Current Perspectives on Herb-Drug Interactions in the European Regulatory Landscape

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Abstract

Herb-drug interactions have turned out not to be a major issue in the European regulatory landscape. For a minority of herbal preparations, herb-drug interactions are clinically relevant, e.g., between high-dose St. John's wort extracts and a number of chemical substances. The inclusion of adequate information on such interactions into the package leaflet is important for the safe use of the products. Information on potential interactions is also part of the official HMPC monographs. However, only for some herbal preparations described in these monographs, such a potential is known. Thus, in accordance with the relevant European guidance documents, potential interactions should be assessed critically for their clinical relevance, and a balanced assessment is required when regulatory documents are established or regulatory measures are implemented.

Introduction

In accordance with the European legislation on medicinal products, herbal medicinal products – whether authorized ("well-established medicinal use") or registered ("traditional use") – have to prove their quality, safety, and efficacy or tradition, respectively, in case of traditional herbal medicinal products. This also includes the discussion of potential interactions and respective information in the package leaflet of the products, if justified by scientific data. For this reason, the relevance of potential herb-drug interactions has to be evaluated, and a decision must be taken whether respective information has to be included in the package leaflet.

Examples for Regulatory Actions

Some herb-drug interactions are well-known, e.g., between high-dose St. John's wort (*Hypericum perforatum*) extract and several chemical substances, e.g., warfarin and cyclosporin, which have been described in some of the first case reports of herb-drug interactions in the literature and nowadays belong to the most well-known examples for herb-drug interactions. Based on these case reports, an official risk assessment ("Stufenplanverfahren") of St. John's wort products was initiated by the German health authority in March 2000. As a consequence, the package leaflets of products with a daily dose of more than 200 mg of the herbal drug or the equivalent amount of extract were obliged to include specific information on potential interactions with a number of chemical substances thus permitting the safe use of the respective products. The decision of the health authority was explained by the ability of hyperforin and hypericum extracts to induce CYP_{450} isoenzymes and P-glycoprotein. The limitation of the daily dose was of particular relevance for traditional herbal medicinal products containing St. John's wort in the German market, because according to the national legal situation existing at that time, the "traditional use" status was not compatible with the labelling of any risks including potential interactions.

In January 2004 the BfArM issued a draft guidance document on the assessment of potential pharmacokinetic interactions with herbal medicinal products [1] for public consultation. This guidance document explained in detail that examinations, on such interactions or, alternatively, information that the use of the respective chemical substance is contraindicated, were generally required for herbal medicinal products. Interested parties who commented on this draft argued that experimental data should only be required in justified cases when valid case reports or scientific

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Bibliography
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literature data point to potential pharmacokinetic interactions. Later on, a list of 12 (out of approximately 180 commonly used) plant species was made available for which the health authority considered a risk of interactions with other medicinal products possible, including some plants for which in fact detailed information on interactions was requested, e.g., *Eucalyptus*, artichoke, milk thistle, St. John's wort, and *Colchicum*.

Between 2005 and 2008, a further official risk assessment was performed in Germany. Based on a study published by Piscitelli et al. (2002) [2], the health authority announced its intention to implement measures for herbal medicinal products containing garlic (*Allium sativum*) due to the suspicion of interactions between garlic and saquinavir. However, the design and the results of the study were put into question because the preparation was not exactly defined, and the decrease mean area under the curve (AUC) of saquinavir was seen in six of the patients whereas in three patients an increase was observed. Furthermore, a control group as well as information on the nutrition which may influence the bioavailability of saquinavir were missing. For these reasons, the measures were not considered justified by interested parties. The final decision of BfArM, however, did not differ from the earlier draft.

Current Regulatory Basis

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Authorized herbal medicinal products as well as registered traditional herbal medicinal products are obliged to submit a summary of product characteristics (SmPC) as part of their application for marketing authorization or registration, respectively. The SmPC serves as a basis, e.g., for information given in the package leaflet. General criteria on its content are laid down in the "Guideline on Summary of Products Characteristics (SmPC)" published as a 2nd revision in September 2009 [3]. In the chapter on interactions, this document states that the respective section 4.5. should provide information on the potential for *clinically relevant* interactions based on the pharmacodynamic properties and *in vivo* pharmacokinetic studies of the medicinal product including *in vivo* interaction results. Interactions not studied *in vivo* but predicted from *in vitro* studies or deducible from other situations or studies should be described if they result in a change in the use of the medicinal product.

