EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 November 2022
EMA/HMPC/679981/2021
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Vaccinium macrocarpon* Aiton, fructus (EMA/HMPC/49135/2017)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Vaccinium macrocarpon* Aiton, fructus, as released for public consultation on 31 May 2021 until 31 August 2021

	Organisations and/or individuals
1	Plantaphile / Thomas Brendler
2	Pharmatoka / LPP
3	United States Pharmacopeia (USP) / Maria Monagas
4	Marucci Center for Blueberry Cranberry Research, Rutgers University, USA / Amy B. Howell
5	AESGP

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Plantaphile	The set of references which informed the assessment report and consequently the monograph draft is incomplete, relevant data have not been considered, for instance, an ESCOP monograph from 2009 is being cited, which however, has been revised in 2020. The most recent review of clinical data is Brendler & Howell 2020, *American Cranberry (Vaccinium macrocarpon Ait.) and the Maintenance of Urinary Tract Health*, in Mathe A. ed. 2020, Medicinal and Aromatic Plants of North America, Medicinal and Aromatic Plants of the World, vol 6.	The references are acknowledged and will be considered for inclusion in the AR.
Plantaphile	An herbal preparation / pharmaceutical form is excluded from informing the monograph for lacking 30 years of use evidence as a commercial product / preparation. Not only does this contradict the assessment of 8 national competent authorities who granted THRs for the product in question and thus considered the criteria laid out in Directive 2004/24/EC as fulfilled, it also ignores precedent for pharmaceutical forms being included in a monograph for which 30 years of traditional use is not substantiated, see e.g., the monograph for valerian. Consequently, the pharmaceutical form "dry, refined extract from the juice of cranberry fruit" as used in the THR Ellura should be included in the monograph.	Not endorsed. As the legislation refers to the 'same active substances' the herbal substance/herbal preparation must be the same in terms of the declaration of active substances. For this product, information about the refinement step is insufficient in the public domain, and the herbal preparation will not be included in the monograph (see EMA/HMPC/104613/2005 – Rev. 1). However, when an application concerns a herbal preparation not mentioned in a monograph, a reference to the monograph could still be possible under certain conditions (see EMA/HMPC/345132/2010 - Rev.5).
Plantaphile	The assessment report considers a number of cranberry food supplements in the EU market. These products are illegal insofar as they are making health claims or are inappropriately registered as medical devices. References to these products should be removed. Indeed, two valid reference products exist, namely Vitabutin (Denmark,	Partly endorsed. Importantly, there are no approved health claims for food supplements in the EU and medical devices containing cranberry are not allowed in the EU, which is also reflected in the last assessor's comment in the assessment report section 2.1.1. Reference to several food

Interested party	Comment and Rationale	Outcome
	no longer active) and Ellura (formerly Urell), THR in 7 EU member states and the UK.	supplements is made in the assessment report, reflecting the problem with different classifications in different member states within the EU. Several of these examples illustrate that there is a medicinal use of cranberry and that borderline issues between medicinal products and food supplements are national matters. However, it is agreed that the information could be reduced to include relevant information on medicinal use only.
Plantaphile	There is insufficient evidence for a relief of UTI symptoms caused of cranberry (see below), therefore indication (1) should be removed from the monograph, and indication (2) should be worded in accordance with the granted THRs for Ellura. This indication is further supported by Jepson *et al.,* 2013, *Cranberry Products and Prevention of Urinary Tract Infections*, who recommend cranberry "for women with recurrent UTIs (the group where some potential benefit is demonstrated), and only if they contain the recommended amount of proanthocyanidins (at least 36 mg/d)".	Not endorsed. The indications in the monograph reflect the traditional use of cranberry according to the Directive 2004/24/EC regarding traditional herbal medicinal products. Hence, the indications are based on a plausible effect originating from the fact that cranberry has been used traditionally in the proposed indications for 30 years (of which 15 years within EU).
Plantaphile	Posology should reference the recommended equivalent daily dose of 36 mg PAC (measured by DMAC method using A2 reference standard) – regardless of preparation – as supported by Brendler & Howell 2020 (see above), and the *American Herbal Pharmacopoeia monograph Cranberry Fruit* (Upton & Brendler ed. 2016): "The preparations used in most positive studies yielded a minimum dose of 36 mg PAC per serving (measured by DMAC method using A2 reference standard) suggesting this is a target dose to achieve".	Not endorsed. Since the suggested indications in the monograph are for traditional use only, the posology is based on the posology described in the references that are taken into account (see table 3a and 3b in the assessment report). See also EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1 that outlines the principles for uniform declaration of herbal substances/preparations in traditional herbal medicinal products.
Plantaphile	All comments below concerning the Assessment report carry over to the draft monograph and hence apply to both documents.	See comments below.

Interested party	Comment and Rationale	Outcome
Pharmatoka/LPP	Pharmatoka/LPP acknowledges the work done by the HMPC on the draft monograph of *Vaccinium macrocarpon* Aiton, fructus in view of harmonization. Pharmatoka/LPP understands the HMPC' strict regulatory viewpoint to include only active substances/medicinal products in the monograph that have demonstrated 15 years of use within the European Union, which does not foresee the reference to corresponding products (as it is the case for national authorizations) and will therefore not comment on the non-inclusion of Ellura/herbal preparation in this monograph, even if this will not facilitate any mutual recognition in Europe.	Agreed. As the legislation refers to the 'same active substances' the herbal substance/herbal preparation must be the same in terms of the declaration of active substances. For this product, information about the refinement step is insufficient in the public domain, and the herbal preparation will not be included in the monograph (see EMA/HMPC/104613/2005 – Rev. 1). However, when an application concerns a herbal preparation not mentioned in a monograph, a reference to the monograph could still be possible under certain conditions (see EMA/HMPC/345132/2010 - Rev.5).
Pharmatoka/LPP	Pharmatoka/LPP has 3 major comments to bring to the attention of the HMPC: 1) The bibliographic review in the assessment report is incomplete and some references should be updated.	Specific references mentioned in the received comments are acknowledged and will be considered for inclusion in the AR. See below.
Pharmatoka/LPP	2) The indication 1 related to "UTI symptoms treatment" is not based on sufficient bibliographic or traditional use evidence and should be deleted from the monograph to avoid confusion for the patient and the HCP.	Not endorsed. From the data presented in Table 3a in the assessment report, HMPC concluded that there is sufficient evidence to suggest an indication related to "relief of symptoms"..
Pharmatoka/LPP	3) Mentioning the many proprietary names and trademarks of food supplements, most of them carrying illicit health claims, and illegal medical devices for cranberry products within the assessment report is not appropriate. Indeed, two valid reference products exist, namely Vitabutin (Denmark) and Ellura, THMP in 7 EU member states and the UK. The herbal preparation of Ellura has been used in the EU for 16 years as a food supplement (brand name Urell). These products are not even mentioned in the assessment report.	Partly endorsed. Importantly, there are no approved health claims for food supplements in the EU and medical devices containing cranberry are not allowed in the EU, which is also reflected in the last assessor's comment in the assessment report section 2.1.1. Reference to several food supplements is made in the assessment report, reflecting the problem with different classifications in different member states within the EU. Several of these examples

Interested party	Comment and Rationale	Outcome
		illustrate that there is a medicinal use of cranberry and that borderline issues between medicinal products and food supplements are national matters. However, it is agreed that the information could be reduced to include relevant information on medicinal use only. In line with the information on registered/authorised medicinal products in the AR, the proprietary names of food supplements and medical devices are not necessary and will be removed from the final AR. The additional information is acknowledged and will be considered for inclusion in the AR.
Pharmatoka/LPP	All comments below concerning the Assessment report carry over to the draft monograph and hence apply to both documents.	See comments below.
USP	1. USP would like to inform the European Medicines Agency (EMA) of the following Cranberry monographs recently published in the Pharmacopeial Forum (PF) (https://www.uspnf.com/pharmacopeial-forum) (attached as Supporting documents): Revised monographs: Cranberry Liquid preparation (PF 45(6), Nov 2019)- future title: *Cranberry Fruit Juice* New monographs: Cranberry Fruit Juice Concentrate (PF 45(6), Nov 2019) Cranberry Fruit Juice Dry Extract (PF 45(6), Nov 2019) Cranberry Dry Juice (PF 47(2), March 2021)	The information is acknowledged and will be considered for inclusion in the AR. However, the reference to USP will be deleted in the footnote in section 2 of the monograph. Instead, the footnote will be in accordance with the MO template: "Detailed specifications for the herbal substance shall be given by references to bibliographic sources in absence of a monograph in the European Pharmacopoeia, a national pharmacopoeia or national codex currently used in a Member State.".

