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Reflection paper on the investigation of drug interactions of herbal medicinal products

Draft

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1. Introduction

The scope of the [ICH M12](#) guideline on drug interaction studies, in force from November 2024, is limited to pharmacokinetic interactions with aspects generally applying to the development of small chemical molecules. It formally supersedes the EMA [Guideline on the investigation of drug interactions](#), but does not address a number of topics to the same extent, e.g. recommendations for investigating the drug interaction potential of herbal medicinal products (HMPs) including traditional herbal medicinal products (THMPs). For further information on topics not covered by ICH M12, see document [implementation strategy-ICH M12](#). In general, the ICH M12 describes the pharmacokinetic investigation of drug interactions for medicinal products. The general pharmacokinetic aspects in ICH M12 are considered applicable also for (T)HMPs. The purpose of this reflection paper is to provide specific recommendations on how drug interaction issues can be investigated and reported for (T)HMP applications. The reflection paper should be read in conjunction with Directive 2001/83/EC, as well as relevant European Union (EU) guidelines, including Notice to Applicants.

Directive 2001/83/EC provides definitions for herbal substances, herbal preparations, HMPs and THMPs. According to these definitions a HMP is any medicinal product, containing as active ingredients exclusively one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations. Thus, (T)HMPs consist of complex mixtures of phytochemical constituents. Moreover, although the products are manufactured in controlled and standardised conditions, their composition may vary to some extent, even between batches of the same product. The situation is further complicated when two or more herbal substances and/or herbal preparations are combined in one (T)HMP. For most herbal substances and herbal preparations, the constituents responsible for potential drug interaction effects are not known, although, in some cases, certain constituents or groups of constituents may be recognised as implicated.

In view of this specific and complex nature of (T)HMPs, guidance is needed on how to evaluate the potential for clinically relevant drug interactions. The recommended approaches will depend on the regulatory basis of the application of the herbal medicine, e.g. whether it is based on Article 10a well-established use (WEU), Article 16a traditional use (TU) or application according to Article 8(3) of Directive 2001/83/EC, as there is a difference in terms of existing data and clinical experience. Therefore, the scope of this reflection paper is broader than the information covered by the ICH M12 on pharmacokinetic interactions, where ICH M12 generally applies to the development of small chemical molecules. In addition, the reflection paper covers aspects related to EU herbal monographs established by HMPC.

2. Discussion

MECHANISMS OF DRUG-DRUG INTERACTIONS (DDIS)

DDIs occur through several main mechanisms, typically classified into three categories: physicochemical, pharmacodynamic, and pharmacokinetic interactions, all of which may be relevant for (T)HMPs. The detailed mechanisms of DDIs are not within the scope of this reflection paper and hence, described only briefly below.

Physicochemical interactions involve direct chemical or physical incompatibility between drugs, for example leading to precipitation or inactivation when mixed together. However, physiochemical interactions are out of scope of this reflection paper.

Pharmacodynamic (PD) interactions involve the combined effects of drugs at their sites of action. Drugs may act on the same or related receptors or physiological systems, leading to additive,

synergistic, or antagonistic effects. These interactions can be competitive (acting at the same receptor) or non-competitive (affecting the same pathway through different mechanisms).

Pharmacokinetic (PK) interactions involve changes in the absorption, distribution, metabolism, or excretion (ADME) of a drug:

- Absorption: One drug may alter the absorption of another drug by changing the pH of the gastrointestinal tract, by modifying the residence time in a section of the tract (e.g. by increasing bowel motility), by chelation or by affecting the activity of transport proteins.
- Distribution: A drug can inhibit or induce transport proteins involved in distribution of drugs between different organs, leading to altered plasma and tissue levels of the involved drug. One drug may also displace another drug from plasma or tissular proteins, leading to increased levels of the free (active) form of the displaced drug.
- Metabolism: One drug may induce or inhibit the enzymes responsible for metabolising another drug, leading to changes in its plasma levels.
 - Inhibition of metabolic enzymes prevents the metabolism of other drugs which can lead to increased plasma concentrations, increasing the risk of adverse effects or, if the drug may not be converted to its active metabolite, reducing its therapeutic effect.
 - Induction of metabolic enzymes occurs when a drug increases the expression of the enzyme, leading to reduced plasma concentrations and consequently decreased therapeutic effect (or increased effect in case of prodrugs).
- Excretion: One drug may alter the renal or biliary excretion of another drug by changing urine pH or by affecting the activity of transport proteins in the kidneys and/or liver. A drug may also alter the excretion by increasing bowel motility.

