31 January 2017
EMA/HMPC/610812/2016
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Public statement on *Paeonia lactiflora* Pall. and/or *Paeonia veitchii* Lynch, radix (Paeoniae radix rubra)

Table 1: Organisations and/or individuals that commented on the Public statement on *Paeonia lactiflora* Pall. and/or *Paeonia veitchii* Lynch, radix (Paeoniae radix rubra) for public consultation on 16 February 2016 until 15 May 2016.

	Organisations and/or individuals
1	Prof. Gou, Shanghai, Shanghai Institute of Materia Medica
2	Department of Chinese Medicine and Pharmacy, Ministry of Health and Welfare, Taiwan, ROC

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Table 2: Discussion of comments

General comments to draft document

None

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Assessment Report Table 1 "Overview of data obtained from marketed medicinal products"	Prof. Gou, Shanghai	New data should be included in the table "Overview of data obtained from marketed medicinal products"	No new data of medicinal products are included in the overview of data obtained from marketed medicinal products for the following reasons: According the document "Agence nationale du securite du medicament et des produits de santé" (ANSM), Liste A des plantes médicinales utilisées traditionnellement, Paeonia Radix Rubra is used only in traditional Chinese medicine (TCM). No traditional European medicinal use in France can be claimed from this document for a specific preparation, indication, strength and posology. According to the request of information from Latvia, the purpose of the "Update published of nearly 5 000 substances used in medicinal products: list in Latvian, Latin and English, 11-03-2015" was to provide translations of substance names in Latvian, Latin and English in order to assist companies in preparations of product information in Latvian, but also for doctors, pharmacists, translators. It is a list for terminology purposes only. According the requested information from Latvia, this list cannot proof traditional medicinal use in Latvia. The "HEEL" preparations are used in homeopathy and cannot

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			proof traditional use for a specific phytotherapeutic preparation, indication, strength and posology.
Assessment Report Table 2 “Other products relevant to other Paeonia plants marketed in the EU/EEA”	Prof. Gou, Shanghai	Comment on the Assessment on the table “Other products relevant to other Paeonia plants marketed in the EU/EEA”	No new data of medicinal products are included in the AR Table 2, other products relevant to other Paeonia plants marketed in the EU/EEA. The proposed products are multi-combination products or homeopathic preparations. A corresponding product is characterized by having the same active ingredients, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration. Therefore other plants, combination products or homeopathic preparations cannot proof traditional medicinal use for a specific phytotherapeutic mono-preparation for implementing a European Union monograph and are not relevant.
Assessment Report table 3 and 4 information on relevant combination medicinal products marketed outside the EU/EMA.	Prof. Gou, Shanghai	Comment on the Assessment on the table information on relevant combination medicinal products marketed outside the EU/EMA. Combination medicinal products of red or white peony root are available in China. According to China Pharmacopoeia (2015 edition) and the public data of CFDA, a total of 70 different combination medicinal products, also named as Chinese Patent Medicines, containing red peony root are marketed in China. These combination medicinal products have different indications as listed in the following table. In addition, information regarding the registration or approval date	The data of combination products do not fulfil the criteria for establishing a European Union monograph for a mono-preparation. Combinations of 7 to 10 active substances cannot proof efficacy and safety for mono-preparations. As they are not relevant, they are not included in the AR. In chapter 2.1.2 of the AR we give the information, red peony root is traditionally used in TCM combination products. The use in combinations generally cannot proof the efficacy and safety for substances of European Union monographs as they do not fulfil the legal conditions of the Directive 2004/24/EC as regards traditional herbal medicinal products.