Interested party	Comment and Rationale	Outcome
	Cranberry Fruit Juice Dry Extract Capsules (PF 47(3), May 2021)	
USP	2. USP recommends using the above-mentioned USP monographs to update the categorization of cranberry ingredients described in the assessment document and monograph draft proposal. In particular, the USP Cranberry Liquid Preparation monograph, referenced in the current proposal, has been revised.	Partly endorsed. The information is acknowledged and will be considered for inclusion in the AR. However, the reference to USP will be deleted in the footnote in section 2 of the monograph. Instead, the footnote will be in accordance with the MO template, see comment above.
USP	3. The term DER 1: 0.6-0.9 used for the Herbal preparation (under *2. Qualitative and quantitative composition*), does not accurately define Cranberry Fruit Juice. DER is an expression of yield and not a measure of strength. Yield depends on the juice processing technology and additives used (including pectolytic enzymes). There is no guarantee that two juices with the same DER will have the same composition of active or marker compounds (polyphenols, sugars and organic acids). DER is not an analytical parameter that can be measured by any test, and thus it is not a quality parameter.	Not endorsed. DER is used in the definition of the herbal preparation, not as a quality marker. Since the suggested indications in the monograph are for traditional use only, the constituents responsible for the therapeutic activity or active markers are unknown. Hence, no adjustments to a particular content of constituents are needed. Instead, for control purposes, one or more constituents are used as analytical markers, but the content is not declared.
USP	4. USP recommends using °Brix or % soluble solids to define this article. This parameter is among the absolute quality requirements defined by the international standards including the International Juice and Vegetable Association (IFU), Code of Practice for Cranberry Juice (https://ifu-fruitjuice.com/) and the Codex Alimentarius Standard for Fruit Juices and Nectars (CODEX STAND 247-2005) (attached as Supporting documents). In addition, the composition of organic acids and sugars should be considered as a parameter for identification and authentication of	Not endorsed. Since the suggested indications in the monograph are for traditional use only, the constituents responsible for the therapeutic activity or active markers are unknown. Hence, no adjustments to a particular content of constituents are needed. Instead, for control purposes, one or more constituents are used as analytical markers, but the content is not declared.

Interested party	Comment and Rationale	Outcome
	Cranberry juice, which is proposed in the current USP Cranberry Liquid Preparation.	
USP	5. USP recommends reviewing and using USP's recently published paper: Safety of Cranberry: Evaluation of Evidence of Kidney Stone Formation and Botanical Drug-Interactions, by authors: Emily Madden, Caleb McLachlan, Hellen Oketch-Rabah, Angela I. Calderón. *Planta Med.* 2021 May 20. (doi: 10.1055/a-1497-624) Including the flowing topics: • Cranberry Phytochemistry and Pharmacopeial Quality • Regulatory Status of Cranberry and Reported Intake Levels • Clinical Evidence of Safety Animal Toxicology, *In Vitro* Studies, and Pharmacokinetics • Adverse Effects Associated with Cranberry • Kidney Stone Formation and Cranberry • Potential Drug Interactions with Cranberry	The reference is acknowledged and will be considered for inclusion in the AR.
USP	6. USP recommends reviewing and citing the updated *Vaccinii macrocarpi* fructus (Cranberry) monograph from the European Scientific Cooperative on Phytotherapy (ESCOP) (https://escop.com/about-escop/) released last December 2020. We note that the older 2009 ESCOP monograph was cited in the descriptions of posology.	The reference is acknowledged and will be considered for inclusion in the AR.
A. Howell, Rutgers University	The statements on UTI symptom relief following cranberry intake should be deleted from the monograph.	Not endorsed. The indications in the monograph reflect the Traditional Use of cranberry according to the Directive 2004/24/EC regarding traditional herbal medicinal

Interested party	Comment and Rationale	Outcome
	The plausibility of traditional use for the symptom relief is not sufficient based on the existent bibliography. The role of cranberry intake in symptom relief of recurrent UTI and the purported effects are mainly anecdotal. There are two clinical studies on cranberry juice, and both found no decrease in UTI symptoms; and three clinical studies using cranberry powder did report some effects, however these studies were of low statistical power and methodologically flawed and do not show that HCPs have long-standing use of cranberry to treat the symptoms. These clinical trials are summarized below: Little, P. *et al.* Dipsticks and diagnostic algorithms in urinary tract infection: Development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technol. Assess.* 2009, 13, 1–73 Little *et al.* analyzed the impact of the different treatment strategies on "frequency symptoms" (daytime and night-time urinary frequency, dysuria and urgency) and "unwell symptoms" (restriction of usual activities, abdominal pain and feeling unwell). There was no significant effect of advice to drink cranberry juice on the severity of frequency symptoms or the severity of unwell symptoms, compared with advice to drink water. Barbosa-Cesnik, C. *et al.* Cranberry juice fails to prevent recurrent urinary tract infection: Results from a randomized placebo-controlled trial. *Clin. Infect. Dis.* 2011, 52, 23–30 Barbosa-Cesnik *et al.* reported that at 3 days and at 1–2 weeks after enrolment in the trial on cranberry juice consumption and its effect on	products. Hence, the indications are based on a plausible effect originating from the fact that cranberry has been used traditionally in the proposed indications for 30 years (of which 15 years within EU). Indeed, as stated in the AR, section 6. Overall conclusion, the requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC is considered not fulfilled. This conclusion is based on the assessment of several clinical studies (see Table 5 in AR), and the conclusion is in line with the comment by A. Howell. The presented references are acknowledged and will be considered for inclusion in the AR. However, Barbosa-Cesnik (2011), Sengupta (2011) and Singh (2011) are already included in the AR and list of references.

Interested party	Comment and Rationale	Outcome
	recurrent UTI, the presence of urinary symptoms and vaginal symptoms was similar between the cranberry and placebo juice groups. Sengupta, K. *et al*. A Randomized, Double Blind, Controlled, Dose Dependent Clinical Trial to Evaluate the Efficacy of a Proanthocyanidin Standardized Whole Cranberry (*Vaccinium macrocarpon*) Powder on Infections of the Urinary Tract. *Current Bioactive Compounds,* Volume 7, Number 1, 2011, pp. 39-46(8) This study conducted in India, published in *Current Bioactive Compounds*, and journal from the United Arab Emirates with an impact factor of 1.3, was statistically under-powered, with only 13 people in the placebo group, and 21 and 23 in the high and low-dose cranberry groups, respectively. The cranberry powdered supplement used in the study only had 1.5% PAC, which is significantly under the efficacious dose of 36 mg. As a result, the researchers did not find a statistically significant difference in UTI between the treatment and control groups at any of the time points over the 90-day period, perhaps due to the low PAC content and the small sample size. They also considered 10^4 *E. coli* bacteria as the indication of clinical UTI, which is lower than the standard of 10^5, so this makes their results even less significant. There were no differences noted in the absolute number of positive cultures for *E. coli* in each of the three groups. The reported amelioration in some UTI symptoms in the treatment group was obtained from a symptom questionnaire that was highly subjective and did not take hygiene habits into account, which can impact symptoms significantly. Singh, I. *et al.* Effect of oral cranberry extract (standardized proanthocyanidin-A) in patients with recurrent UTI by pathogenic *E.*	

Interested party	Comment and Rationale	Outcome
	coli: a randomized placebo-controlled clinical research study. *Int Urol Nephrol*. 2016 Sep; 48(9):1379-86 The participants in this study were not a homogeneous group and suffered from coexisting urological disorders (some were catheterized patients that may have had infections caused by bacteria other than *E. coli*), making the overall results confounded. The placebo group was not a true placebo group because they ingested 400 mg of *Lactobacillus* as the placebo treatment. *Lactobacillus* has been tested clinically on its own for management of UTI (Minardi D. *et al.* Urinary tract infections in women: etiology and treatment options. *Int J Gen Med*. 2011; 4:333-343) and can affect the adherence and growth of uropathogenic bacteria. In this study, bacteriuria was assessed as a symptom rather than a sign of infection. Symptom evaluation was a secondary endpoint based on a subjective "well-being" score, which is notoriously flawed. Lifestyle advice measures like personal hygiene and fluid intake which could have partly contributed to amelioration of recurrent UTI signs and symptoms could not be entirely excluded. There are two reviews that evaluate UTI symptom relief: Bass-Ware, A. *et al.* Evaluation of the Effect of Cranberry Juice on Symptoms Associated with a Urinary Tract Infection. *Urologic Nursing* May/Jun 2014, Vol. 34 Issue 3, p 121-127 Study participants completed the Interstitial Cystitis Symptom Index (ICSI) tool and the Interstitial Cystitis Problem Index (ICPI) tool to determine symptom relief. Cranberry juice consumption over an eight-week time frame elicited a statistically significant reduction in	