In ICH M12 it is emphasised that the potential for an investigational drug to be involved in pharmacokinetic interactions, both as an object (effect of other drugs on the investigational drug, victim) and as a precipitant (effect of the investigational drug on concomitant drugs, perpetrator) should be evaluated. For (T)HMPs, the precipitant perspective is usually the most studied, while the object perspective is less well understood, partly because the compounds responsible for effect and adverse reactions are often not known, which makes it difficult to design meaningful pharmacokinetic interaction studies.

GENERAL PRINCIPLES

Data sourcing

Literature data

Although the interaction potential of one specific (T)HMP is difficult to extrapolate from other products produced from the same herbal substance, literature data to be considered in the evaluation of potential DDI risk should be searched broadly. Data concerning herbal preparations that differ from the intended product as well as food preparations with the same herbal substance ought to be included in the search for interaction potential. In addition, data on isolated constituents should be included.

Post-marketing experiences

Information from post-marketing experience for the (T)HMP or other products with the same herbal substance or preparation is of importance as it provides an opportunity to discover clinically relevant DDIs. Post-marketing data can demonstrate interaction problems in the form of (increased) adverse reactions or as an increased/attenuated effect of another drug. If adverse reactions or increased effects of a medicinal product (i.e. object drug) occur when given together with an herbal preparation

or its constituents, it may indicate that the elimination of the medicinal product is reduced. If, instead, an attenuated drug effect is observed, the cause may be a reduced uptake or an increased elimination of the drug. A clear example is the reports that revealed significant DDIs associated with the consumption of St. John's wort. In the end of the 1990s, cases of prothrombin complex elevation during warfarin treatment with concomitant use of St. John's wort were described. It is now known that St. John's wort extracts induce cytochrome P450 enzymes and the efflux transporter protein Pgp, which leads to a reduced effect of some drugs, e.g. warfarin, ciclosporin and hormonal oral contraceptives.

New product-specific studies

When performing new product-specific pharmacokinetic drug-drug interaction studies, the general outlines in ICH M12, are applicable (see also recommendations on Article 8(3) of Directive 2001/83/EC applications below).

EU herbal monographs

When an EU herbal monograph is already established by HMPC, the Q&As R7 and R8 in the 'Regulatory questions and answers on herbal medicinal products' (EMA/HMPC/345132/2010) describe how to relate new products to that EU herbal monograph. In principle, the EU herbal monographs give applicants and national competent authorities a clear reference point when preparing or assessing an application for marketing authorisation or registration of herbal medicinal products in EU Member States. This also includes known data on DDIs. It should also be noted, as described in the Guideline on the use of the common technical document (CTD) format in the preparation of a registration application for traditional herbal medicinal products (EMA/HMPC/71049/2007), that the applicant should perform own literature research to fill the temporal gap between the application and the compilation of the assessment report for the monograph. This should also be taken into account for WEU applications.

Data evaluation and interpretation

In the ICH M12 guideline, general information on *in vitro* and clinical evaluation of pharmacokinetic DDIs mediated through enzyme or transporter inhibition or induction are described. There is also a chapter on interpreting DDI study results. The applicant should also take into consideration herbal specific guidance documents established by HMPC. Below, (T)HMP specific considerations are outlined and summarised in Figure 1.

Data from different herbal preparations

In case interaction data are only available for other preparations that differ from the herbal substance in question, the applicant should discuss to what extent the information is applicable to their product. The general information in Q&As R7 and R8 in the 'Regulatory questions and answers on herbal medicinal products' (EMA/HMPC/345132/2010) could support the discussion.

