09 July 2025
EMA/HMPC/423470/2024
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Revision 1 of the 'Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin' (EMA/246816/2005)

Final

Discussion in Committee on Herbal Medicinal Products (HMPC)	January 2025 March 2025 May 2025 July 2025
Adoption by HMPC	09 July 2025

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Table 1: Organisations and/or individuals that commented on the draft Revision 1 of the 'Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin' (EMA/246816/2005) as released for public consultation on 15 April 2024 until 15 July 2024 date

	Organisations and/or individuals
1	AESGP
2	Dagmar Honsbein, Technical Advisor to GIZ BioInnovation Africa Project, Phase II
3	EUROPAM – EUROPEAN HERB GROWERS ASSOCIATION
4	German committee on medicinal, aromatic and spice plants
5	Parceval Pty - 38b Lady Loch Road, Wellington 765, South Africa
6	PharmaRolly DOOEL Petrovec, North Macedonia
7	Q-CERT S.A.
8	RQC Partners
9	Southern African Botanical Products Association (SABPA) – c/o 38b Lady Loch Road, Wellington 765, South Africa
10	Tillotts Pharma AG, CH-4310 Rheinfelden, Baslerstrasse 15

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	We welcome the revision of the guideline, which should be brought up to date with the current state of practice, science and technology following its publication in 2005. It is appreciated that new cultivation techniques such as indoor cultivation have been included, even though today this type of cultivation is mainly relevant in practice for cannabis. Indoor cultivation for the whole segment of good agriculture cultivating practice of medicinal plants is still a niche segment. We deliberately address this in order to point out that possible new and realisable standards in this new area of indoor cultivation cannot generally be transferred to current growing outdoor practice, as these increased standards cannot be fulfilled neither for outdoor field cultivation nor for wild growing plants. It would hence be preferred to dedicate a specific section (e.g. an annex) to the requirements linked to indoor cultivation. However, it should be noted that from our point of view the draft of the updated guideline partly introduces stricter regulations, which may pose further challenges for all stakeholders being involved in the whole supply chain. It is important that the language used in the guideline is the one pertaining to 'soft legislation' (except when a legal requirement is cited) and that alternative ways of doing can be used and presented as long as the main objective is fulfilled. Additionally, in our opinion the evaluation of the current state of practice, science and technology (as well as changes thereof) should always be based on evidence and should technically be feasible and proportionate concerning quality and safety of the final herbal medicinal product.	Partially agreed. A separate annex has been compiled for the specific provisions related to the indoor cultivation. The Guideline is intended for all stakeholders within the supply chain. The guideline was amended as deemed necessary. The outcome for the specific comments is explained below.

Interested party	Comment and Rationale	Outcome
	Naturally, all stakeholders have a high interest in growing and processing medicinal plants of high quality in order to guarantee efficacy, safety and high and consistent quality of herbal medicinal products produced thereof. However, the requirements should not be such that they are untenable and unsustainable from an economic point of view. We would also like to underline that a number of herbal substances used as starting materials are grown in non-EU regions with varied local requirements. It will not be possible to reflect every single case in this guideline and the plea is made to establish a guideline with proportionate requirements and fit-for-purpose. Unfortunately, the distinction between organic and conventional cultivation as in the existing GACP guidelines is no longer made. As a result, a lot of detailed information is requested that is not necessary when it comes to organic cultivation. It is also noticed that throughout the draft GACP guideline the same requirements regarding conducting of audits are applied for herbal substances used as APIs (e.g. for teas) as for herbal substances used as starting materials / raw materials for production of APIs / herbal preparations (e.g. extracts, essential oils). Article 8(3)(ha) of Directive 2001/83/EC, places a legal obligation on the applicant to provide information in the MA application concerning the GMP compliance status of the manufacturer of the active substance, and in this regard, reference is made to audits of that manufacturer and to provide a written confirmation. In the guidance for the QP declaration template EMA/196292/2014 the tasks of the MIAHs (Manufacturing and Importation Authorization Holders) are thoroughly described.	