Interested party	Comment and Rationale	Outcome
	Interstitial Cystitis Symptom Index score. However, interstitial cystitis is often mistaken for UTI, but is not normally associated with bacterial infection. Therefore, it is not equated with symptom relief in recurrent UTI, so this study is not applicable in this situation. Gbinigie OA, Spencer EA, Heneghan CJ, Lee JJ, Butler CC. Cranberry Extract for Symptoms of Acute, Uncomplicated Urinary Tract Infection: A Systematic Review. Antibiotics (Basel). 2020 Dec 25, 10(1):12 The aim of this systematic review was to synthesize the evidence for the use of cranberry products in the management of symptoms of acute, uncomplicated UTIs. The review conclusion: The current evidence base for or against the use of cranberry extract in the management of acute, uncomplicated UTI symptoms is inadequate; rigorous trials are needed. There is one *in vitro* study that attempted to look at specific pathways associated with *E. coli*-induced inflammation that occurs in UTIs and contributes to symptoms: Huang Y. *et al.* Effects of cranberry extracts and ursolic acid derivatives on P-fimbriated *Escherichia coli*, COX-2 activity, pro-inflammatory cytokine release and the NF-kappabeta transcriptional response *in vitro*. *Pharm Biol.* 2009, 47(1):18-25 Researchers found that the methanol extract from cranberry inhibited the activity of cyclooxygenase-2, NF-κβ transcriptional activation in human T lymphocytes, and the release of interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor-α from *E. coli* lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells *in vitro*. Based on these findings, the researchers then propose that cranberry may reduce	Article written by Huang Y. *et al.* has been already considered in the Assessment report (see section 3.1.1) and list of references.

Interested party	Comment and Rationale	Outcome
	the symptoms of UTI through its anti-inflammatory effects. However, such a hypothesis has not been verified in a clinical setting. The main issue is that researchers used cranberry extract fractions and incubated these directly in cell cultures. This was all done *in vitro*, with extract components that will never be in direct contact with the intended cells to influence these processes *in vivo*. The overall conclusion after reviewing the *in vitro* and clinical studies is that there is not enough traditional/long-standing proof and scientific evidence to support the notion that cranberry intake effectively reduces symptoms when taken for recurrent UTI prevention.	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Assessment report Pages 8-10	Plantaphile	Data on composition of and health claims associated with supplements and medical devices containing cranberry are irrelevant: as the assessor correctly states, these products are non-compliant in one way or another and should not be included here.	Partly endorsed. Importantly, there are no approved health claims for food supplements in the EU and medical devices containing cranberry are not allowed in the EU, which is also reflected in the last assessor's comment in the assessment report section 2.1.1. Reference to several food supplements is made in the assessment report, reflecting the problem with different classifications in different member states within the EU. Several of these examples illustrate that there is a medicinal use of cranberry and that borderline issues between medicinal products and

Section number and heading	Interested party	Comment and Rationale	Outcome
			food supplements are national matters. However, it is agreed that the information could be reduced to include relevant information on medicinal use only.
Assessment report Page 11ff, table 2	Plantaphile	Utilizing historical investigations (e.g., Moen, 1962; Sternlieb, 1963; Papas, 1966; Tyler, 1994) to substantiate a curative effect is not appropriate. By modern standards of clinical assessment this evidence is at best anecdotal, and certainly insufficient to derive effects of symptom relief. The only indication that is reasonably well documented in the body of clinical data is that prevention, given the correct dosage and posology.	Not endorsed. The listed literature references are not aiming to prove clinical efficacy. Taken together, the sum of the data reflects the Traditional Use of cranberry according to the Directive 2004/24/EC on traditional herbal medicinal products. Hence, the indications are based on a plausible effect originating from the fact that cranberry has been used traditionally in the proposed indications for 30 years (of which 15 years within EU).
Assessment report Pages 18-19	Plantaphile	See general comment above regarding indications 1 and 2. The posology is incomplete and should include juice extract powders as registered as THRs in multiple member states.	Not endorsed. As the legislation refers to the 'same active substances' the herbal substance/herbal preparation must be the same in terms of the declaration of active substances. For this product, information about the refinement step is insufficient in the public domain, and the herbal preparation will not be included in the monograph (see EMA/HMPC/104613/2005 – Rev. 1). However, when an application concerns a herbal preparation not mentioned in a monograph, a reference to the monograph could still be possible under certain conditions (see EMA/HMPC/345132/2010 - Rev. 5).
Assessment report	Plantaphile	Successful prevention of recurring UTIs has been associated with a minimum daily dose of 36 mg PAC,	Not endorsed. The monograph is reflecting only traditional use of cranberry. Therefore, reference to a

Section number and heading	Interested party	Comment and Rationale	Outcome
Page 19		measured using the DMAC method. DMAC, despite its limitations, is the current industry standard and should therefore be utilized to determine the strength of a product. In fact, the 36 mg of PAC are broadly referenced in section 4 of the Assessment report.	minimum daily dose of 36 mg PAC to get "successful prevention" (i.e. clinical effect) is not appropriate. See also EMA/HMPC/CHMP/CVMP/287539/2005 Rev. 1 that outlines the principles for uniform declaration of herbal substances/preparations in traditional herbal medicinal products.
Assessment report Page 19	Plantaphile	If there had not been sufficient traditional use evidence presented to demonstrate 15/30 years of use, member states would not have granted THRs. Further, there is precedent in other HMPC monographs for the inclusion of preparations for which 30-year evidence is lacking.	Not endorsed. As the legislation refers to the 'same active substances' the herbal substance/herbal preparation must be the same in terms of the declaration of active substances. For this product, information about the refinement step is insufficient in the public domain, and the herbal preparation will not be included in the monograph (see EMA/HMPC/104613/2005 – Rev. 1). However, when an application concerns a herbal preparation not mentioned in a monograph, a reference to the monograph could still be possible under certain conditions (see EMA/HMPC/345132/2010 - Rev. 5).
Assessment report Pages 4; 13; 15	Pharmatoka/LPP	The ESCOP monograph was updated in 2020 and conclusions should be taken into account and included in this assessment report.	The present reference is acknowledged and will be considered for inclusion in the AR.
Assessment report Page 5	Pharmatoka/LPP	Paragraph "Proanthocyanidins (PACs)" We propose an adaptation of this paragraph with the contribution from C. Krueger, Complete Phytochemical Solutions, LLC. Proposed replacement text:	The present references and the proposed text are acknowledged and will be considered for inclusion in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
		"Proanthocyanidins (PACs). There are two common series of procyanidin (PAC) dimers. The "B-type" series are dimers linked either in the C4–C6 or C4–C8 position whereas the "A-type" series are dimers linked in the C4–C8 position with an additional C2–O–C7 ether linkage. Cranberry PAC oligomers with a degree of polymerization >2 may incorporate both "A-type" and "B-type" interflavan linkages. By extension of this definition, and for purposes of discussion, PAC oligomers that contain one or more "A- type" interflavan linkages in their structure are referred to as "A-type" PAC, whereas PAC oligomers that contain only "B-type" interflavan linkages are referred to as "B-type" PAC (Krueger *et al.,* 2013). The relative abundance of "A-type" to "B-type" PAC at each degree of polymerization can be determined with high accuracy by Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (Feliciano *et al.,* 2012a, 2012b; Esquivel-Alvarado *et al.,* 2021a, 2021b, 2021c). Cranberry PAC have been shown to contain predominantly (>90%) one or more "A-type" bonds at each degree of polymerization (Feliciano *et al.* 2012a; Esquivel-Alvarado *et al.,* 2021a, 2021b). Cranberry has been reported to contain PAC oligomers greater than 26 degrees of polymerization (Feliciano *et al.,* 2012b). The relative ratio of "A-type" to "B-type" PAC can be used to substantiate authenticity of cranberry foods, beverages and dietary	

Section number and heading	Interested party	Comment and Rationale	Outcome
		supplements (Esquivel-Alvarado *et al.,* 2021a, 2021b, 2021c)." References: Esquivel-Alvarado D, Alfaro-Viquez E, Krueger CG, Vesling MM, Reed JD. Classification of proanthocyanidin profiles using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) spectra data combined with multivariate analysis. *Food Chem* 2021a, 336:127667 Esquivel-Alvarado D, Alfaro-Viquez E, Krueger CG, Vestling MM, Reed JD. Identification of A-type proanthocyanidins in cranberry-based foods and dietary supplements by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, First Action Method: 2019.05. *J AOAC Int* 2021b, 104(1):223-231 Esquivel-Alvarado D, Reed JD, Krueger CG. Chapter 5 Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) of proanthocyanidins to determine authenticity of functional foods and dietary supplements. In: Reed JD, Pereira de Freitas VA, Quideau S, editors. Recent Advances in Phytochemical Research. Vol. 7. John Wiley & Sons Ltd, 2021c, 113-129 Feliciano RP, Krueger CG, Shanmuganayagam D, Vestling MM, Reed JD. Deconvolution of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry	