Pharmacodynamic interactions

Pharmacodynamic interactions may be caused by a large variety of mechanisms. It is therefore not possible to give detailed guidance regarding pharmacodynamic interaction studies. The information needed should be determined on a case-by-case basis. The potential for pharmacodynamic interactions should be investigated for drugs which compete at the pharmacological target and/or have similar or opposing pharmacodynamic (therapeutic or adverse) effects. If such drugs are likely to be used concomitantly, pharmacodynamic interaction studies should be considered. Extensive pharmacological and toxicological knowledge about the drug is important for the planning of pharmacodynamic interaction studies. It is recommended that both *in vitro* studies and *in vivo* studies are used to characterise the pharmacodynamic interaction profile.

148 *Pharmacokinetic in vitro data*

149 Evaluating the DDI potential of an investigational drug as a precipitant involves characterising the
150 effect of the drug on major enzymes and transporters.

151 According to ICH M12, for small chemical molecules, this evaluation often starts with *in vitro*
152 experiments (enzyme inhibition and induction assays) to elucidate an eventual interaction potential,
153 followed by clinical DDI studies based on this mechanistic knowledge.

154 (T)HMP are often multi-component mixtures containing several chemical components that are
155 generally not defined in terms of quantity or quality. *In vitro* drug interaction studies may provide
156 information on the potential for interactions between (T)HMPs and other substances and on possible
157 mechanisms involved. However, for these mixtures it is challenging to draw conclusions about the
158 clinical relevance of an observed *in vitro* interaction, given that the identity(ies) and plasma level(s) of
159 the substance(s) responsible for the *in vitro* interaction are usually not known. In addition, tannins that
160 may be present in extracts, can cause enzymes (proteins) to precipitate, which could be misinterpreted
161 as enzyme inhibition. However, the *in vitro* studies when performed with a high concentration may
162 support the decision on the need for dedicated clinical interaction studies for evaluating the risk of the
163 specific (T)HMP causing interactions.

164 For extracts with one or a few known constituents, the situation may be more similar to small chemical
165 molecule medicinal products, taking into account the 'Reflection paper on the level of purification of
166 extracts to be considered as herbal preparations' (EMA/HMPC/186645/2008). In case information
167 regarding PK for the constituent(s) is available, *in vitro* findings can also be used to address the risk of
168 a clinically relevant DDI as described in ICH M12.

169 *Pharmacokinetic animal data*

170 Although animal studies have been a crucial part of drug development for many years, when it comes
171 to investigating DDIs for small molecules, these studies are not recommended due to limited
172 predictivity, due to species differences, as DDI mechanisms may not be accurately reflected in animal
173 models. However, if animal studies are available in the scientific literature, the applicant should discuss
174 the predictability of animal data for the clinical situation for the applied (T)HMP.

175 It is advised that no product-specific pharmacokinetic drug-drug interaction animal studies should be
176 performed for new HMPs.

177 *Pharmacokinetic clinical data*

178 Clinical DDI studies provide the best basis for evaluating the risk of specific (T)HMP causing
179 interactions, whether found as public data or as product specific studies. A clinical DDI study with a
180 sensitive and selective index substrate may elucidate a mechanism and the results can usually be
181 extrapolated to effects on other drugs as objects of interaction, i.e. drugs with similar metabolic and
182 distribution pathways. Considerations of importance when designing prospective clinical DDI studies
183 are described in ICH M12, section 3.2. Recommendations regarding the overall design, population and
184 number of subjects, dosing, route of administration etc. are valid also for studies with (T)HMPs.

185 **Recommendations on different kinds of applications**

186 *Applications according to Article 10a (WEU) and Article 16a (TU) of Directive 2001/83/EC*

187 Information about interactions (PK and PD) between medicinal products and HMPs based on WEU or TU
188 should, in general, be based on broadly sourced scientific literature, other contributing public data, and
189 post-marketing experiences, as described above.

The available data should be evaluated as described above and the risk for DDI(s) should be discussed in the application. In certain cases, if the mechanism of an observed interaction is known (i.e. if a clinical DDI study with a sensitive index substrate has been performed), the risk can be extrapolated to other drugs as objects of interaction, e.g. drugs with similar metabolic or distribution pathways.

