical products may be:
- *External - on the surface of the physiological barrier;*
- *Internal - at and about the physiological barrier; and*
- *Regional - beyond the physiological barrier in adjacent tissues."*

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The underlined lines of the above text translate into German as: "Topische Produkte sind beispielhaft durch Arzneimittel zur kutanen Anwendung veranschaulicht, aber in umfassenderem Rahmen sind sie lokal angewandte, lokal wirkende Produkte. Sie können auf jede der zahlreichen äußerlichen Oberflächen des Körpers angewandt werden, die eine physiologische Barriere zur Arzneimittelabsorption bilden, wie z.B. Haut, Auge und Ohr."
Furthermore the Belgian Federal Agency for Medicines and Health Products (FAGG-AFMS) states in its Guidance for Labelling of medicinal products from 2010 on page 9 the following (translated from French into English):
If a pharmaceutical product is intended to be used parentally or topically (i.e. not only those medicaments intended for an external dermal application but also all medicaments applied via the oral, nasal, rectal and vaginal mucosa), an ocular product or is used for inhalation, ...

3. Excerpts from Literature

3.1 Classification systems

3.1.1 Intravascular and extravascular application

A different approach to looking at the application forms, is the classification into *intravascular* (direct application into the bloodstream via injection or infusion) and *extravascular* application (all forms of application which are not intravascular; outside a blood or lymph vessel) as laid down in several references (Hunnius, 2014; Hänsel / Sticher, 2004; Mutschler, 2001; and Hauschild, 1961):

Intravascular application: intravenous (i.v.), intra-arterial (i.a.), intracardiac.
Extravascular application: e.g. intramuscular (i.m.), subcutaneous (s.c.), oral, sublingual, rectal, vaginal, dermal, pulmonary, and nasal.

3.1.2 Local and systemic application

The classification into "local" and "systemic" is not diametrically opposed to "oral", and it is important to understand it. The term "external use" is not really handled in literature and where it is mentioned, it is done so in a way that is not helpful for the discussed question.

When searching through the regulations and guidance, the question of whether a product is acting locally or systemically becomes apparent. In principle this topic has to be answered case by case, but the following general statements have been compiled from literature (see list in chapter 5). Information regarding this topic is also found in an official document of the EDQM (presented on the next page).

According to Kuschinksky, Lüllmann, Mohr (1993) a characteristic of local therapy is that the concentration of the drug is high enough to have an effect only at the site of application, but the amount of drug resorbed into the whole organism at the same time stays subtherapeutic.

EDQM Standard Terms
(Internal controlled vocabularies for pharmaceutical dose forms)
Excerpts from the table "**Intended site**"

Name	Definition
Auricular	Relating to the ear as the intended site of administration, usually where the pharmaceutical product is intended for action in the auditory canal (external auditory meatus).

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Cutaneous/ Transdermal	Relating to the skin or its appendages (e.g. hair, nails) as the intended site of administration, including where the pharmaceutical product is intended for action on the surface of the skin, within the skin, or systemically after passing through the skin.
Nasal	Relating to the nose as the intended site of administration, including where the pharmaceutical product is intended for local action in the nasal cavity or for systemic action after absorption through the mucous membrane; the lower respiratory tract is excluded.
Ocular	Relating to the eye as the intended site of administration, including where the pharmaceutical product is intended for action on the surface of the eye or conjunctiva, around the eye, or within the eye.
Oral	Relating to the mouth as the intended site of administration, but where the pharmaceutical product is administered with the intention of passing into the stomach via the oesophagus; the mucosa of the mouth itself is not the intended site of action (see oromucosal).
Oromucosal	Relating to the mouth as the intended site of administration, where the pharmaceutical product is administered with the intention of acting on the mucosa of the mouth, whether for local or systemic use.
Parenteral	Relating to the internal body as the intended site of administration, other than the natural openings and cavities such as the gastrointestinal tract, auditory canal, nasal cavity, lungs, etc.; the pharmaceutical product is usually administered by breaking the skin, such as by injection, infusion, and implantation.
Pulmonary	Relating to the lungs as the intended site of administration, where the pharmaceutical product is administered, usually by inhalation, for local action in the lower respiratory tract or for systemic action after absorption via the lower respiratory tract.
Rectal	Relating to the rectum as the intended site of administration, where the pharmaceutical product is administered via the anal canal, for local action in the rectum or for systemic action after absorption via the rectum.
Vaginal	Relating to the vagina as the intended site of administration, where the pharmaceutical product is administered via the vaginal opening, usually for local action in the vagina but sometimes for systemic action after absorption via the vagina.