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		earlier than 2010 is not available for these CPMs. Combination medicinal products are also marketed in Hong Kong. According to the official data provided by Chinese Medicine Council of Hong Kong, 14 different combination medicinal products are marketed in Hong Kong.	The TGP-Products and paeoniflorin do not have a tradition of 30 years, neither in China nor in Europe. Paeoniflorin is considered a purified compound and thus is not considered within the scope of Directive 2004/24/EC as regards traditional herbal medicinal products.
Assessment Report chapter 3, non-clinical data	Prof. Gou, Shanghai	Comment on the Assessment report *Paeonia lactiflora* Pall. and *Paeonia veitchii* Lynch, radix (Paeoniae radix rubra) chapter 3, non-clinical data	Abstracts of pharmacodynamic studies performed with isolated substances as paeoniflorin or TGP were submitted, without literature references and without the original literature. They analysed the hematopoietic function, anti-allergic-activity, analgesic activity, hypnotic effects, effects on Sjogren´s syndrome, necrotizing pancreas, liver protective activity, arthritis activity, antitumor activity, anti-colitis activity. From the comments received, no information is available on the route of administration of the isolated substances in the in-vivo studies. Because of missing literature data, the abstracts are not included in the assessment report. When administered orally, paeoniflorin is absorbed poorly in gastrointestinal tract, leading to a very low bioavailability of 3-4%. In the comment-assessment report of Prof. Gou no information is given on the route of administration in the experiments with paeoniflorin and TGP, so they are considered of unknown clinical relevance for the use of the crude herb. Herbal preparations with anti-tumour-activity or rheumatoid arthritis effects are not appropriate for self-medication. In summary, existing data are not adequate to support

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			establishment of a European Union monograph. As no herbal preparations were marketed in the EU, no efficacy for an European indication can be concluded. The clinical assessor recommends a public statement.
Assessment Report chapter 4.1.2. Overview of pharmacokinetic data	Prof. Gou, Shanghai	Comment on the Assessment Report chapter 4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents Li xiaobing et al. (2014) applied a sensitive LC-MS/MS method to a pilot pharmacokinetic study of amygdalin (AD) and paeoniflorin (PF) in healthy volunteers after intravenous infusion administration of 6 g Huoxue-Tongluo lyophilized powder for injection. The maximum plasma concentration (C_{max}) for AD and PF were 692.4±173.4 and 919.1±253.0 ng/mL, respectively. The area under the curve (AUC0–24) for AD and PF were3294±522 and 4023±884 ng h/mL while the elimination half-life(t1/2) were 2.4±0.1 and 2.4±0.1 h, respectively.	No conclusion for human pharmacokinetic can be drawn from Paeoniflorin and amygdalin of Huoxue-Tongluo injection for oral use.
Assessment Report	Prof. Gou, Shanghai	Li XB et al. (2016) investigated the safety profile, tolerability and pharmacokinetic properties of amygdalin (AD) and paeoniflorin (PF) after single and multiple intravenous infusions of Huoxue-Tongluo lyophilized powder for injection (HTLPI) in healthy Chinese volunteers. In single-dose study, 12 subjects received a single intravenous infusion of 3 g, 6 g and 9	No conclusion for human pharmacokinetic can be drawn from injection for oral use.

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		g HTLPI, respectively. In multiple-dose study, 9 subjects received a single intravenous infusion of 6g (containing 25.3 mg AD and 35.8 mg PF) of HTLPI once daily for 7 days. The results showed that in the single-dose phase of the study, the mean maximum plasma concentration and the mean area under the plasma concentration time curve of AD and PF increased proportionally with each dose escalation (all $P>0.05$). In the multiple-dose phase, the steady state was achieved by day 4 after multiple-dose administration of 6 g HTLPI. Mean pharmacokinetic parameters achieved on day 1 were similar to those on day 7. No significant accumulation was observed after repeat doses of 6 g HTLPI. Approximately 79.6% of the administered AD and 48.4% of the administered PF were excreted unchanged in urine within 24 hours. No serious adverse events were observed during the entire study.	
Assessment Report	Prof. Gou, Shanghai	Cheng C et al. (2016) assessed the monoterpene glycosides from Peaonia lactiflora roots in human receiving an intravenous infusion and multiple infusions of XueBiJing injection. Twelve healthy volunteers aged from 19 to 31 were in group A in the treatment of a 75-min infusion of 100 mL of the herbal injection diluted in 100 mL of 0.9% sodium chloride (NaCl) injection. Twelve healthy volunteers were in group B in the treatment of 150-min infusion of 100	No conclusion for human pharmacokinetic can be drawn from paeoniflorin, oxypaeoniflorin and albiflorin of XueBiJing injection for oral use of the plant.