Section number and heading	Interested party	Comment and Rationale	Outcome
		isotope patterns to determine ratios of A-type to B-type interflavan bonds in cranberry proanthocyanidins. *Food Chem* 2012a, 135:1485-1493 Feliciano RP, Shea MP, Shanmuganayagam D, Krueger CG, Howell AB, Reed JD. Comparison of Isolated Cranberry (*Vaccinium macrocarpon* Ait.) Proanthocyanidins to Catechin and Procyanidins A2 and B2 for Use as Standards in the 4-(Dimethylamino) cinnamaldehyde Assay. *J Agric Food Chem* 2012b, 60:4578-4585 Krueger CG, Reed JD, Feliciano RP, Howell AB. Quantifying and characterizing proanthocyanidins in cranberries in relation to urinary tract health. *Anal Bioanal Chem* 2013, 405:4385-4395 Krueger CG, Chesmore N, Chen X, Parker J, Khoo C, Marais J, *et al.,* Critical reevaluation of the 4-(dimethylamino)cinnamaldehyde assay: Cranberry proanthocyanidin standard is superior to procyanidin A2 dimer for accurate quantification of proanthoccyanidins in cranberry products. J Functional Foods 2016, 22:13-19	Article written by Krueger *et al.,* 2013 has been assessed in the Assessment report (see section 1.1.).
Assessment report Page 5	Pharmatoka/LPP	**Cranberry juice** The monograph of cranberry liquid preparation published in the United States Pharmacopeia has been revised, and new monographs have been published. Revision:	The present references are acknowledged and will be considered for inclusion in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
		• Cranberry Liquid preparation (PF 45(6), Nov 2019)- future title: Cranberry Fruit Juice New monographs: • Cranberry Fruit Juice Concentrate (PF 45(6), Nov 2019) • Cranberry Fruit Juice Dry Extract (PF 45(6), Nov 2019) • Cranberry Dry Juice (PF 47(2), March 2021) • Cranberry Fruit Juice Dry Extract Capsules (PF 47(3), May 2021)	
Assessment report Page 5	Pharmatoka/LPP	Dried, refined extract of cranberry juice (Austria, France, Netherland, Spain and United Kingdom). It should be added Portugal, Sweden, and Belgium (MAs obtained in 2021).	Endorsed. This reference originates from the outcome of the market review performed in 2016. Hence, it reflects the status at that point. Since then, additional registrations have been finalised. The number of registered THMPs within EU will be updated in the AR.
Assessment report Pages 6-7	Pharmatoka/LPP	Information on medicinal products marketed in the EU/EEA Table 1: Overview of data obtained from marketed medicinal products * For the active substance: lines 2, 3 and 4: it should be corrected as follows to be aligned with the granted	Not endorsed. This information originates from the outcome of the market review performed in 2016 and reflects the information received from Member States at that point.

Section number and heading	Interested party	Comment and Rationale	Outcome
		marketing authorizations: "extract (as dry extract, purified) from the juice of the cranberry fruit".	
Assessment report Pages 6-7	Pharmatoka/LPP	Information on medicinal products marketed in the EU/EEA Table 1: Overview of data obtained from marketed medicinal products * For the posology: lines 2 and 3 (UK, Spain): it should be deleted "At the first sign of any symptoms, take one capsule each day." To be in line with the approved posology.	Not endorsed. This information originates from the outcome of the market review performed in 2016 and reflects the information received from Member States at that point. The wording originates from respective Member State.
Assessment report Pages 6-7	Pharmatoka/LPP	Information on medicinal products marketed in the EU/EEA Table 1: Overview of data obtained from marketed medicinal products * For the indication: line 4 (The Netherlands): it should be replaced by "used to prevent recurrent cystitis in healthy non-pregnant adult women. The application is based exclusively on traditional use and not on clinical evidence" to be in line with the approved indication.	Not endorsed. This information originates from the outcome of the market review performed in 2016 and reflects the information received from Member States at that point. The wording originates from respective Member State.
Assessment report Pages 6-7	Pharmatoka/LPP	Information on medicinal products marketed in the EU/EEA Table 1: Overview of data obtained from marketed medicinal products * Also, the information regarding France, Austria, Portugal, Sweden, and Belgium should be added according to the	Endorsed. The number of registered THMPs within EU will be updated in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Marketing Authorizations granted in 2020/2021, to reflect to current situation. Therefore, it is of note that except Vitabutin (in DK) and ellura (in all other countries), there are no other cranberry based THMP on the EU markets.	
Assessment report Pages 8-10	Pharmatoka/LPP	Information on other products marketed in the EU/EEA (where relevant) It is surprising to see information about non-medicinal products (food supplements and medical devices) with the brand names mentioned. In addition, it is clearly mentioned that there is no authorized health claim for food supplements containing cranberry or cranberry constituents. The Commission decision dated 8 August 2017 clearly states the following: "the group of products whose principal intended action, depending on proanthocyanidins (PAC) present in cranberry extract, is to prevent or treat cystitis, are not medical devices within the meaning of Article 1 (2) (a) of the Medical Devices Directive. Metabolites of PAC and other constituents of cranberry exhibit most probably a pharmacological activity". Therefore, the relevance of including all this information for the EU market in the assessment report is questionable. We propose to shorten this paragraph by limiting it to valid	Partly endorsed. Importantly, there are no approved health claims for food supplements in the EU and medical devices containing cranberry are not allowed in the EU, which is also reflected in the last assessor's comment in the assessment report section 2.1.1. Reference to several food supplements is made in the assessment report, reflecting the problem with different classifications in different member states within the EU. Several of these examples illustrate that there is a medicinal use of cranberry and that borderline issues between medicinal products and food supplements are national matters. In line with the information on registered/authorized medicinal products in the AR, the proprietary names of food supplements and medical devices are not necessary and will be removed from the final AR. However, it is agreed that the information could be reduced to include relevant information on medicinal use only.

Section number and heading	Interested party	Comment and Rationale	Outcome
		and authorized products and to delete, at least, the information on the illegal medical device status. The food supplement Urell should therefore be added. It is worth noting that Urell is the oldest cranberry food supplement in capsules with 36 mg PAC available on the EU market since 2005, based on the French Government's cranberry health claim of 2004 (France, Belgium, Italy, Spain, Portugal).	
Assessment report Page 11	Pharmatoka/LPP	The following sentence should be adjusted "Since than lots of clinical studies have been performed with different preparations (see 4.2 Clinical efficacy) and the use of *V. macrocarpon* juice to treat UTI is reported in different manuals of phytotherapy". By modern standards of clinical assessment, the evidence is insufficient to support effects of symptom relief or UTI treatment. The clinical studies supporting the treatment of UTIs are underpowered and done with insufficiently characterized cranberry preparations. The only indication that is reasonably well documented in the body of clinical data and for traditional/long standing use is the prevention of recurrent UTIs.	Partly endorsed. The sentence is deleted since it is not considered necessary. The indications in the monograph reflect the Traditional Use of cranberry according to the Directive 2004/24/EC regarding traditional herbal medicinal products. Hence, the indications are based on a plausible effect originating from the fact that cranberry has been used traditionally in the proposed indications for 30 years (of which 15 years within EU). From the data presented in table 3a in the assessment report, HMPC concluded that there is sufficient evidence to suggest an indication related to "relief of symptoms".
Assessment report Page 11	Pharmatoka/LPP	Also, we recommend that the Assessment report clears up the huge semantic issues with clinical concepts and definitions, like - treatment of acute UTIs (with antibiotics,...):	Endorsed. The comment is acknowledged and changes in the AR will be considered.