Interested party	Comment and Rationale	Outcome
	There is also further guidance in the CMDh Q&A QP declaration CMDh/340/2015/Rev.7: Thus, the MIAH does not and cannot audit the manufacturing site of the starting material since he does not know the manufacturing site(s) of the starting material as the information is only provided in the restricted part of the ASMF. The CMDh Q&A QP declaration CMDh/340/2015/Rev.7 Further outlines that for chemically synthesised active substances, it is acknowledged that details of the suppliers of designated starting materials may be confidential. Their suitability should be assessed indirectly by audit of the active substance manufacturer's quality system for starting materials. The herbal substance is directly used as API, audits are conducted by the manufacturer of the bulk finished product as per current GMP guidelines. If the herbal substance is used as a starting material / raw material which is further processed to a herbal preparation conducting of audits should be performed by the API manufacturer. Conducting of audits of herbal substance primary producers (cultivators, harvesters or collectors) located globally and who possibly deliver the herbal substance to several herbal preparation manufacturers, which themselves deliver the API to several finished product manufacturers would multiply audits and increase the administrative burden significantly and in an unproportionate way without any additional positive impact on the quality of the starting material and / or API. Also, for products with chemical APIs there is no request to conduct audits of the manufacturers of raw materials / starting materials. Therefore, conducting audits should be in the responsibility of the API manufacturer who uses the herbal substance as a raw material / starting material	

Interested party	Comment and Rationale	Outcome
	for further processing. Manufacturing authorisation holders will gain assurance that the active substance they use is manufactured in accordance with GMP by conducting audits of the active substance manufacturers and their quality systems. The increased number of requirements in the GACP guidelines in particular at administrative level may endanger the viability of SMEs in the EU. It should be noted that the phytopharmaceutical sector is also competing against other regulatory categories of products. We therefore ask to keep the requirements pragmatic and applicable by any phytopharmaceutical companies, including the SMEs	
Dagmar Honsbein	1. The amended GACP guidelines, while being called guidelines' de facto enforce production standards. Therefore, suppliers of natural herbal medicinal substances and ingredients are now also forced to adapt to GMP certified production standards. This means, without such markets, European manufacturers will be in a unique position to source such input materials, without passing at least some of the benefits of primary processing to producer countries. (change from "general" to "scope" with divers implications) 2. While the GACP acknowledges CITES, it is completely silent on the more important enabling international legislation, the NAGOYA Protocol on equitable access and benefit sharing mechanisms, as well as the Global Biodiversity Framework. 3. This is disturbing as the new/amended GACP guidelines now allows for biopiracy. Sourcing seed or propagation materials from unique habitats and allowing for indoor cultivation of medicinal plants, optimally in European countries.	Partially agreed. The Guideline is intended for all stakeholders within the supply chain. The guideline was amended as deemed necessary. The outcome for the specific comments is explained below.

Interested party	Comment and Rationale	Outcome
	What is the relationship between the EMA amended GACP guidelines (2024) and the WHO GACP guidelines? If a producers adheres to the WHO guidelines, will s/he be automatically excluded to deliver input materials to European suppliers?	
EUROPAM	Europam was one of the first associations in the world to develop GACP from the end of the last century. A significant portion of the EMA's 2006 GACP is based precisely on the texts developed by our association. This has always been our vocation: to improve the quality of herbal substances and, consequently, that of herbal preparations by writing and disseminating appropriate guidelines. These guidelines must have the primary objective of improving quality, traceability, and environmental sustainability without heavily burdening the activities of farmers, most of whom are small-scale. We congratulate the EMA for deciding to revise the 2006 text and remain available for any questions regarding the comments below.	See outcomes for the specific comments.
German committee on medicinal, aromatic and spice plants	None	
Parceval Pty	This comment comes from the Southern African Botanical Product Association (SABPA), representing farmers, wild harvesters, processors and brand owners in South Africa and beyond.	Partially agreed. The Guideline is intended for all stakeholders within the supply chain. The guideline was amended as deemed necessary.

Interested party	Comment and Rationale	Outcome
	The proposed amendments carry several challenges for stakeholders in an already challenging industry. Whilst it is understandable that upgrading and improving of guidelines may be necessary from time to time, it should not only serve a well-established industry in developed and industrialised nations. There are many stakeholders in developing nations around the world that struggle already with compliance issues when supplying raw material, primary extracts or more complex into the EU or other sophisticated markets. On the one hand, development agencies from Europe (e.g. CBI, GIZ, SECO, etc.) are investing into many laudable projects to uplift lesser privileged communities, rural operators, producers of botanical raw material and ingredients. Behind this is the spirit of using trade as a tool for upliftment and development, fostering the first steps of industrialised production and with it a chance of creating value chains close to the origin of botanicals. These value chains can and do make huge differences for income generation and rural livelihoods, increasing human dignity, improved education and becoming less dependent on aid programs in the future. These projects are aimed to support the 17 Sustainable Development Goals of the United Nations (https://sdgs.un.org/goals) – so direly needed and where the world is lagging behind on a grand scale. On the other hand, we experience again and again that the hurdles to actually supply goods from the developing world to the developed world are becoming more and more complex and cumbersome. Instead of simplifying trade, it becomes more difficult – mainly because of compliance issues. Compliance with e.g. GACP, organic certification, sustainability certification, Nagoya Protocol, SEDEX, etc. to name but a few. When then, on top of it, existing regulatory requirements have just been mastered and they are then "upgraded" to a higher level, the question must be asked, whom does this serve? Certainly not the developing nations!	The outcome for the specific comments is explained below.