Applications according to Article 8(3) of Directive 2001/83/EC

The potential for interactions (PK and PD) should be investigated by the applicant, based on publicly available data, as described above, and as product-specific studies if sufficient published data are not found.

In vitro studies on the enzyme inhibition and induction potential may be performed to indicate potential interaction mechanism(s) (see ICH M12 guideline, section 2).

Determination of endogenous biomarkers of enzymes or transporters in blood or urine in clinical studies may be useful to get indications of the HMP's potential as a precipitant (see ICH M12 guideline, section 3.2.7).

If clinical DDI studies are needed to obtain product specific information about an HMP, they should follow the ICH M12 guideline, section 3, as far as possible. For extracts with one or a few known constituents and a known mechanism of action, DDI studies should be considered also from the object perspective.

The strategy used to determine which clinical studies to perform must be selected on a case-by-case basis. The applicant should justify the choice of study design and substrates.

Topical products (Articles 10a (WEU), 16a (TU) and 8(3) of Directive 2001/83/EC)

For topical products, the degree of absorption needs to be evaluated. If systemic absorption is negligible, the focus should be on possible interactions with other topical products, with attention to medicinal products that are likely to be administered concomitantly to the target population. If systemic absorption cannot be excluded, the risk for systemic DDIs needs to be addressed in line with the sections above.

Product information

The Guideline on summary of product characteristics (SmPC) (EudraLex Vol. 2C) gives advice on how to present information about interactions. Information about drug interactions should be presented in the SmPC sections 4.5 and 5.2 and cross-referred to the sections 4.2, 4.3 or 4.4 when relevant. Section 4.5 should contain all detailed information on drug interactions and only the recommendation should be given in the cross-referred sections.

Regardless of the prescription status, the conclusions of the evaluation regarding potential risk of interactions should be translated into actionable recommendations for use of the product, to be included in its product information.

In case *in vivo* interaction studies from other preparations of the herbal substance in question are considered relevant, the data should be presented in the product information. In such cases, the magnitude of the interaction could be given in the SmPC of the (T)HMP together with information on the difficulty to extrapolate the magnitude of interactions from other (T)HMPs or food products manufactured with the same herbal substance.

For (T)HMPs, in line with EU herbal monographs, the SmPC section 4.5 '*Interactions with other medicinal products and other forms of interaction*', and corresponding text in patient leaflet (PL) and labelling, commonly state that "*None reported*" or "*No interaction studies have been performed*". Both

statements mean that no interaction studies have been performed, and no clinically relevant interactions have been found in the scientific literature for the time being.

Importantly, if there is a lack of data on DDI, patients should be made aware that there is no information available on possible interactions and that interactions may occur. Since over-the-counter (OTC) medicines are in most cases avoidable, it is important that the patients are made aware that herbal medicinal products could cause interactions, just like any other medicinal product.

3. Conclusion

The complexity of (T)HMPs requires guidance on the evaluation of their potential for clinically relevant drug interactions. The recommended approaches will depend on whether the product is applied for as an Article 8(3) of Directive 2001/83/EC application, or as a WEU or TU, due to differences in terms of data generation versus existing data and clinical experience.

In general, information to be considered in the evaluation of potential DDI risk should be gathered broadly and include scientific literature, other contributing public data and post-marketing experiences.

For Article 8(3) of Directive 2001/83/EC application, published data could be a part of the evaluation, but product-specific clinical DDI studies may be needed. Although the testing strategy may be decided on a case-by-case basis, depending on the product characteristics, product-specific interaction studies should follow the ICH M12 guideline, section 3, to the extent possible.

For WEU and TU applications the evaluation is based on available published data.

The risk for DDI(s) of the (T)HMP should be concluded based on all available data and translated into general recommendations to be included in its product information.