In April 2010, a revised version of the "Guideline on the Investigation of Drug Interactions" was published as a draft [4]. As compared to the existing document, the new draft includes an additional chapter specifically addressing the issue of herbal medicinal products and specific food products. As a basic principle of this chapter, the potential for interactions should be investigated for new herbal preparations. For traditional and well-established herbal preparations, such a potential should be clarified if reports point to clinically relevant interactions in humans. *In vitro* studies on the enzyme inhibitory potential of the constituents or the herbal preparations are encouraged in case *in vivo* information may give rise to clinically relevant drug interactions. The guideline also mentions the option of extrapolation from one herbal preparation to other ones. An *in vivo* drug interaction study with a specific herbal product should be considered in case product-specific labeling information is required. Finally, some advice is given on how to proceed if there is a wish to investigate the effect of an herbal medicinal product or a special kind of food on the pharmacokinetics of a medicinal product. All in all, this guideline takes into account the specific issues of existing herbal preparations with regard to interaction studies and restricts the need to perform them to specific cases.

With a view to the existing regulatory framework and the recommendations of the respective guidelines, it can be concluded that on a European level, herb-drug interactions have so far not been a major issue, and recent guidance documents demonstrate that the need to perform interaction studies should not be overestimated.

HMPC Monographs

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Specific assessment criteria for herbal medicinal products which can be used by applicants and health authorities are provided by the documents elaborated by the Committee on Herbal Medicinal Products (HMPC) and published by the European Medicines Agency (EMA). In this context, the community herbal monographs are of particular interest. They consist of basic information on benefit and risk of herbal medicinal products and traditional herbal medicinal products and can be used as reference documents for marketing authorization/registration applications.

Out of more than 100 HMPC monographs published or drafted so far, only approximately 20% include information on potential interactions, whereas the majority of the available monographs state "none reported".

As an example, the monograph on the well-established medicinal use of St. John's wort (*Hypericum perforatum*, herba) [5] is mentioned which states under 4.5. 'Interactions': "Hypericum dry extract induces the activity of CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein. The concomitant use of cyclosporine, tacrolimus for systemic use, amprenavir, indinavir and other protease inhibitors, irinotecan and warfarin is contraindicated (see section 4.3. 'Contraindications'). Special care should be taken in case of concomitant use of all drug substances the metabolism of which is influenced by CYP3A4, CYP2C9, CYP2C19 or P-glycoprotein (e.g., amitriptyline, fexofenadine, benzodiazepines, methadone, simvastatin, digoxin, finasteride), because a reduction of plasma concentrations is possible. The reduction of plasma concentrations of oral contraceptives may lead to increased intermenstrual bleeding and reduced safety in birth control. Women using oral contraceptives should take additional contraceptive measures. Prior to elective surgery possible interactions with products used during general and regional anaesthesia should be identified. If necessary the herbal medicinal product should be discontinued. The elevated enzyme activity returns within 1 week after cessation to normal level."

In contrast to this, the final monograph on the traditional use of low dose St. John's wort (*Hypericum perforatum*, herba) [6] states for the internally used preparations: "In the case of a daily intake of hyperforin less than 1 mg and of a duration of use not longer than 2 weeks (see section 4.2. 'Posology and method of administration'), no clinically relevant interactions are to be expected. Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum."

However, as the draft monograph on the traditional use of low doses had included the same information on interactions like the monograph on the clinically proven high-dose preparations, interested parties had submitted detailed comments demonstrating that traditionally used, low-dose St. John's wort products do not bear a risk of interactions with other medicines. In the past few years several studies were performed in order to eluci-

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date the potential risk of various *Hypericum* preparations and to provide arguments for a balanced assessment with the German "Stufenplanverfahren", e.g., several studies in healthy volunteers using various marker substances such as digoxin, cyclosporine A, or midazolam, respectively [7–10], and one study in patients receiving ciclosporin A as a permanent medication after kidney transplantation [11].

Accordingly, the HMPC assessment report [12] concluded that the extent of induction of CYP3A4 is well-documented and directly correlated with the content of hyperforin in the herbal preparation. Products containing only small amounts of hyperforin (< 1%) have not been shown to produce clinically relevant enzyme induction. For high-dose preparations attached to the well-established medicinal use, the assessment report mentions pharmacokinetic interactions for several drug substances metabolized via CYP3A4 having a narrow therapeutic range. Thus it is concluded that *Hypericum* extracts should not be used concomitantly with these substances, or doses have to be adjusted.