Interested party	Comment and Rationale	Outcome
	And another question needs to be asked: what prompts thie kind of higher requirements? Is this just for a sense of higher order and wanting to be in control? Has anyone come to harm (or worse…) due to the current requirements being insufficient? Is public health and safety at risk? Has there been any input requested from developing nations or is there representation for these concerns in the committees drafting and therefore demanding these changes? Experience shows that, when regulations are out for public comment, it is usually too late and there is no willingness to make substantial changes to what has been published. Instead of assisting developing nations to develop through trade, this review takes us in the opposite direction. It keeps developing nations and suppliers firmly out of the markets and thus have a protectionist character. It favours (often large and corporate) companies that are already compliant or close to it and have the staff and resources to further invest in costly upgrades. It further marginalises small scale entrepreneurs, wild harvesters, rural and disadvantaged communities or enterprises as they most likely will not have the resources for additional infrastructure, staff, quality systems and associated documentation.	
PharmaRolly DOOEL	None	
Q-CERT S.A.	None	

Interested party	Comment and Rationale	Outcome
RQC Partners	The revisions to the guideline provide additional clarity to the alignment between GACP and Good Manufacturing Practices requirements, however, could be further specified: • Additional clarity regarding ICH Q7A, Annex 7 and Primary processing boundaries (and allowability for primary processing tasks that reduce the overall risk of product cross-contamination (e.g., local GACP trimming, drying to specified moisture content/ water activity) consistent with food safety processes. • Consideration for removal of language regarding validation requirement (e.g., GMP statements regarding equipment qualification) within the cultivation text. Guidance regarding personnel gowning and protection has been reduced in this revision, additional statements regarding this are suggested. Risk profile for organic and other fertilisers: • Additional criteria for the use of organic fertilisers are suggested, so that safely transformed materials that are substantially free from pesticide and other contaminants may be used. • Alignment with organic food certification requirements for such fertiliser use. Section: Personnel & Training Comment: No mention of gowning procedures. A requirement for protection of plant materials and operators from therapeutic plants should be made. Section: Documentation Comment:	Partially agreed. The Guideline is intended for all stakeholders within the supply chain. The guideline was amended as deemed necessary. The outcome for the specific comments is explained below.

Interested party	Comment and Rationale	Outcome
	Add supplier, training records, sanitation, and maintain retention policy Footnote 3: Part 1 referenced in title of the link – should be Part 2 Section: Definitions Comment: Add GACP, GMP, Collector, Harvester, Calibration, and Primary Processing to Definitions section	
Southern African Botanical Products Association	See comments from Parceval Pty	
Tillotts Pharma AG	None	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
43-46	AESGP	Comment: From our point of view, the existing requirements i.e. that GACP is part of the quality assurance system in production of medicinal	Not agreed. The quality assurance system has not been newly introduced and already was present in

Section number and heading	Interested party	Comment and Rationale	Outcome
		products, are sufficient to ensure the quality and safety of the product. Therefore, it is not necessary to claim a quality assurance system here. (see also lines 99-101) Furthermore, it should be noted that plants become medicinal plants once they have been qualified according to quality analyses. Proposal: Due to the inherent complexity of ~~medicinal~~ plants and herbal substances the quality of these starting materials requires adequate rules for the collection and/or cultivation, harvest, and primary processing.	the existing GACP Guideline. Therefore, this text is maintained. Also, the term medicinal plant has been used in the existing GACP Guideline and therefore it is not changed. A definition has been added.
54-55		Comment: This sentence could be understood in a manner that collection is only permitted if cultivation is not possible. This contradicts the reality of the procurement of plant-based raw materials. Controlled collection must continue to be possible without justification. Proposed change: Please delete this sentence.	Agreed. The sentence has been adapted.
59		Even though the information relating specifically to indoor cultivation is indicated in italics, the whole guideline seems to be more focused on indoor growing and therefore stricter in overall. This guideline is not feasible for outdoor cultivation. Proposed change (if any):	Agreed. The specific information for indoor growing has been placed in a separate ANNEX.