Section number and heading	Interested party	Comment and Rationale	Outcome
		- prevention of recurrent UTIs (with cranberry products,…) - relief of symptoms (out of the scope of cranberry monograph because cranberry products do not exert any activity directly on the symptoms)	
Assessment report Page 12	Pharmatoka/LPP	Health Canada monograph The reference to Health Canada monograph (revision 18/12/2018) should be deleted because not sufficiently solid and confusing in terms of recommendations: - no pertinent evidence regarding the antioxidant effect - rUTIs: the recommended dosage of preparations equivalent to 90 to 950 ml/day is confusing. The daily use of 950 ml of Fruit juice (pure juice) per day seems totally inadequate from a medical point of view	Not endorsed. The text reflects the wording of the monograph.
Assessment report Page 13	Pharmatoka/LPP	American Herbal Pharmacopoeia The whole AHP 2016 recommendation should be cited. The following sentence should be added: "The preparations used in most positive studies yielded a minimum dose of 36 mg PAC per serving (measured by DMAC method using A2 reference standard) suggesting this is a target dose to achieve".	The information is acknowledged and will be considered for inclusion in the AR.
Assessment report Page 14	Pharmatoka/LPP	UTIs guidelines After mentioning (Jepson *et al.,* 2008), its subsequent publication commenting the Cochrane review of 2012	The information is acknowledged and will be considered for inclusion in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
		(Jepson, 2013, JAMA) should be cited with the following recommendation: "Therefore, further studies of cranberry products, such as tablets and capsules, maybe justified, but primarily for women with recurrent UTIs (the group where some potential benefit is demonstrated), and only if they contain the recommended amount of proanthocyanidins (at least 36mg/day) and are quantified using standardized and validated measures".	
Assessment report Page 14	Pharmatoka/LPP	The full sentence of American Urological Association article should be cited as follows: "The American Urological Association, the Canadian Urological Association and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, recommend cranberries despite a fairly low level of evidence for UTI with a grade C of recommendation: Clinicians may offer cranberry prophylaxis for women with rUTIs".	Partly endorsed. The comment is acknowledged, and the correction in the wording will be considered in the AR: "The guidelines of the American Urological Association, the Canadian Urological Association and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, conclude that clinicians may propose cranberries in prophylaxis for women with rUTIs despite a fairly low level of evidence for UTI with a grade C of recommendation (Anger *et al.,* 2019)".
Assessment report Page 17	Pharmatoka/LPP	Table 3a: Overview of evidence on period of medicinal use for the relief of symptoms of recurrent urinary tract infections The evidence of traditional use of cranberry in the relief of symptoms of UTI is not substantiated and will lead to confusion with patients and HCPs. The table 3a should therefore be deleted as well as the Indication 1 in the draft Monograph.	Not endorsed. The indications in the monograph reflect the Traditional Use of cranberry according to the Directive 2004/24/EC regarding traditional herbal medicinal products. Hence, the indications are based on a plausible effect originating from the fact that cranberry has been used traditionally in the proposed indications for 30 years (of which 15 years within EU). From the data presented in table 3a in the assessment report, HMPC concluded that there is

Section number and heading	Interested party	Comment and Rationale	Outcome
		- MOEN 1962 does not support the relief of symptoms; the cases the author mentions concern the effect of prolonged uptake of Cranberry juice on the relief of symptoms « as long as they continue to take two 6-ounce glass-full of cranberry juice daily », this is an indication for prevention, not for "symptoms treatment". A further patient with chronic pyelonephritis went on cranberry juice for 2,5 years and Moen observed " if cranberry juice is taken daily at the end of 9 months …" in fact there were no new episodes of UTI. This is a clear indication for a prophylactic long-term treatment - STERNLIEB 1963 does not support the relief of symptoms: the author tried the use of cranberry Juice cocktail and "cranberry juice" on some renal problems like kidney stones, with the intention to cure or to prevent. The intention was not to relieve the "symptoms" - TYLER 1994 does not support the relief of symptoms - (VITABUTIN) 1996, Denmark, Iceland, MA: the SPC has no mention of treatment "of symptoms"	sufficient evidence to suggest an indication related to "relief of symptoms".
Assessment report Page 19	Pharmatoka/LPP	Posology The posology should be better clarified and confirmed: there is a huge spread in the posology for prevention (15-80 ml twice daily) and it is not clear what kind of "juice" it is referred to (pure juice or juice cocktail). We also suggest linking the posology to the equivalent fresh fruit in order to	Partly endorsed. The comment is acknowledged and a clarification in the AR will be considered.

Section number and heading	Interested party	Comment and Rationale	Outcome
		avoid any confusion in the markets both for patients and for HCPs.	
Assessment report Page 18	Pharmatoka/LPP	**Traditional use:** "Thirty years of medical use for prevention and relief of symptoms of recurrent UTI is documented in several sources": the term "relief of symptoms" should be deleted. The traditional use therapeutic indication should be limited to the prevention of recurrent uncomplicated lower urinary tract infections in women, after serious conditions have been excluded by a medical doctor. Indeed, the indication on the symptom's relief is not substantiated as traditional use and may confuse and harm the patients and the HCPs.	Not endorsed. From the data presented in table 3a in the assessment report, HMPC concluded that there is sufficient evidence to suggest a traditional use related to "relief of symptoms".
Assessment report Pages 18-19 and 99 and Draft Monograph Indication 1)	Pharmatoka/LPP	**Therapeutic indication:** Indication 1) should be deleted (cf. previous comments on the relevance of this indication in traditional use that is not demonstrated).	Not endorsed. The indications in the monograph reflect the Traditional Use of cranberry according to the Directive 2004/24/EC regarding traditional herbal medicinal products. Hence, the indications are based on a plausible effect originating from the fact that cranberry has been used traditionally in the proposed indications for 30 years (of which 15 years within EU). From the data presented in table 3a in the assessment report, HMPC concluded that there is sufficient evidence to suggest an indication related to "relief of symptoms".

Section number and heading	Interested party	Comment and Rationale	Outcome
Assessment document 1. Introduction 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof Herbal Preparations and Draft proposal 2. Qualitative and quantitative composition	USP	In relation to: • Herbal preparation(s) USP would like to inform to the European Medicines Agency (EMA) of the following published Cranberry monographs published in the Pharmacopeial Forum (PF) (https://www.uspnf.com/pharmacopeial-forum): Revised monographs: • Cranberry Liquid preparation (PF 45(6), Nov 2019)- future title: *Cranberry Fruit Juice* New monographs: • Cranberry Fruit Juice Concentrate (PF 45(6), Nov 2019) • Cranberry Fruit Juice Dry Extract (PF 45(6), Nov 2019) • Cranberry Dry Juice (PF 47(2), March 2021) • Cranberry Fruit Juice Dry Extract Capsules (PF 47(3), May 2021) These monographs are not yet official because we are developing new associated USP Reference Standards.	Endorsed. The information is acknowledged and will be considered for inclusion in the AR. However, the reference to USP will be deleted in the footnote in section 2 of the monograph. Instead, the footnote will be in accordance with the MO template: "Detailed specifications for the herbal substance shall be given by references to bibliographic sources in absence of a monograph in the European Pharmacopoeia, a national pharmacopoeia or national codex currently used in a Member State".
Assessment document	USP	In relation to*:* Herbal Preparations	Partly endorsed. The information is acknowledged and will be considered for inclusion in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
1. Introduction 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof Herbal Preparations AND Draft proposal 2. Qualitative and quantitative composition		Cranberry Fruit Juice A monograph of cranberry liquid preparation is published in the United States Pharmacopeia (USP24 2000 and USP 32 2009): bright red juice derived from the fruits of Vaccinium macrocarpon or *V. oxycoccos* (Ericaceae). It contains no added substances. The pH is between 2.4 and 2.6. The content requirements of the United States Pharmacopoeia include: not less than 2.4% of dextrose, 0.7% of fructose, 0.9% of quinic acid, 0.9% of citric acid and 0.7% of malic acid; a quinic acid to malic acid ratio of not less than 1.0 and not more than 0.05% each of sorbitol and sucrose. The Definition of USP Cranberry Liquid Preparation (PF 45(6)) (title changing to: Cranberry Fruit Juice) has been revised as follows: "Cranberry Fruit Juice is a bright red juice derived from the fruits of *Vaccinium macrocarpon* Aiton (Family Ericaceae) having a content of soluble solids corresponding to a refractive index of 1.3435-1.3445. It contains no added substances." We recommend linking the Herbal preparation described in the current proposal (*2. Qualitative and quantitative composition*) to the revised USP monograph, and define this article in terms of %soluble solids using refractive index test, as indicated in the Specific test section of this revision:	However, the reference to USP will be deleted in the footnote in section 2 of the monograph. Instead, the footnote will be in accordance with the MO template: "Detailed specifications for the herbal substance shall be given by references to bibliographic sources in absence of a monograph in the European Pharmacopoeia, a national pharmacopoeia or national codex currently used in a Member State".

Section number and heading	Interested party	Comment and Rationale	Outcome
		SPECIFIC TESTS ACCEPTANCE CRITERIA: Refractive Index: 1.3435–1.3445 % Soluble solids: 7.5±0.5 (1) Soluble solids by refractometric method is that concentration by weight of sucrose in solution that has same refractive index (*n*) as solution analyzed. By definition 1 °Brix is equal to 1 g of sugar in 100 g of solution, or 1% sugar (w/w). °Brix not corrected for acidity is equivalent to % soluble solids.	
Assessment document 1. Introduction 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof Herbal Preparations	USP	In relation to: Dried cranberry juice (Denmark) The new USP Cranberry Fruit Dry Juice monograph (PF 47(2)), defines this article as follows: "Cranberry Fruit Dry Juice is prepared by drying Cranberry Fruit Juice Concentrate onto suitable carriers and anti-caking agents. It contains NMT 50% suitable carriers and anti-caking agents. It contains NLT 80% and NMT 120% of the labeled amount of total proanthocyanidins, calculated as procyanidin A_2 ($C_{30}H_{24}O_{12}$) on the dried basis. It also contains NLT 12% of total organic acids, and NLT 90% and NMT 110% of the labeled amount of total organic acids, both as the sum of quinic acid, malic acid, and citric acid,	Not endorsed. The referred section on page 5 of the AR is just a list of herbal preparations that has been reported as constituents of medicinal products on the EU market. The wording originates from respective Member State, see more information in section 2 "Data on medicinal use".