The table shows that most of the application forms act locally, and after absorption can also act systemically, whereas "auricular" and "ocular" applied medicines solely act locally. The text for "oral" gives a differentiation between "into the stomach" (for "oral") and "oromucosal" where the mouth is the intended site of application. For "oromucosal" application local and systemic are equally mentioned ("*acting on the mucosa of the mouth, whether for local or systemic use*").

The following table represents a summary of information mainly taken from Griffin, Posner, Barker, 2013; Aktories et al, 2005; Aulton, 2002; Ritschel, Bauer-Brandl, 2002; Kuschinsky, Lüllmann, Mohr, 1993:

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Main wording of the application form is taken from EDQM standard terms; (in brackets other terms used e.g. in literature or FDA guidance).

Application form	**local**	comment	**systemic**	comment
oral	+	e.g. local treatment in the gastrointestinal tract (e.g. kaolin, laxatives, contrast agents)	+++	

Application form	**local**	comment	**systemic**	comment
Cutaneous (topical, dermal)	+++	e.g. Arnica ointment for bruises	(+)	e.g. transdermal systems, e.g. homeopathic dilutions, especially for deep-rooted chronic conditions in addition to internal application (Genneper, 2004[1])
Pulmonary (inhaled)	+++	e.g. broncholytic drugs	(+)	e.g. insulin; explored for the delivery of peptides
Nasal (intranasal)	+++		(+)	explored for the delivery of peptides
Ocular (ophthalmic)	+++		-	solely used for local treatment, although some systemic exposure occur
Auricular (aural, otic)	+++		-	solely used for local treatment, although some systemic exposure occur
Vaginal	+++		-	solely used for local treatment, although some systemic exposure occur
Rectal	++	mostly used for local treatment	+	e.g. paracetamol, diazepam

[1] Remark: For chronic conditions high potencies are used, with no substantial amount of active present.

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Application form: injectables	**local**	comment	**systemic**	comment
intravenous (i.v.)	-		+++	the most prompt onset of action
Intramuscular (i.m.)	+	e.g. Ruta or Rhus injection in painful muscles	++	injection of depot preparations
subcutaneous (s.c.)	?		++	injection of depot preparations
intra-artricular (into the joint)	+++		(+)	
intra-dermal	+++	e.g. diagnostic tests as allergy tests	(+)	
intrathecal	+++	e.g. local anaesthetics into the spinal	(+)	

Legend:+++ Mainly or solely "local" OR "systemic" effect
++ Mostly "…" effect
+ Sometimes "…" effect
(+) Rarely "…" effect
- Not "…" effect
? Use is unclear

It appears that the application forms from cutaneous up to rectal (i.e. cutaneous, pulmonary, nasal, ocular, auricular, vaginal, rectal) act solely, mainly or mostly locally in contrast to oral, intravenous and intramuscular applications which mainly act systemically.

3.2 Oral application

"Oral" (or in German: "peroral") derives from the Latin "per os" meaning "by way of the mouth", "by mouth", "through the mouth". Many different medications are taken orally (are swallowed) but the active ingredient can partly already be absorbed in the mouth and therefore oral administration of medication includes buccal and sublingual administration (Actories, 2005; IOWiG, oral medication, 2012; Mosby's Medical dictionary, 2009).

"Homeopathic medicines [e.g. homeopathic pillules, homeopathic tablets] are thought to be absorbed in the mouth (Kayne, 2006). Homeopathic preparations demonstrate their activity through the mucous membranes of the tongue and mouth" (Genneper, 2004).

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In German-language literature there is a differentiation between (German:) "orale" administration meaning sublingual or buccal application (e.g. lozenges) and (German:) "perorale" administration, meaning administration through the mouth (throat) into the gastrointestinal tract (GI-tract) and achieving absorption or local effect in the GI-tract (e.g. "standard" or coated tablets) (Ritschel, Bauer-Brandl, 2002; Meier, Rettig, Hess, 1981). The advantages given by the "orale" application are (a) onset of action can be fast; (b) the first pass effect through the liver is avoided, because this application route can be regarded as parenteral route; (c) better absorption of non-ionic substances.

The EDQM Standard Terms gives in the chapter "intended site" the following definition for "oral": *"Relating to the mouth as the intended site of administration, but where the pharmaceutical product is administered with the intention of passing into the stomach via the oesophagus; the mucosa of the mouth itself is not the intended site of action (see oromucosal)*" and for "oromucosal": "*Relating to the mouth as the intended site of administration, where the pharmaceutical product is administered with the intention of acting on the mucosa of the mouth, whether for local or systemic use*."