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		Separate GACP guideline or annex for indoor cultivation would be preferred.	
76-78		Comment: As stated in the Executive summary (line 31-33) this guideline is intended to provide guidance to ensure appropriate and consistent quality of herbal substances. The word "standard" as stated in line 76 is far stricter than the term "guidance" as mentioned above. Therefore, we propose to replace "standards" by "recommendations", as it is also stated in line 87. Proposed change: This Guideline provides additional recommendations for the production and processing of medicinal plants/herbal substances insofar as they mainly focus on identifying those critical production steps that are needed to ensure good quality.	Agreed, "standard" has been changed into "recommendations".
82-83		Comment: We suggest pointing out "human pathogens" in the context of microbiological load. Proposed change: The handling of the herbal substance should be in accordance with good hygiene practices, to ensure microbiological load is kept to a minimum, especially human pathogens.	Not agreed. Microbiological load is meant in a general sense in this chapter.
85-88		Comment:	Agreed. The sentence has been changed accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		During the growing season, plants are not usually exposed to a large number of environmental contaminants. The term "large numbers" is therefore not appropriate. From our point of view, the phrase "plants may be exposed to environmental contaminants....." is more appropriate. Proposed change: During growth, harvest, collection, and primary processing, medicinal plants, herbal substances may be exposed to environmental contaminants of both biotic and abiotic origin.	
92-94		Comment: The guideline should take into account the different depths. If the manufacturer does not grow the medicinal plants himself, he always has contracts with the manufacturer of the active ingredient. In addition to this contract, the delimitation of responsibilities of both parties is usually regulated. This applies in particular to the rights and obligations of legal requirements and recommendations, including GACP, as well as auditing for the entire supply chain. The guidance document for the QP declaration template EMA/196292/2014 MIAHs (Manufacturing and Importation Authorization Holders) *states that "where the MIAH is not directly responsible for audit of the active substance manufacturing site(s), the QP of the MIAH should ensure that appropriate technical arrangements / agreements are in place with the companies responsible for such audits."* This means that there is no requirement that MIAH conducts audits for starting material suppliers. The CMDh Q&A QP declaration	Partially agreed. It is not necessary to mention audits in the scope section. Therefore, the sentence is deleted here. It has been addressed in section 3 Quality Management.

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		CMDh/340/2015/Rev.7 further outlines that "*for chemically synthesised active substances, it is acknowledged that details of the suppliers of designated starting materials may be confidential. Their suitability should be assessed indirectly by audit of the active substance manufacturer's quality system for starting materials."* In conclusion according to current legislation there is no requirement to conduct audits of raw material / starting material suppliers by the manufacturer of the finished product / MIAH but audits have to be conducted for manufacturers of APIs. Regarding requirements for audits, distinction should therefore be made between herbal substances which are used as APIs and herbal substances which are used as starting material / raw material for manufacture of herbal preparations (e.g. by extraction, distillation). If (please refer to general comments above): if the herbal substance is directly used as API, audits are performed/conducted by the manufacturer of the bulk finished product as per current GMP guidelines. If the herbal substance is used as a starting material / raw material which is further processed, the conduct to a herbal preparation conducting of audits should be performed by the API manufacturer. Furthermore, for products with chemical APIs there is no request for conducting audits of the manufacturers of starting materials. Alone responsibility of the medicinal product manufacturer for audits would also violate IP rights of the parties. Thus, the existing regulations are adequate to ensure quality and safety along the entire supply chain.	

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		Moreover, as the audit is already mentioned under Quality Management (line 102-103) (comments see below) and better belongs to Quality Management than to the Scope of the Guideline, it should be deleted in lines 92-94. Proposed change: The manufacturer of medicinal product **and in case the herbal substance is used as a starting material /raw material for further API processing, the active substance manufacturer** should ensure that regular audits of the primary producers (cultivators, harvesters, and collectors) are performed. For the above reasons, the sentence "The manufacturer … are performed" should be deleted.	
99-101		For the first time, a GACP quality assurance system is mentioned for growers of medicinal plants. From our point of view, the existing requirements i.e that GACP is part of the quality assurance system in production of medicinal products, are sufficient to ensure the quality and safety of the product. In case GACP is intended to represent an own quality assurance system, this is from our point of view not in line with existing GMP rules (Art. 6 GMP Directive) and leads to unnecessary over-regulation. Proposed change: "Agreements … should make reference to the GACP guideline."	Agreed. The sentence has been modified accordingly.
102-103		Comment: Furthermore, it is questionable if "regular audits of the cultivation or collection sites and processing facilities by expert representatives of producers and buyers" are necessary and	Partially agreed. Audits are the responsibility of the API- manufacturer. The use of self-evaluation questionnaire or remote audits is a possibility.