Further examples of HMPC monographs with relevant and justified information on interactions are mentioned in the following:

The monograph on Agnus castus (*Vitex agnus-castus*, fructus) [13] states: "Because of the possible dopaminergic and oestrogenic effects of Vitex agnus-castus, fructus, interactions with dopamine agonists, dopamine antagonists, oestrogens and antioestrogens cannot be excluded." The same wording is included in the assessment report; a proof for this assumption by clinical data, however, is not given.

The monographs on bulk-forming laxatives, e.g., linseed (*Linum usitatissimum*, semen) [14] and ispaghula (*Plantago ovata*, semen; *Plantago ovata*, seminis tegumentum) [15,16], explain that because of their pharmacodynamic properties the enteral absorption of other concomitantly administered medicines may be delayed, and therefore the laxative should not be taken ½ to 1 hour before or after intake of other medicinal products. Further information is given with regard to concomitant use of medicinal products which inhibit peristaltic movement as well as of thyroid hormones or insulin.

Furthermore, all of the six monographs on anthraquinone-containing herbal substances (e.g., *Cassia senna*, fructus, folium [17, 18], *Rhamnus frangula*, cortex [19], etc.) include the following statement: "Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, with medicinal products, which induce reversion to sinus rhythm (e.g. quinidine) and with medicinal products inducing QT-prolongation. Concomitant use with other medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance." This corresponds to current scientific knowledge and is in principle also part of the respective ESCOP monographs [20].

The monograph on willow bark (*Salix*, cortex) [21] states: "Willow bark may increase the effects of anticoagulants such as coumarin derivatives." Detailed justification for this statement can be found in the assessment report [22], though its clinical relevance may be low, as it is partly based on marginal differences in a small numbers of patients [23,24].

More recently, a draft on *Glycyrrhiza glabra* and/or *Glycyrrhiza inflata* and/or *Glycyrrhiza uralensis*, radix [25] was published for public consultation with the following statement: "Liquorice root may counteract antihypertensive action of prescribed medications. Not to be used concomitantly with thiazide diuretics, cardiac glycosides, corticosteroids, stimulant laxatives or other medications which may aggravate electrolyte imbalance." These interactions are known for the intake of high doses and are also included, e.g., in the respective ESCOP monograph [20].

Some other monographs, however, include statements on potential interactions with other drugs which should be assessed in a more critical manner, e.g., two monographs on tannin-containing herbal drugs, Tormentil rhizome (*Potentilla erecta*, rhizoma) [26] and oak bark (*Quercus robur, Q. petraea, Q. pubescens*, cortex) [27]. They both include the following statement: "Internal absorption of concomitantly administered medicine may be delayed. For this reason the product should be taken 1 hour or more before or after intake of other medicinal products." As there is no evidence on potential interactions available from the assessment reports, except that there are no concerns about interactions with oak bark preparations [28,29], the statement of the monograph seems to be based on theoretical considerations, and its clinical relevance may be further questioned in case the preparations are taken for the treatment of diarrhea, a condition significantly influencing the absorption of medicines.

According to the monograph on valerian (*Valeriana officinalis*, radix) [30], "only limited data on pharmacological interactions with other medicinal products are available. Clinically relevant interaction with drugs metabolised by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway has not been observed. Combination with synthetic sedatives requires medical diagnosis and supervision." As the mentioned interactions with various cytochrome P_{450} enzymes have not been observed, it is questionable whether such statements should be made under "interactions" in the monograph and therefore in the SPC and package leaflet of the products or should better be only part of the HMPC's assessment report.

From a scientific point of view, the statement on interactions in the monograph of sage leaf (*Salvia officinalis*, folium) [31] is not quite understandable: "The intake of Salviae folium preparations might influence the effect of medicinal products acting via GABA receptor (e.g. barbiturates, benzodiazepines), even if not seen clinically. Therefore the concomitant use with such medicinal products is not recommended." In accordance with the "Guideline on Summary of Product Characteristics" [3], information on interactions should be provided when they are *clinically relevant*. The assessment report [32] explains that no drug interactions are documented clinically, but assumes that preparations of sage might interact with other medicines due to the effect of α-thujone on the γ-aminobutyric acid (GABA) type A receptor. However, in order to exclude any neurotoxic effects, the presence of thujone in sage leaf preparations is restricted to a daily intake of 5.0 mg/person for a maximum duration of 2 weeks in the HMPC monograph. Bearing in mind that the content of thujone is restricted and the suspect of potential interactions are solely deduced from pharmacological data without any clinical evidence, the statement on interactions of sage leaf preparations should be discussed critically.