In the European Pharmacopeia (Ph. Eur.) "Oromucosal preparations" ("Praeparationes buccales") are listed in the section "dosage forms". They are defined:
"Oromucosal preparations are solid, semi-solid or liquid preparations, containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect. Preparations intended for a local effect may be designed for application to a specific site within the oral cavity such as the gums (gingival preparations) or the throat (oropharyngeal preparations).
Preparations intended for a systemic effect are designed to be absorbed primarily at one or more sites on the oral mucosa (e.g. sublingual preparations). Mucoadhesive preparations are intended to be retained in the oral cavity by adhesion to the mucosal epithelium and may modify systemic drug absorption at the site of application. For many oromucosal preparations, it is likely that some proportion of the active substance(s) will be swallowed and may be absorbed via the gastrointestinal tract."

"Several categories of preparations for oromucosal use may be distinguished:
- gargles,
- mouthwashes,
- gingival solutions,
- oromucosal solutions and oromucosal suspensions,
- semi-solid oromucosal preparations (including for example gingival gel, gingival paste, oromucosal gel, oromucosal paste),
- oromucosal drops, oromucosal sprays and sublingual sprays (including oropharyngeal sprays),
- lozenges and pastilles,
- compressed lozenges,
- **sublingual tablets and buccal tablets**,
- oromucosal capsules,
- mucoadhesive preparations
- orodispersible films."

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Ph. Eur. monograph "Homoeopathic preparations" states: "Homoeopathic dosage form 'pillule' …. and … homoeopathic dosage form 'tablet' are intended for sublingual or oral use."

Looking at the official US-FDA page "Route of administration" the term "oral" is explained as "Administration to or by way of the mouth"."Oromucosal" does not appear in the list, but instead "Oropharyngeal" with the definition "Administration directly to the mouth and pharynx".

4. Discussion, conclusion and recommendation

The Directive 2001/83/EC as amended states "administered orally or externally" but it gives no definitions for these terms.
More than 40 references from European Guidance and from published literature in German and English have been examined to seek definitions and explanations regarding the terms "oral use" and "external use". Different classification systems were found in literature: "local and systemic", and "intravascular and extravascular" application (explained in the paper). The classification "external" and "oral" as given in the Directive 2001/83/EC does not exist in the literature.

There does not seem to be one truth.

The definitions for "oral application" in the literature differ from each other which gives potential for misunderstanding. Oral medication in English literature is mainly seen as a swallowed medication including application within the mouth as a smaller part and acts therefore mainly systemically. The term "oromucosal" is missing. Is "oromucosal" a subtype of oral? In English literature and as well in the Directive 2001/83/EC it could be answered with yes.

Since oromucosal application is a traditional application in homeopathy e.g. for sublingual pillules, it is logical, that this application is included in the term "oral" of Article 14 of the Directive 2001/83/EC as Article 14 was explicitly written for homeopathic preparations.

The same should apply to the term "external". As in the term "oral" the "oromucosal" application is included, it seems logical to include application forms as nasal, ocular, auricular, vaginal, and rectal in the term "external (use)". Not doing it would be seen as applying double standards.

With excerpts from guidelines, guidance and literature, the current status of the term "external use" has been highlighted and explored. It seems likely that products applied topically, pulmonarily, nasally, ocularly, auricularly, and vaginally would fulfil the requirements for "external use", and accordingly "local use". Also some injections (into the joint, intra-dermal and intrathecal) would fall into the category "local use".
The rectal application might require more investigation and argumentation based on the specific product, case by case.

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Recommendation:

Although there are different definitions and subcategories of the term "oral" administration it is clear that all of these are applicable with regard to the simplified registration procedure of homeopathic medicinal products according to Article 14(1) of Directive 2001/83/EC.

Taking it all together and in consideration of the lack of clarity of the definition of "external" use it is recommended to apply for homeopathic medicinal products undergoing simplified registration procedure the principles of the statement of the HMPC laid down for traditional herbal medicinal products in ***"Public statement on the interpretation of the term "external use" for use in the field of traditional herbal medicinal products" from 12 May 2006*** of the HMPC (Committee on Herbal Medicinal Products):

"For the purpose of traditional use registration, the term 'external use' shall be interpreted as "application to the skin"; however if the traditional use of a herbal substance, preparation or medicinal product refers to the delivery to the oral, nasal, rectal, vaginal mucosae or to ocular or auricular use, such use may be acceptable if no safety concerns exist and if local action is intended."