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		practically realizable. As described by Raiser et al 2017 [1] there are many more options of qualification of suppliers e.g. self-evaluation questionnaire, including general information and suppliers' quality management system, technical visits, quality control results and batch-specific documentation. These processes should follow an individual risk assessment and are part of individual agreements between growers/collectors and suppliers or manufacturers. Therefore, qualification of cultivation or collection sites and processing facilities needs not to be regulated in this guideline. Proposed change: Please delete the newly added sentence completely or replace by: GACP compliance should be verified through appropriate tools of supplier qualification.	
128-129		Comment: The vast majority of plant pests do not necessarily affect the quality of the raw material. Training of collectors should enable to take appropriate measures. Proposed change: Collectors must have sufficient knowledge about the presentation of plant pests to recognize diseased plants/plant parts in order **to take appropriate measures e.g. perform selective collection** ~~not to collect~~ ~~them~~.	Agreed. The sentence has been modified accordingly.
129-131		Comment:	Agreed. The sentence has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Collectors necessarily do not need the knowledge about the importance of primary processing. It is more suitable if the collectors have knowledge about the post-harvest technique. Proposed change: Collectors should have sufficient knowledge about the best time to harvest as well as harvesting and post harvesting technique, to guarantee the best possible quality.	
140-143		Comment: Most plant pests do not necessarily affect the quality of the raw material. Training of personnel should enable to take appropriate measures. Proposed change: Personnel must have sufficient knowledge about the presentation of plant pests to recognize diseased plants/plant parts in order **to take appropriate measures e.g.** not to harvest them.	Agreed. The sentence has been modified accordingly.
144-146		The sentence in the beginning of this chapter "all primary processing procedures should fully conform with regional or national guidelines on hygiene and personnel entrusted with handling of medicinal plants/herbal substances." includes the sense of this paragraph already. Therefore, this paragraph is redundant. Moreover, working according to these requirements is not feasible, as those plants don't grow always in a sterile environment like in indoor cultivation. Please differentiate between indoor cultivation and outdoor cultivation. Proposed change (if any):	Not agreed. The cleaning of equipment is important to avoid any form of contamination.