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		mL of the herbal injection diluted in 200 mL of the NaCl injection. Twelve healthy volunteers were in group C in the treatment of a 75 minutes infusion of 50 mL of the herbal injection diluted in 100 mL of the NaCl injection. The result showed that unchanged paeoniflorin exhibited considerable levels of systemic exposure with elimination half-lives of 1.2–1.3 h; no significant metabolite was detected. Oxypaeoniflorin and albiflorin exhibited low exposure levels, and the remaining minor monoterpene glycosides were negligible or undetected. Glomerular-filtration-based renal excretion was the major elimination pathway of paeoniflorin, which was poorly bound to plasma protein.	
		Sadakane C et al. (2015) analysed plasma concentrations of active components after SKT was administered as a single oral dose of 2.5 or 5.0 g per day per person. 10 healthy adult Japanese volunteers enrolled in each group, two dosages were exchanged after 7 days wash out.	No conclusion for human pharmacokinetic can be drawn from studies with the substances albiflorin and paeoniflorin and Shakuyakukanzoto, a combination product with unknown composition which contains Glycyrrhizae radix.
	Prof. Gou, Shanghai	Xie HJ et al. (2002) clarified the effect of Paeoniae Radix (PR) on losartan oxidation by the measure of CYP2C9 activity. Three healthy volunteers received a single oral dose of losartan (25 mg) before and after PR treatment. Losartan and E-3174, an active metabolite of losartan, were analysed in 8 hours urine. The result showed that PR did not have an effect on	Basic information on the Paeoniae radix (art of preparation, dose) is missing.

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		CYP2C9 activity when the losartan/E-3174 ratios were compared before and after PR treatment (P=0.56).	
Assessment Report chapter 4.2.2. Clinical studies	Prof. Gou, Shanghai	Comment on the Assessment Report chapter 4.2.2. Clinical studies (case studies and clinical trials) <u>Patients with Alopecia Areata</u> Yang DQ et al. (2013) examined the efficacy and safety of total glucosides of paeony capsule (TGPC) and compound glycyrrhizin tablets (CGT) for severe alopecia areata in children. Sixty children aged between 2 and 14 years in treatment group were given oral TGPC 3×300 mg per day and CGT 3×25 mg per day for 12 months. Fifty seven children aged between 2 and 14 years in control group. Both groups were given 5 mg of vitamin B2 twice daily. The result demonstrated that TGPC plus CGT and CGT alone can lower the alopecia areata severity, and both groups had good clinical efficacy for the treatment of severe alopecia areata in children. The alopecia areata severity scores of the treatment group were much lower (around 2) than those of control group (P<0.05), and the effective rate was 81.67% in treatment group after 12 months (P<0.05).	Only abstracts of the clinical studies were submitted, without literature references and without the original literature. For TGP no tradition of 30 years has been established. Two preparations were administrated to the children with alopecia areata, total glucosides of paeony capsule (TGPC) and compound glycyrrhizin tablets (CGT). No conclusion for the efficacy of TGP alone can be drawn from this study.
Assessment Report	Prof. Gou, Shanghai	<u>Patients with preventing restenosis after percutaneous coronary intervention</u> Shang QH et al. (2011) evaluated the safety and	Paeoniflorin is a substance and not a herbal preparation, with no traditional European medicinal use in preventing restenosis after percutaneous coronary intervention. Two drugs were

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		efficacy of Xiongshao Capsule (XS), consisting of Chuangxiongol and peaoniflorin, in preventing restenosis after percutaneous coronary intervention (PCI) in senile coronary heart disease (CHD) patients. Onehundred sixty nine CHD patients were in the placebo group, 166 CHD patients were in the treatment of plus XS 3×250 mg per day for 6 months after successful PCI. The subgroup analysis of 152 senile patients showed the results that the restenosis rates in the XS group (24.32%) was lower than the placebo group (38.71%, P>0.05). The incidence of recurrent angina at 3 and 6 months after PCI was also significantly reduced in XS group (4.11% and 12.33%) as compared with those in the placebo group (17.72% and 43.04%), but there was no significant difference in the combined incidence of clinical outcomes (6.85% in the XS group vs. 11.39% in the placebo group, P>0.05).	administrated to the patients. No conclusion for the efficacy of paeoniflorin alone can be drawn from this study.
Assessment Report	Prof. Gou, Shanghai	Patients with rheumatoid arthritis Xiang N et al. (2015) investigated the effect of total glucosides of paeony (TGP) on hepatic dysfunction caused by methotrexate (MTX) and Leflunomide (LEF) in patients with active rheumatoid arthritis (RA). Experimental group received MTX (Shanghai Xinyi Pharmaceutical Company, China) 10 mg per week orally if body weight b60 kg or 15 mg per week if body weight ≥60 kg LEF (Fujian Huitian Pharmaceutical	No traditional medicinal use is evident for TGP in use on hepatic dysfunction. The results do not show significant differences in the clinical effect between the groups.