Section number and heading	Interested party	Comment and Rationale	Outcome
and Draft proposal 2. Qualitative and quantitative composition		on the dried basis. The ratio of quinic acid to malic acid is NLT 1, and the ratio of quinic acid to citric acid is NLT 0.5". USP recommends using the revised monograph to properly define this article.	
Assessment document 1. Introduction 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof Herbal Preparations and Draft proposal 2. Qualitative and quantitative composition	USP	In relation to: Dried, refined extract of cranberry juice (Austria, France, Netherland, Spain and United Kingdom) The new USP Cranberry Fruit Juice Dry Extract (PF 45(6)) monograph, defines this article as follows: "Cranberry Fruit Juice Dry Extract is prepared from the Cranberry Fruit Juice Concentrate after hydroalcoholic extraction over an adsorbent resin. The extract contains NLT 10% and NMT 24% of total proanthocyanidins calculated as procyanidin A_2 ($C_{30}H_{24}O_{12}$) as is. It may contain suitable added substances". USP recommends using the proposed monograph to properly define this article.	Not endorsed. The referred section on page 5 of the AR is just a list of herbal preparations that has been reported as constituents of medicinal products on the EU market. The wording originates from respective Member State, see more information in section 2 "Data on medicinal use".

Section number and heading	Interested party	Comment and Rationale	Outcome
Assessment document 2. Data on medicinal use 2.1. Information about products on the market 2.1.1. Information about products on the market in the EU/EEA Member States	USP	In relation to: Table 1: Overview of data obtained from marketed medicinal products USP recommends categorizing these ingredients according to the new nomenclature used in the USP cranberry monographs: Revised monographs: • Cranberry Liquid preparation (PF 45(6), Nov 2019)-future title: *Cranberry Fruit Juice* New monographs: • Cranberry Fruit Juice Concentrate (PF 45(6), Nov 2019) • Cranberry Fruit Juice Dry Extract (PF 45(6), Nov 2019) • Cranberry Dry Juice (PF 47(2), March 2021) • Cranberry Fruit Juice Dry Extract Capsules (PF 47(3), May 2021)	Not endorsed. The market overview in Table 1 is presented in accordance with information from the Member States.
Assessment document 2. Data on medicinal use	USP	In relation to: Information on other products marketed in the EU/EEA (where relevant)	Not endorsed. The assessment report, section 2.1.1 includes information about products on the market, where medicinal products are listed in Table 1, and other products are mentioned in the text below. This is for informative purposes only.

Section number and heading	Interested party	Comment and Rationale	Outcome
2.1. Information about products on the market 2.1.1. Information about products on the market in the EU/EEA Member States		Cranberry Juice Cocktail is typically composed of 27% juice (7.5° Bx) with water and sweetener added. This beverage can be made either from juice, juice concentrate, or a blend of the two (Upton & Brendler, 2016). This product is not the pharmacopeial grade article as defined by USP Cranberry Liquid preparation (PF 45(6), Nov 2019)- future title: *Cranberry Fruit Juice,* which only includes the 100% juice (7.5 °Brix) with not additives such as ascorbic acid. Because this product is usually a blend of ingredients containing other fruit juices and additives, USP suggests not to consider this product as an herbal preparation in the assessment document.	
Assessment document 2. Data on medicinal use 2.1. Information about products on the market 2.1.1. Information about products	USP	In relation to: Information on other products marketed in the EU/EEA (where relevant) In 1993 Craisins® Sweetened Dried Cranberries of the Company were introduced, becoming increasingly popular in supermarkets and bakeries all over the world. Because this product is a food commodity and not an herbal preparation, USP suggests excluding this product from the assessment document.	Endorsed. The assessment report, section 2.1.1 includes information about products on the market, where medicinal products are listed in Table 1, and other products are mentioned in the text below. This is for informative purposes only. However, it is agreed that the information could be reduced to include relevant information on medicinal use only.

Section number and heading	Interested party	Comment and Rationale	Outcome
on the market in the EU/EEA Member States			
Assessment document 2. Data on medicinal use 2.1. Information about products on the market 2.1.1. Information about products on the market in the EU/EEA Member States	USP	In relation to: Czech Republic Food-supplements Cys Control ®, Arkopharma Powder for solution in bags containing 0.648 g of concentrated extract per 1 bag corresponding to 18 mg of procyanidin… Apo-brusinky, ProPharma-Produkt One capsule contains 500 mg of CranRich™ extract (36:1) 500 mg equivalent to 18 g of fresh fruits. Max brusinky, Swiss Herbal Remedies Ltd. Tablets containing Cran Max® extract (34:1) 250 mg/tbl equivalent to 8.5 g of whole fruits … Max Cranberry (Swiss Herbal Remedies Ltd., Canada) Tablets containing 250 mg extract Cran Max® (DER= 34:1) … Cran Urin™ Barnys®	Not endorsed. The market overview is presented in accordance with information from the Member State. However, the information will be reduced to include relevant information on medicinal use only.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Urinary and genital dietary supplements. Liquid containing CranRichPAC™ extract 400 mg/10 ml … Urinal, Walmark The product helps maintain urinary tract health before or at the time you feel signs of infection. Capsules containing concentrated dried juice 200 mg/cps… Urinal® Syrup (Idelyn-Walmark) The product cleanses the body, removes waste material and removes toxins. 5ml (1 teaspoon)… NutriCran (dry cranberry extract) 500 mg. A maximum daily dose (15 ml) corresponds to a minimum of 37 500 mg of cranberry fruit … USP recommends to label dosage forms in mg of PAC/capsule, as proposed in new monograph for Cranberry Fruit Juice Dry Extract Capsules (PF 47(3), May 2021). USP would also like to inform the EMA that some of the ingredients declared in these products are not considered extracts derived from juices, but dried juices or preparations composed of dried juice and pomace. The use of DER in these products could be misleading because it might be referred to an exhausted material (like pomace) instead of whole/fresh fruits as starting raw material. Thus, USP recommends that DER should not be used to describe the strength of juices or dry juices.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		It is also important to mention that the Health Canada monograph for Dried Cranberry Juice, dated February 18, 2018, was revised to eliminate Appendix I which included labelling examples referring to DER 25:1. Under DOSE, the revised monograph also includes the following note: "Applicants are not provide a quantity of crude equivalents (QCE) and/or extract ratio".	
Assessment document 2.1.2 Information on products on the market outside the EU/EEA	USP	In relation to: "In addition to the herbal preparation reported as constituents of medicinal products, there is a broad range of dietary cranberry products on the market worldwide, including liquid cranberry juice products of various dilutions, both sweetened and unsweetened, and cranberry juice concentrates in liquid and dry (powdered, flaked, or granulated) forms, the latter available in capsules, tablets, and teabag-infusion products, as well as products made from the pomace (micronized dried cranberry pulp and skins, seeds, stems; also known as press cake)"... USP recommends categorizing these ingredients according to the new nomenclature used in the USP cranberry monographs: Revised monographs: • Cranberry Liquid preparation (PF 45(6), Nov 2019)-future title: *Cranberry Fruit Juice*	Not endorsed. The assessment report, section 2.1.2 includes information on products on the market outside the EU/EEA. This is for informative purposes only.

Section number and heading	Interested party	Comment and Rationale	Outcome
		New monographs: • Cranberry Fruit Juice Concentrate (PF 45(6), Nov 2019) • Cranberry Fruit Juice Dry Extract (PF 45(6), Nov 2019) • Cranberry Dry Juice (PF 47(2), March 2021) • Cranberry Fruit Juice Dry Extract Capsules (PF 47(3), May 2021) In addition, USP is planning to develop new monograph for Cranberry Fruit Powder, targeting PF 48(2) March/April 2022, defined as the ingredient derived from whole fruit after fluid drying and pulverization. The seeds are usually removed before the drying process and the added back in powdered form. In relation to pomace-derived materials, the assessment of Cranberry Pomace Powder, as a pharmacopeial article, is still under consideration by the USP Botanical and Herbal Medicines Expert Committee.	
Assessment document 2.2. Information on documented medicinal use		In relation to: Manuals of phytotherapy: Cranberry Liquid preparation was included in the 19th edition of the United States Pharmacopeia-	The present reference is acknowledged and will be considered for inclusion in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
and historical data from Literature Manuals of phytotherapy		National Formulary (2000). USP would like to inform the EMA about the revision of the Cranberry Liquid preparation monograph published in PF 45(6), Nov 2019. The future title of this monograph will be: Cranberry Fruit Juice	
Assessment document 2.2. Information on documented medicinal use and historical data from Literature Manuals of phytotherapy		In relation to: Cranberry juice is included in many pharmacognostical texts and handbooks, e.g. ESCOP, 2009; WHO, 2009; Martindale (Parfitt, 1999, Sweetman, 2011); Potter's (Williamson, 2003); Bartram, 1995; Tyler, 1994. USP would like to inform the EMA that the ESCOP monograph for VACCINII MACROCARPI FRUCTUS was updated in 2020.	The present reference is acknowledged and will be considered for inclusion in the AR.
Assessment document 2.3. Overall conclusions on medicinal use and Draft proposal	USP	In relation to: Traditional use Expressed juice from the fresh fruit - (DER 1: 0.6-0.9) Assessor's comment: 1 litre juice can be pressed from 1500 g of cranberry (Bodel et al 1959). The obtained yield is approx. 58 - 66 %, using frozen berries approx. 70 %, using pectolytic	Not endorsed. DER is used in the definition of the herbal preparation, not as a quality marker. Since the suggested indications in the monograph are for traditional use only, the constituents responsible for the therapeutic activity or active markers are unknown. Hence, no adjustments to a particular content of constituents are needed. Instead, for control purposes, one or more constituents are used as analytical markers, but the content is not declared.