4. References

Guideline on summary of product characteristics (SmPC), EudraLex Vol. 2C

Guideline on the investigation of drug interactions, CPMP/EWP/560/95

Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products, EMA/HMPC/71049/2007

ICH M12 Guideline on drug interaction studies, EMA/CHMP/ICH/652460/2022

Implementation strategy of ICH Guideline M12 on drug interaction studies, EMA/460496/2024

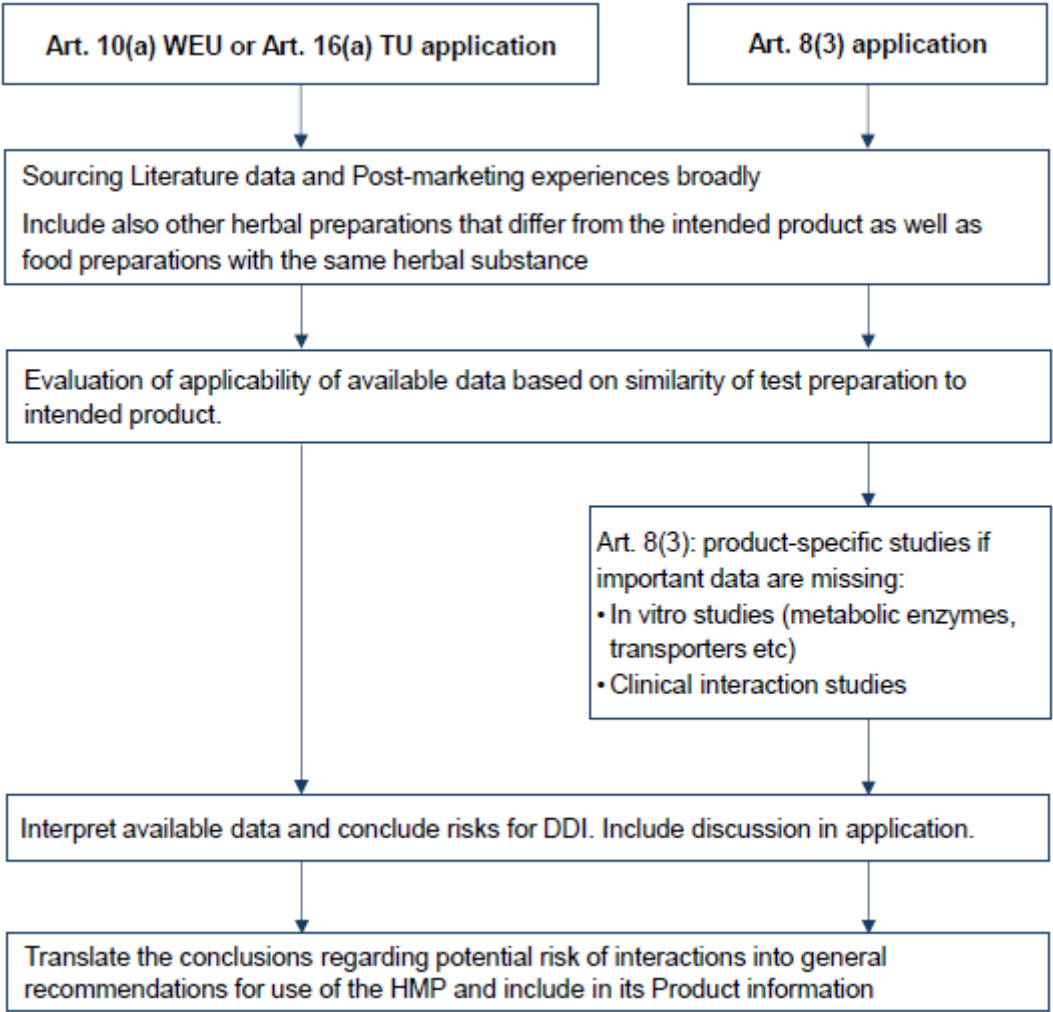
Notice to Applicants Vol. 2A 'Procedures for marketing authorisation, Chapter 1 Marketing Authorisation

Reflection paper on the level of purification of extracts to be considered as herbal preparations EMA/HMPC/186645/2008

Regulatory questions and answers on herbal medicinal products, EMA/HMPC/345132/2010

265 **Figure 1-** Paths for consideration for the general collection of relevant DDI data.

266 The articles (Art.) refer to the corresponding Articles of Directive 2001/83/EC.



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