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		Company, China) was used 20 mg per day in combination with TGP (Ningbo Lihua pharmaceutical company, China) at a dosage of 1.8 g per day orally (0.6 g each time, three times a day). Control group received MTX in combination with LEF at the same dosage of the experimental group. After 12-week, the result showed that the incidence of abnormal liver function within 12 weeks in TGP group was significantly lower than that in control group (11.38% vs 23.26%, P=0.013). The proportion of patients with ALT/AST >3 times ULN (upper limits of normal) was significantly lower in TGP group than control group (1.63% vs 7.75%, P=0.022). More patients achieved remission, good and moderate response in TGP group than control group at 4, 8 and 12 weeks, but the difference was not significant (P>0.05).	
Assessment Report	Prof. Gou, Shanghai	<u>Patients with oral lichen planus</u> Zhou et al. (2016) assessed the effect and adverse reaction of total glucosides of paeony capsule (TGPC) in combination with corticosteroids for the treatment of oral lichen planus (OLP). ROLP patients (17 in group A and 22 in group B) were treated with compound powder of adrenocorticoids twice daily until symptom resolution. Group B patients also received TGPC 3×400 mg per day for 6 months, which contained no<104 mg of total glucosides of paeony. EOLP patients (17 in group C and 17 in group D) treated with prednisolone	No traditional medicinal use is evident for TGP in oral lichen planus.

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		15 mg per day for six months. Group D patients received TGPC in addition to prednisolone. The result showed that In the ROLP patient group, combined treatment significantly reduced the visual analogue scale (VAS) at months 3, 5, and 6. The effective rates of combined treatment were statistically higher versus control groups both in ROLP and EOLP patients. For ROLP patients, the effective rates of group B were significantly higher at the M1, M3, and M6 visits (50% vs. 23.5%, 90.9% vs. 64.7%, and 100% vs. 64.7%, respectively; $p<0.01$). For EOLP patients, group D showed obviously higher effective rates than group C at M1, M3, andM6 (82.4% vs. 64.7%, 88.2% vs. 64.7%, and 100% vs. 88.2%, respectively; $p<0.01$).	
Assessment Report	Prof. Gou, Shanghai	Patients with diabetes mellitus Zhu QJ et al. (2016) investigated the efficacy and safety of Total glucosides of paeony (TGP) for treating diabetic kidney disease (DKD) in type 2 diabetes mellitus patients. The losartan group comprised 38 patients with Diabetic kidney disease (DKD) and received basic hypoglycemic therapy plus losartan. The TGP group comprised 38 patients with DKD and received TGP in addition to standard anti-diabetic therapy plus losartan. Both groups were observed over a treatment period of 6 months. The daily dose was 50 mg losartan at the start of the study, with a gradual increase up to 100 mg, and 600 mg TGP three times	No traditional medicinal use is evident for TGP in use for treating diabetic kidney disease.

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		daily. Losartan was administrated at the same dose as the control group. The results showed that urinary albumin excretion rate (UAER) decreased in the TGP group compared with baseline (132.58 ± 32.42 vs. 56.87 ± 11.71 mg/24 h, t = 13.88, P<0.01). UAER in the losartan group decreased to a level lower than before treatment (24.7%, 138.4 ± 38.64 vs. 104.22 ± 34.24 g/24 h, t=4.08, P<0.05). The rate of decline in the losartan group was significantly lower than the TGP group (t=8.26, P<0.01). There were no significant differences in serum creatinine and albumin levels between TGP and losartan groups at the end-point, and no significant differences in the levels of fasting blood glucose, HbA1c, triglycerides, and total cholesterol in the TGP group compared with the losartan group for a corresponding period.	
Assessment Report	Prof. Gou, Shanghai	<u>Patients with necrobiotic xanthogranuloma</u> Li S et al. (2014) reported a case of isolated necrobiotic xanthogranuloma (NXG) that responded very well to total glucosides of paeony treatment. The patient was prescribed systemic treatment of oral TGP by capsule with the dose of 300 mg t.i.d. (900 mg per day) for 2 weeks at the beginning of treatment and the increased dosage to 600 mg t.i.d. (1800 mg per day) for 14 weeks. The result showed that the lesions improved as the cutaneous plaques decreased in size. In the follow-up 6 months telephone track, the patient	No traditional medicinal use is evident for TGP in use of necrobiotic xanthogranuloma.