We recommend the following exceptions:
- For rectal use a case by case assessment and decision seems appropriate
- Certain injections such as "into the joint", "intra-dermal" and "intrathecal", should be included as they are for local use. Beside these, other types of injections might also be regarded as exceptions, as long as they are foreseen to act locally due to their therapeutic intention. A case-by-case decision is to be taken here.
- Although some homeopathic solutions for deep-rooted chronic conditions are applied to the skin (in addition to the internal application), in order to reach a systemic effect, they are regarded as acceptable, as for chronic conditions high potencies/dilutions are used, with no substantial amount of active ingredient present. As long as no safety concern exist.

With this approach we believe that the intentions of Article 14 of Directive 2001/83/EC laid down in the Council Directive 92/73/EEC are fulfilled:
"*Whereas, having regard to the particular characteristics of these medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, it is desirable to provide a special, simplified registration procedure for those traditional homeopathic medicinal products which are placed on the market without therapeutic indications in a pharmaceutical form and dosage which do not present a risk for the patient.*"

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5. Literature

1. Aktories K,Förstermann U, Hofmann FB, Starke K. Allgemeine und spezielle Pharmakologie und Toxikologie. Elsevier GmbH, Urban & Fischer Verlag, München, 9. Auflage, 2005.
2. Ammon. Hunnius – Pharmazeutisches Wörterbuch. Walter de Gruyter, Berlin, 9. Auflage, 2004.
3. Ammon HPT; Schubert-Zsilavecz M. Hunnius – Pharmazeutisches Wörterbuch. Walter de Gruyter, Berlin, 11. aktualisierte Auflage, 2014.
4. Aulton ME. Pharmaceutics – The Science of Dosage Form Design. Churchill Livingstone, Edinburgh. Secon Edition, 2002.
5. Bundesverband der Arzneimittelhersteller e.V. BAH um Vier. Ausgabe 75 – 23.04.2015.
6. Council Directive 92/73/EEC of 22 September 1992. Online available: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31992L0073, 15.08.2015
7. Damodharan, N. Dosage Forms Unit I. Online available: http://www.srmuniv.ac.in/downloads/Dosage_forms.pdf, 18.02.2015
8. Directive 2001/83/EC of the European Parliament and of the European council of 6 November 2001, amended and consolidated until 2012. Online available: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf, 01.06.2015.
9. Human Medicines Regulations. Part 7, Traditional herbal registrations. TSO (The Stationery Office), United Kingdom, 2012.
10. EDQM (European Directorate for the Quality of Medicines & HealthCare / Direction européenne de la qualité du médicament & soins de santé). Standard Terms – Pharmaceutical dosage forms, Routes of administration, Containers. 5th Edition, December 2004. Online available: https://standardterms.edqm.eu, 26.03.2015.
11. EDQM (European Directorate for the Quality of Medicines & HealthCare / Direction européenne de la qualité du médicament & soins de santé). European Pharmacopoeia 8.0. Oromucosal preparations. 2014.
12. EMA (European medicines agency – Science, Medicines, Health). Concept paper on the development of a guideline on quality and equivalence of topical products. 2 December 2014. Online available: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500186088&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc, 01.06.2015.
13. EMA (European medicines agency - CHMP). Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. 20 December 2010. Online available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf, 01.06.2015.

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14. EMA (European medicines agency - CPMP). Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents. CPMP/EWP/239/95 final. June 1996. Online available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003687.pdf , 01.06.2015.

15. FAGG-AFMPS (Belgian Federal Agency for Medicines and Health Products): "Etiquetage des medicaments". 2010. Online available: http://www.fagg-afmps.be/fr/binaries/verpakking-finaal%20fr-2010-08_tcm291-106539.pdf , 23.10.2015.

16. Genneper T. Homöopathische Gabenlehre. In: Genneper T, Wegener A (Hrsg.). Lehrbuch der Homöopathie. Haug Verlag, Stuttgart, 2. Auflage, 2004.

17. Griffin JP, Posner J, Barker GR. The Textbook of Pharmaceutical Medicine. Wiley-Blackwell, 7th Edition, 2013.

18. Hänsel R, Sticher O. Pharmakognosie – Phytopharmazie. Springer Verlag, Heidelberg. 7. Auflage, 2004.

19. Hauschild F. Pharmakologie und Grundlagen der Toxikologie. VEB Georg Thieme, Leipzig, 1961.

20. HMPC (Committee on Herbal Medicinal Products). Public statement on the interpretation of the term 'External use' for use in the field of traditional herbal medicinal products. EMEA (European Medicines Agency – Evaluation of Medicines for Human Use), London, 12.05.2006.