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition		enzymes approx. 86 – 90 % (Weiss 1977). DER 1: 0.60-0.90 includes both references. The use of DER 1: 0.6-0.9 does not accurately define Cranberry Fruit Juice, as DER is an expression of yield and not a measure of strength. Yield depends on the juice processing technology and additives used (including pectolytic enzymes). There is no guarantee that two juices with the same DER will have the same composition of active or marker compounds (polyphenols, sugars and organic acids). DER cannot be measured by any test, and thus it is not a quality parameter. USP recommends using °Brix or % soluble solids to define this article, as proposed in the revision proposal for USP Cranberry Liquid preparation (PF 45(6), Nov 2019)- future title: Cranberry Fruit Juice. This parameter is among the absolute quality requirements defined by the international standards including the International Juice and Vegetable Association (IFU), Code of Practice for Cranberry Juice and the Codex Alimentarius Standard for Fruit Juices and Nectars (CODEX STAND 247-2005). In addition, the composition of organic acids and sugars needs to be considered as a parameter for identification and authentication of Cranberry juice, as proposed in the current USP Cranberry Liquid Preparation.	See also EMA/HMPC/CHMP/CVMP/287539/2005 Rev. 1 that outlines the principles for uniform declaration of herbal substances/preparations in traditional herbal medicinal products.

Section number and heading	Interested party	Comment and Rationale	Outcome
Assessment document 2.3. Overall conclusions on medicinal use AND Draft proposal 2. Qualitative and quantitative composition		In relation to: Posology and method of administration Indication 1): 30-80 ml daily 2-4 times daily Indication 2): 15-80 ml twice daily Assessor's comment: The liquid and solid cranberry preparations that are recommend are commercial products, variously, and often inadequately described as cranberry juice, cranberry juice cocktail concentrated juice, dried juice concentrates, dried refined juice, etc. The posology of the traditional medicinal products registered in EU Member States are comparable with the posology recommended by Tyler (1994). The product that is authorized in Denmark and Iceland is not included in the monograph because the DER of the refined extract is not known. The dry refined extract which is registered as a traditional medicinal product in several Member States is also not included in the monograph due the fact that 15/30 years of use of this refined extract are not yet demonstrated. However, based on the DER.	Partly endorsed. The comment is acknowledged and a clarification in the AR is considered.

Section number and heading	Interested party	Comment and Rationale	Outcome
		provided by NL, 195-216 mg of the extract corresponds with 49-54 g fresh cranberries. According to Tyler (1994) 45 g fresh/frozen cranberries corresponds with 30 ml of juice. Hence, the posology the range is the of the monograph. USP recommends expressing the strength of juices in Brix or % soluble solids to differentiate between regular strength juices (7.5 % soluble solids) vs. cranberry juice concentrates (50% soluble solids) according to international Codes of Practice. As explain above, the technology used for juice processing affects the yields; and thus, the yield does not correlate to juice composition (sugars, organic acid and polyphenols). Also, yields or DER is not an analytical parameter that can be measured by any test, and thus is not a quality parameter. In addition, the posology for both uses seems very low compared to other monographs. For example: Health Canada (Recurrent) urinary tract infection: 90-950 ml of juice, per day	Health Canada refers to different articles mentioning pure juice or diluted juice: - Stothers *et al.,* 2002, where 250 ml of pure unsweetened cranberry juice was taken three times a day. - Avorn *et al.,* 1994, where the 300 ml of juice Cranberry juice cocktail per a day (Ocean Spray) was

Section number and heading	Interested party	Comment and Rationale	Outcome
		ESCOP Prevention of urinary tract infection Adults: 240-750 mL per day of a cranberry liquid preparation containing 25-100% of cranberry juice, divided into 2 or 3 portions.	administered throughout 6 months. Cocktail contains only 27% of pure juice. ESCOP also refers to different articles mentioning juice or diluted juice (McMurdo *et al.,* 2003; Stothers, 2002, Walker *et al.,* 1997; Avorn *et al*., 1994 and Haverkorn *et al*.).
Assessment document 3.3.2 Repeat dose toxicity	USP	No guideline toxicology studies are available (e.g., studies conducted according to ICH or OECD test guidelines). However, there are experimental repeat dose studies in animals that are recommended for discussion. These include a dietary study in rats administered commercial extracts at one dose level for 14 weeks (Palikova *et al.,* J Agric Food Chem 2010; 58:1672–1678) and a 6-month study in dogs given cranberry extract (Chou *et al.,* J Vet Res 2016; 77:421–427). USP recommends review of these studies, which are also described in Madden *et al.* Planta Med. 2021 May 20. (doi: 10.1055/a-1497-624) and in the 2020 ESCOP Monograph *Vaccinii macrocarpi* fructus (Cranberry).	Endorsed, the present references are acknowledged and will be considered for inclusion in the AR. The study by Chou, 2016 is not designed to study adverse effects, but to examine bacterial adherence. It is discussed in section 3.1.1. Primary pharmacodynamics and is also included in Table 4 Overview of the main non-clinical data/conclusions related to anti-adherence activity.
Assessment document	USP	Although it is not a not a guideline genotoxicity study (e.g., ICH or OECD test guidelines), a Comet assay was performed in peripheral lymphocytes of rats administered commercial cranberry extracts in the diet (Palikova *et al.,* J Agric Food Chem 2010; 58: 1672–1678). USP recommends	Endorsed, the present references are acknowledged and will be considered for inclusion in the AR.

Section number and heading	Interested party	Comment and Rationale	Outcome
3.3.3 Genotoxicity		review of this study, which is also described in Madden *et al.,* Planta Med. 2021 May 20. (doi: 10.1055/a-1497-624)	
Assessment document 3.3.5 Reproductive and developmental toxicity	USP	The Bałan *et al. (*2017) study on pregnant and lactating mice was described in the current EMA assessment document but no conclusion can be drawn from the results. Additionally, there was no mention if the study was a standard guideline reproductive and developmental toxicology study (e.g., ICH or OECD test guidelines). USP recommends adding a clarification to current assessment document to understand if a conclusion can be drawn from the study and if the study is a standard guideline reproductive and developmental toxicology study.	Endorsed. This is now further clarified in the AR.
2. Qualitative and quantitative composition	AESGP	ii) Herbal preparations expressed juice from the fresh fruit (DER 1:0.6-0.9). Comments: The equivalence between fresh fruit and juice can be also obtained between fresh fruit and dried fruit, considering the water content of the fruit (approx. 87.5%). Proposed change: Under ii) Herbal preparations, add: Powdered dried fruits	Not endorsed. HMPC has not found references supporting use of powdered dried fruits for 30 years (of which 15 years within EU).

Section number and heading	Interested party	Comment and Rationale	Outcome
3. Pharmaceutical form	AESGP	Proposed change: Add: Herbal preparations in solid dosage forms for oral use.	Not endorsed. HMPC has not found references supporting use of powdered dried fruits for 30 years (of which 15 years within EU), see comment above.
4.1 Therapeutic indication	AESGP	Comments: Indication 1) Traditional herbal medicinal product used for relief of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination in women, after serious conditions have been excluded by a medical doctor. Indication 2) Traditional herbal medicinal product used for prevention of recurrent uncomplicated lower urinary tract infections in women, after serious conditions have been excluded by a medical doctor. We propose to add the name of the condition 'cystitis' in the indication in parenthesis. Cystitis is known to lay patients. In addition, we suggest replacing 'after serious conditions have been excluded by a medical doctor' by 'upon medical advice' as the first wording can be rather scary for the patient. The wording 'upon medical advice' makes it clear that the indication is within the 'collaborative care concept' ie first diagnosis and treatment is done by the doctor and then when the patient experiences the symptoms for the	Indication 1) Not endorsed, the term cystitis may be known in various countries, whereas the term is not common knowledge in others, so as not to confuse cystitis will not be included. This is also in line with the adopted EU monograph on Uvae ursi folium. Indication 2) Not endorsed. The standard phrase used in EU monographs is "after serious conditions have been excluded by a medical doctor" and changing of the wording would be of a principal nature and not for the current assessment report and monograph, see also 'Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs' (EMA/HMPC/473587/2011).