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		said the condition continues to improve.	
Assessment Report	Prof. Gou, Shanghai	Patients with Severe Cholestatic hepatitis He JP et al. (1997) studied the curative effect of Radix Paeoniae Rubra in treatment of severe cholestatic hepatitis (SCH). Three-hundred fifty patients of SCH with total bilirubin level ≥ 171 μmol/L were treated with Radix Paeoniae Rubra (80-120 g), Persicae Semen (15 g) and Croci Stigma (15 g) decoction one time daily for 4 to 8 weeks. The results showed that 314 out of 350 subjects showed markedly effectivity, the effective rate was 89.7%.	Basic information on the Paeoniae Radix (DER of the decoction) is missing. The effect of three drugs was analysed. No conclusion can be drawn for efficacy of the monopreparation for the treatment of cholestatic hepatitis.
Assessment Report	Prof. Gou, Shanghai	Patients with Liver fibrosis Yang DG et al. (1994) studied the effects of a heavy dosage of Radix Paeoniae Rubra to the reabsoptive action of liver collagen fibers. 10 patients with chronic active hepatitis caused liver fibrosis received Radix Paeoniae Rubra (60 g), Salviae Miltiorrhizae (30 g) and Puerariae Lobatae Radix (30 g) once per day, six times per week for 3 months. The result showed that the effective rate was 77.8%.	Basic information on the Paeoniae Radix (art of preparation, dose) is missing. No traditional medicinal use is given for the treatment of liver fibrosis.
Assessment Report	Prof. Gou, Shanghai	Patients with acute hepatitis Lee CH et al. (2008) designed a case-crossover study on 200 000 randomly selected individuals from the National Health Insurance Research Database who	Basic information on the Paeoniae Radix formule is missing (herbs, doses). In TCM, combinations of various herbs are usually prescribed. No traditional European medicinal use is given for the treatment of acute hepatitis and no efficacy can be

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		were then followed from 1997 to 2002. All medications taken in the 30- and 60-day periods prior to hospitalization were explored and compared with four control periods (the 180- and 360-day periods prior to and after the hospitalization). The result revealed that the odds ratio increased to 4.2 for those prescribed formulae containing Radix Paeoniae (95% CI: 1.1, 15.7).	concluded from this study. The clinical studies listed in this comment cannot proof efficacy and safety for paeoniflorin, TGP or of Radix Paeoniae Rubra preparations in alopecia areata, preventing restenosis after percutaneous coronary intervention, rheumatoid arthritis, oral lichen planus, diabetes mellitus, necrobiotic xanthogranuloma, cholestatic hepatitis or acute hepatitis. Because of missing literature data in the received comment and no relevance for the outcome of the assessment, the abstracts are not included in the AR.
Assessment Report chapter 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof	Department of Chinese Medicine and Pharmacy, Ministry of Health and Welfare, Taiwan, ROC	Comment on the Assessment Report chapter 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof: Proposed inclusion of the Paeoniae radix rubra monograph of the Taiwan Herbal Pharmacopeia. (PAEONIAE RUBRA RADIX; 赤芍; Chih Shao / Chi Shao/Red Peony Root)	Chapter 1.1 and 2.2 of the assessment report HMPC contains the information that the drug is also described in the Taiwan Herbal Pharmacopoeia. The detailed text of this pharmaceutical monograph is not included in the HMPC assessment report, as pharmaceutical monographs are not part of the HMPC-assessment report.
Assessment Report chapter 6. Overall	Department of Chinese Medicine and Pharmacy,	Paeoniae radix rubra is used in Traditional Chinese medicines. The herbal substance is described in the Taiwan Herbal Pharmacopeia 2nd. In Taiwan, there are 1054 drug license containing Paeoniae radix rubra	No efficacy and safety for specific European mono-preparation and indications for establishing a European Union monograph can be concluded from the information.

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conclusions (benefit-risk assessment)	Ministry of Health and Welfare, Taiwan, ROC	issued by the Ministry of Health and Welfare.	The overall conclusion is not changed.