21. Homeopathic medicinal product working group (HMPWG). 20th meeting, 4-5 December 2014, Rome, Italy; HMA (Heads of Medicines Agencies); Public Report.

22. Homeopathic medicinal product working group (HMPWG). 21th meeting, 28-29 May 2015, Strasbourg, France; HMA (Heads of Medicines Agencies); Public Report.

23. Homeopathic medicinal product working group (HMPWG). Points to consider on safety of homeopathic medicinal products from biological origin. EMEA (European Medicines Agency – Evaluation of Medicines for Human Use), London, January 2015.

24. IQWiG (Institute for Quality and Efficiency in Health Care). Oral medications. PubMed Health. Informed Health Online [Internet]. Cologne, Germany, 2006, last update: 2012. Online available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0005195/

25. IQWiG (Institute for Quality and Efficiency in Health Care). Topical medications. PubMed Health. Informed Health Online [Internet]. Cologne, Germany, 2006, last update: 2012. Online available: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0005203/

26. Kayne SB. Homeopathic Pharmacy – Theory and Practice. Elsevier, Churchill Livingstone, Edinburg 2006

27. Kuschinsky G, Lüllmann H, Mohr K. Kurzes Lehrbuch der Pharmakologie und Toxikologie. Georg Thieme Verlag, Stuttgart, 1993.

28. Le J. Drug Absorption. [see Merck Manuals]

29. List PH. Arzneiformenlehre – Ein Lehrbuch für Pharmazeuten. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1976.

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30. Meier J, Rettig H, Hees H. Biopharmazie, Theorie und Praxis der Pharmakokinetik. Georg Thieme Verlag, Stuttgart, 1981. Pages 16,17,35.

31. Merck Manuals. Professional Version. Drug Absorption by Le J. Online available: http://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/drug-absorption, 01.06.2015.

32. Møller KO. Pharmakologie als theoretische Grundlage einer rationellen Pharmakotherapie. Schwabe & Co Verlag, Basel/Stuttgart, 5. Auflage, 1966.

33. Mosby's Medical Dictionary. Oral administration of medication. TheFreeDictionary. Elsevier, 8th edition, 2009. Online available: http://medical-dictionary.thefreedictionary.com/oral+administration+of+medication

34. Müller RH, Hildebrand GE. Pharmazeutische Technologie: Moderne Arzneiformen. Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1998.

35. Mutschler E, Geisslinger G, Kroemer HK, Schäfer-Korting M. Mutschler Arzneimittelwirkungen – Lehrbuch der Pharmakologie und Toxikologie. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 8. Auflage, 2001.

36. Pschyrembel - Klinisches Wörterbuch. Walter de Gruyter, Berlin, 260. Auflage, 2004.

37. Richtlinie 2001/83/EG des europäischen Rates und des Rates vom 6. November 2001, unter Einarbeitung der Ergänzungen, konsolidiert bis 2014. Online available: http://www.pei.de/SharedDocs/Downloads/gesetze/richtlinie-2001-83-eg-gemeinschaftskodex-humanarzneimittel-2001-11-06.pdf;jsessionid=7A5926F0245706B75D9CF84649449A9D.1_cid329?__blob=publicationFile&v=2, 01.06.2015.

38. Ritschel WA, Bauer-Brandl A. Die Tablette – Handbuch der Entwicklung, Herstellung und Qualitätssicherung. Editio Cantor Verlag, Aulendorf, 2. Auflage, 2002. Pages 30,32.

39. Römpp – Online-Lexikon Chemie. Thieme Verlag, Stuttgart. Online available: https://www.thieme.de/de/thieme-chemistry/roempp-54843.htm, 5.3.2015.

40. Scheler W. Grundlagen der Allgemeinen Pharmakologie. Gustav Fischer Verlag, Stuttgart, 2. Auflage, 1980.

41. Schmid B, Hartmeier C, Bannert C. Arzneimittellehre für Krankenpflegeberufe. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 8. Auflage, 2007.

42. U.S. Food and Drug Administration. Drugs – Dosage Form. Online available: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm, 17.02.2015.

43. U.S. Food and Drug Administration. Route of Administration. Online available: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071667.htm, 17.02.2015.

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