Section number and heading	Interested party	Comment and Rationale	Outcome
		second time she will be able to do her own diagnosis and treat it by herself. In addition the short duration of use and the fact that patients should consult a doctor if symptoms persists during treatment (indication 1) or appear (indication 2) act as an additional safeguard. Proposed change: Indication 1) Traditional herbal medicinal product used for relief of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination (cystitis) in women, upon medical advice Indication 2) Traditional herbal medicinal product used for prevention of recurrent uncomplicated lower urinary tract infections (cystitis) in women, upon medical advice	
4.2. Posology and method of administration	AESGP	Posology Comments: A posology based on powdered dried fruit is proposed, respecting the equivalence with the posology based on the "expressed juice from the fresh fruit (DER 1:0.6-0.9)" of the monograph.	Not endorsed. HMPC has not found references supporting use of powdered dried fruits for 30 years (of which 15 years within EU).

Section number and heading	Interested party	Comment and Rationale	Outcome
		Indeed, considering the juice density (1.5) and the water content of the fresh fruit (approx. 87.5%), the following posology is within the range of the monograph: Proposed change Under Indication 1), add: 10 g of dried fruits powder (2 to 3 times daily) Under indication 2), add: 3 à 10 g of dried fruits powder (twice daily)	
4.2. Posology and method of administration	AESGP	**Posology** Indication 2) "The use in children and adolescents under 18 years of age is not recommended" **Comments:** The use in children and adolescents under 18 years of age is not recommended in case of "symptoms of mild recurrent lower urinary tract infections" (indication 1) because "these populations require medical supervision". However, in case of "prevention » (indication 2) the use of cranberry juice in children from 6 years of age, under medical supervision, should be added considering that:	Not endorsed. The use in children and adolescents under 18 years of age is not recommended because data is not sufficient and medical advice should be sought. Traditional herbal medicinal products should have indications intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.

Section number and heading	Interested party	Comment and Rationale	Outcome
		- Cranberry juice is a fruit juice consumed in every diet worldwide. - the use of cranberry juice in the case of prevention of urinary tract infections in children is supported by several monographs: ESCOP monograph 2020: In the prevention of urinary tract infection, the recommended daily dosage in children from 2 to 18 years of age is: 2-15 mL of cranberry juice per kg body weight or other equivalent preparations. Mills *et al.,* 2005: Adverse effects are not expected in children if taken at the recommended dosage. Vidal, 2010: No contraindications to use cranberry preparations in the prevention of urinary tract infections, in children from 3 years of age, under medical supervision. Upton, 2016: Cranberry is safe in children. Arnal, 2008: There is no known contraindication, cranberry can be taken in children. - A safe and natural approach utilising cranberry to reduce the incidence of urinary tract infections has significance due to the potential for reducing antibiotic treatment in children and the consequent development of resistance to these drugs [Upton, 2016] Proposed change:	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Under Indication 2), add: We recommend adding the following target population: Children over the age of 6 years of age, adults and elderly The use in children under 6 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').	
4.4. Special warnings and precautions for use	AESGP	"The use in children and adolescents under 18 years of age is not recommended because the data is not sufficient and medical advice should be sought." Comments: - The permitted use of cranberry juice in children from 6 years of age, under medical supervision, should be added, for indication 2) only, considering the previous comments. Proposed change: Replace: "The use in children and adolescents under 18 years of age is not recommended because the data is not sufficient and medical advice should be sought." By: Indication 1)	Not endorsed. The use in children and adolescents under 18 years of age is not recommended because data is not sufficient and medical advice should be sought. Traditional herbal medicinal products should have indications intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.

Section number and heading	Interested party	Comment and Rationale	Outcome
		"The use in children and adolescents under 18 years of age is not recommended because the data is not sufficient and medical advice should be sought." Indication 2) The use in children under 6 years of age has not been established due to lack of adequate data.	
4.4. Special warnings and precautions for use	AESGP	"The use in […] pregnant women is not recommended because lower urinary tract symptoms in these populations require medical supervision." Comments: The permitted use of cranberry juice in pregnant women under medical supervision should be added, consistent with typical consumption patterns as a beverage, for indication 2) only, considering that: - Cranberry juice is a fruit juice consumed in every diet worldwide. - the use of cranberry juice in the case of prevention of urinary tract infections in women is supported by several monographs: ESCOP monograph, 2020: Use in pregnancy only under medical supervision in prevention of urinary tract infection. Mills *et al.,* 2005: No proven increase in the frequency of malformation or other harmful effects on the foetus despite	Not endorsed. The use in pregnant women is not recommended because lower urinary tract symptoms in this population require medical supervision. Traditional herbal medicinal products should have indications intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment.

Section number and heading	Interested party	Comment and Rationale	Outcome
		consumption by a large number of women. Cranberry is safe and widely used prophylactically as a beverage against urinary tract infections in pregnancy. Barnes, 2007: There are no known problems with the use of cranberry during pregnancy. Doses of cranberry greatly exceeding the amounts used in foods should not be taken during pregnancy and lactation. Vidal, 2010: No contraindications to use cranberry preparations in the prevention of urinary tract infections, in pregnant women, under medical supervision. Upton, 2016: Cranberry is safe in pregnancy. Arnal, 2008: There is no known contraindication, cranberry can be taken during pregnancy. - Literature reviews of pregnant women taking cranberry showed no adverse effects on the mother or infants including no increased risk of malformations, nor any of the following pregnancy outcomes: stillbirth/neonatal death, preterm delivery, low birth weight, small for gestational age, low Apgar score, and neonatal infection, suggesting that cranberry consumption during pregnancy has no safety concern (Heitmann, 2013; Wing, 2015; Wing, 2008; Nordeng and Havnen 2004; Trabace, 2015; Chung, 2017; Upton, 2016). Only one reference (Heitmann (2013) – see attached) reports vaginal bleeding but neither the products used nor	

Section number and heading	Interested party	Comment and Rationale	Outcome
		the doses were clearly identified. Moreover, this association was considered by Heitmann as "no longer significant after adjustment was made". At that time, Heitmann study revealed "no increased risk of malformation nor any pregnancy outcomes". Finally, no adverse effect on the mother or infants has been observed. Upton and Brendlers (2016 – see attached), who refer to that trial, also conclude that "bleeding outcomes did not support a significant risk" and that "Cranberry is safe in pregnancy". To our knowledge, no new data on this specific topic has been published to date. - Several reviews report that cranberry is among the most commonly used herbs in pregnancy [Upton 2016]. - Thus, the benefit/risk balance for cranberry in the prevention of UTIs in pregnant women is positive. - Finally, as an UTI may progress into a pyelonephritis that can cause miscarriage, growth stunting or premature delivery, a safe treatment that can be used during pregnancy is needed (Epp and Larochelle 2010). According to the French High Health Authority (HAS), cystitis in pregnant women falls into the class of cystitis with "a risk of complication". For that reason, it should be supervised by a medical doctor (see : https://www.has-sante.fr/upload/docs/application/pdf/2021-08/fiche_memo_cystite_durees_antibiotherapies_.pdf).	

Section number and heading	Interested party	Comment and Rationale	Outcome
		The draft HMPC monograph also states that: "The use in men and pregnant women is not recommended because lower urinary tract symptoms in these populations require medical supervision". Considering the good risk/benefit balance for cranberry in the prevention of UTIs in this population) to widen the indication 2) (prevention of recurrent uncomplicated lower urinary tract infections in women) to pregnant women. Proposed change: Replace: "The use in men and pregnant women is not recommended because lower urinary tract symptoms in these populations require medical supervision." By: "The use in men is not recommended because lower urinary tract symptoms in these populations require medical supervision. indication 1: The use in pregnant women is not recommended because lower urinary tract symptoms in these populations require medical supervision."	
4.6. Fertility, pregnancy and lactation	AESGP	It is stated that: "Safety during pregnancy and lactation has not been established."	Not endorsed. It is the HMPC opinion that safety during pregnancy and lactation has not been established. In absence of sufficient data, the use

Section number and heading	Interested party	Comment and Rationale	Outcome
		"In absence of sufficient data, the use during pregnancy and lactation is not recommended." Comments: The safe use of cranberry during pregnancy has been established in light of literature data (cf. above comments) Proposed change: Replace: "Safety during pregnancy and lactation has not been established." "In absence of sufficient data, the use during pregnancy and lactation is not recommended." By: "Safety during pregnancy and lactation has been established." The use during pregnancy in a preventative indication is possible upon medical advice.	during pregnancy and lactation cannot be recommended. See also comment above.