As could be shown by the examples mentioned above, only a small number of the existing HMPC monographs include information on potential interactions. Most of them are scientifically justified and based on sound data showing clinical relevance. Some of them, however, must be put into question because they seem to be deduced from theoretical considerations only. For most of the herbs which are of relevance in the European market and for which HMPC monographs exist, there is no evidence of interactions with chemical drugs.

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Discussion

With some exemptions, the discussion of herb-drug interactions does not seem to be of high relevance on a European level. Information on potential interactions, e.g., of high-dose St. John's wort products with chemical substances such as cyclosporine, indinavir, tacrolimus, warfarin, etc., is mandatory and must be included in SPCs and the package leaflet in order to guarantee the safe use of herbal medicinal products and thus contribute to the protection of patients and consumers. However, potential interactions which are described in the literature and which are deduced from *in vitro* or animal data should be assessed critically for their clinical relevance.

Butterweck et al. [33] had already stated earlier that systematic *in vitro* screenings led to contradictory results and showed low predictability for clinical effects. As drug interactions can also be mediated by food, beverages, etc., a preventive risk assessment should at first be done for synthetic drugs with a narrow therapeutic range. Thus it would be more important to provide information on the interaction to the persons using the synthetic drugs instead of informing the wide population using herbal medicinal products or food which contains herbal preparations [33]. Furthermore, the European regulatory situation of herbal and traditional herbal medicinal products is not comparable to the situation in the United States where herbal preparations are classified as dietary supplements without the need of being authorized or registered before gaining access to the market. Presumed increased risks of interactions as described for unauthorized products with a potential high variability in their phytochemical contents [34] can therefore not be transferred uncritically to medicinal products which are obliged to prove their quality, safety, and efficacy or traditional use, respectively.

Conclusion and Perspectives

Information on clinically relevant interactions is an important part of the package leaflet of herbal medicinal products and traditional herbal medicinal products and allows for the safe use of these products. However, published reports on *in vitro* interactions should be checked case-by-case for their clinical and regulatory relevance. This is in line with regulatory guidelines stating that the potential of interactions should be clarified if reports point to clinically relevant interactions in humans. It does not seem justified to demand the conduct of clinical studies demonstrating the lack of clinical relevance based on theoretical considerations only.

Therefore a balanced assessment of potential interactions is absolutely required, and information on the interactions in the package leaflet of synthetic medicinal products, in particular those with a narrow therapeutic range, is required as well. All in all, a sense of proportion should be kept when regulatory documents such as monographs are established or regulatory actions are undertaken.

Conflict of Interest

The author did not declare any conflict of interest.

References

1 *Bundesinstitut für Arzneimittel und Medizinprodukte.* Draft „Bewertung möglicher pharmakokinetischer Arzneimittel-Interaktionen mit Phytopharmaka". 16 January 2004. Available at http://www.bfarm.de/DE/Arzneimittel/2_zulassung/zulArten/besTherap/amPflanz/ampflanznode.html;jsessionid=D52D4B0383AACA4367BAD290195E0215.1_cid103. Accessed January 2012

2 *Piscitelli S, Burstein A, Welden N, Gallicano K, Falloon J.* The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis 2002; 34: 234–238

3 *European Commission.* A guideline on summary of product characteristics (SmPC) Rev. 2 of September 2009. The rules governing medicinal products in the European Union, Volume 2C Notice to Applicants. Available at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

4 *Committee for Human Medicinal Products (CHMP).* Draft Guideline on the Investigation of Drug Interactions. CPMP/EWP/560/95/Rev. 1 – Corr. 22 April 2010

5 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Hypericum perforatum* L., herba (well-established medicinal use). EMA/HMPC/101304/2008

6 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Hypericum perforatum* L., herba (traditional use). EMEA/HMPC/745582/2009

7 *Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, Hehl EM, Sievers H, Frank B, Riethling AK, Drewelow B.* Effect of St. John's wort dose and preparations on the pharmacokinetics of digoxin. Clin Pharmacol Ther 2004; 75: 546–557

8 *Mueller SC, Majcher-Peszynska J, Uehleke B, Klammt S, Mundkowski RG, Miekisch W, Sievers H, Bauer S, Frank B, Kundt G, Drewelow B.* The extent of induction of CYP3A by St. John's wort varies among products and is linked to hyperforin dose. Eur J Clin Pharmacol 2006; 62: 29–36

9 *Mueller SC, Peszynska JM, Mundkowski RG, Uehleke B, Klammt S, Sievers H, Lehnfeld R, Frank B, Thurow K, Kundt G, Drewelow B.* No clinically relevant CYP3A induction after St. John's wort with low hyperforin content in healthy volunteers. Eur J Clin Pharmacol 2009; 65: 81–87

10 *Arold G, Donath F, Maurer A, Diefenbach K, Bauer S, Henneicke-von Zepelin HH, Friede M, Roots I.* No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract. Planta Med 2005; 71: 331–337

11 *Mai I, Bauer S, Perloff ES, Johne A, Uehleke B, Frank B, Budde K, Roots I.* Hyperforin content determines the magnitude of the St. John's wort cyclosporine drug interaction. Clin Pharmacol Ther 2004; 76: 330–340

12 *Committee on Herbal Medicinal Products (HMPC).* Assessment report on *Hypericum perforatum* L., herba. EMA/HMPC/101303/2008

13 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Vitex agnus-castus* L., fructus. EMA/HMPC/144006/2009

14 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Linum usitatissimum* L., semen. EMEA/HMPC/340849/2005

15 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Plantago ovata* Forssk., semen. EMEA/HMPC/340861/2005

16 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Plantago ovata* Forssk., seminis tegumentum. EMEA/HMPC/340857/2005

17 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Cassia senna* L., fructus and *Cassia angustifolia* Vahl, fructus. EMEA/HMPC/51871/2006 Corrigendum

18 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Cassia senna* L., fructus and *Cassia angustifolia* Vahl, folium. EMEA/HMPC/51869/2006 Corrigendum

19 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Rhamnus frangula* L., cortex. EMEA/HMPC/76307/2006 Corrigendum

20 *European Scientific Cooperative on Phytotherapy.* ESCOP monographs, 2nd edn. Exeter, Stuttgart: ESCOP, Thieme; 2003

21 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Salix*, cortex. EMEA/HMPC/295338/2007

22 *Committee on Herbal Medicinal Products (HMPC).* Assessment report on *Salix*, cortex. EMEA/HMPC/295337/2007

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23 *Krivoy N, Pavlotzky E, Chrubasik S, Eisenberg E, Brook E.* Effect of *Salicis cortex* extract on human platelet aggregation. Planta Med 2001; 67: 209–212
24 *Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C.* Risk of warfarin-related bleeding events and supratherapeutic INRs associated with CAM: a longitudinal analyis. Pharmacotherapy 2007; 27: 1237–1247
25 *Committee on Herbal Medicinal Products (HMPC).* Draft community herbal monograph on *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch, radix. EMA/HMPC/571119/2010
26 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Potentilla erecta* (L.) Raeusch., rhizoma. EMA/HMPC/5513/2010
27 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Quercus petraea.* (Matt.) Liebl., *Quercus pubescens* Willd. EMA/HMPC/3203/2009
28 *Committee on Herbal Medicinal Products (HMPC).* Assessment report on *Potentilla erecta* (L.) Raeusch., rhizoma. EMA/HMPC/5511/2010
29 *Committee on Herbal Medicinal Products (HMPC).* Assessment report on *Quercus petraea* (Matt.) Liebl., *Quercus pubescens* Willd., cortex. EMA/HMPC/3206/2009
30 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Valeriana officinalis* L., radix. EMEA/HMPC/340719/2005
31 *Committee on Herbal Medicinal Products (HMPC).* Community herbal monograph on *Salvia officinalis* L., folium. EMA/HMPC/331653/2008
32 *Committee on Herbal Medicinal Products (HMPC).* Assessment report on *Salvia officinalis* L., folium and *Salvia officinalis* L., aetheroleum. EMA/HMPC/330383/2008
33 *Butterweck V, Derendorf H, Gaus W, Nahrstedt A, Schulz V, Unger M.* Pharmacokinetic herb-drug interactions: are preventive screenings necessary and appropriate? Planta Med 2004; 70: 784–791
34 *Gurley BJ.* Pharmacokinetic herb-drug interactions (part 1): origins, mechanisms, and the impact of botanical dietary supplements. Planta Med 2012, advance online publication Febr 9, 2012; DOI: 10.1055/s-0031-1298273

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