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		Please delete this paragraph.	
173-175		Comment: If "qualified" means the same as in the GMP environment (incl. documentation), then it is too narrowly defined for the GACP scope. Proposed change: Change "qualified" to "suitable".	Partially agreed. The sentence has been changed, adding "appropriate for the intended use" instead of "qualified".
182-184		Comment: We fully agree that the equipment should be appropriate for the intended use. However, from our point of view this needs not to be documented additionally, since it is common practice during cultivation and processing that only equipment suitable for its intended use is utilised. An extra documentation would lead to unnecessary bureaucratic burden. Proposed change: Please delete the newly added sentences completely or change to "Equipment and other supportive systems used in the critical steps of cultivation, processing, packaging and storage, should be appropriate for the intended use."	Not agreed. Even if it was not clearly mentioned in the previous version of the guideline, documentation is necessary to show the appropriate use of the equipment. The level of documentation may be agreed upon between the supplier and manufacturer.
186		Comment: As there are different participants in the supply chain from the herbal substance to the finished product (please refer to our	Agreed. The sentence has been changed accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		comment on lines 92-94), it should be clarified that the documentation should be agreed with the API manufacturer. Proposed change: The following should be documented as agreed with the **active substance manufacturer or the** manufacturer **respectively.**	
194-195		Comment: Referring to the GACP concept paper EMA/HMPC/398706/2021 *"the revision of the guideline will address the need for clarification and consistency (e.g. demarcation/overlap GMP vs. GACP, certification and dossier submission…)."* In the sense of consistency with the updated Guideline on quality of herbal medicinal products / traditional herbal medicinal products EMA/HMPC/CHMP/CVMP/201116/20051 Rev. 3 the origin should be stated on country level. Information on the country of origin is sufficient to know which local requirements apply. Information on country/region/area/province does not add to the quality of the herbal starting material / raw material. Quality is determined by full compliance with approved specifications and the requirements laid down in this GACP guideline and not by province borders. In contrast, the addition of dedicated regions / areas or provinces would add to the issue of supply shortages of herbal substances if differences between geographical sources would be made just because e.g. some fields may belong to another province. Especially in these days of change of climate conditions any restrictions of flexibility for primary producers to adopt locally should be strictly avoided.	Partially agreed. Minor change to the text has been implemented; The geographical location should be described as precise as possible. Agreed. The sentence has been changed accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		With regard to the documentation of the geographical location (3rd and 4th bullet point), we think that it is sufficient (like in the existing version of the guideline) to describe the geographical location and the harvest period as precise as possible. Further documentation of the listed details will in no way improve the quality. Moreover, according to the current variation classification, any changes to the geographical region currently result in a type II variation resulting in a lack of flexibility in the cultivation area. Proposed change: For cultivated medicinal plants: the geographical source i.e. exact country ~~and region/area/province~~. Please delete the newly added sentences completely or use the wording of item 7.6. of the existing guideline:" The geographic location of the collection area and the harvest period should be described as precise as possible." Comment: In case of organic cultivation, this will be controlled anyways. Therefore, it is needed to differentiate. Proposed change (if any): In conventional cultivation: Site records showing previous crops, varieties and/ or cultivars and plant protection products used	
198-199		Please refer to comment on line 194/195:	See above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change: For wild collection of medicinal plants: the geographical location i.e. exact country ~~and region/area/province~~.	
205-207		Comment: Please refer to comment on line 194/195-199. Same applies for combination batches. It is to describe the geographical location as precise as possible. Proposed change: Single and combination batches of the same plant species harvested from different geographical location, ~~i.e. exact country and region/area/province~~, and/or subject to different cultivation conditions.	See above.
212-213		Comment: A full documentation of "all materials" for indoor cultivation is too wide from our point of view, since it should only refer to the materials that are relevant for the quality of the cultivated plants. Proposed change: Change from "all materials" to "materials relevant with respect to quality".	Agreed. The sentence has been modified accordingly.
225		Comment: In nature it is not possible that the starting material is 100% free from pests or very strong pesticide coating might be needed. Furthermore, plants with pests won’t grow well, which means no	Agreed. The sentence has been modified accordingly. The additional information for indoor cultivation has been placed in a separate ANNEX.

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		one will intentionally obtain starting material with pests. This might be more problematic for indoor cultivation, where the sterility has a bigger importance than outdoor cultivation. This is one of a reason why it is better to do a separate GACP just for indoor cultivation. Proposed change (if any): *The starting material should be <u>as far as reasonably achievable</u> free from pests and diseases in…*	
226		Comment: The term "stable varieties" is not clear. If hybrid seed are meant, this again is more relevant for indoor cultivation or for the use of herbal substances further in an unprocessed state. But not in every situation. Proposed change (if any): *Please change to: "Where possible ~~stable varieties and~~ cultivars naturally…"*	Not agreed. For clarification a definition of stable varieties is given in the definition section. A stable variety is a variety for which relevant characteristics remain essentially the same after repeated propagation.
232-234		Comment: Qualifying of suppliers of materials used in cultivation would introduce an additional administrative level without increase in quality of herbal substances. Moreover, change control is a GMP process that should not play a role for GACP. The cultivation process is still at the very beginning of the supply chain and should therefore not be assigned GMP processes. Proposed change:	Partially agreed. Indeed, GMP processes should not be applied to cultivation processes, and therefore part of the sentence that refers to the change control procedure has been deleted; however, the supplier has to be qualified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Suppliers of materials used in cultivation must be evaluated ~~and qualified~~ according to established procedures. ~~Changing~~ The source of supply of materials should be **documented in accordance with established procedures** ~~handled through the Change Control procedure.~~	
236-237		Comment: Cultivation of medicinal plants is a global operation and the requested level of documentation is not feasible in some local conditions. Proposed change: The chosen method of cultivation should **be defined and documented** ~~described in a SOP~~, taking care to avoid ~~any~~ negative environmental impact **in accordance with applicable local regulations.**	Agreed. The sentence has been modified accordingly.
258-259		Comment: Especially EU regulations on water often aren't captured by national or regional legislation and can't be fully implemented locally. It should be accepted that national/regional quality standards on water apply as reflected in WHO principles since even in the EU the respective national requirements on water differ. Proposed change (if any): Water used in irrigation should comply with ~~the country of destination's~~ respective regional/ national quality standards.	Agreed. The sentence has been modified accordingly.
260-261		Comment:	Partially agreed. The sentence has been modified as follows: "During the cultivation season, toxic weeds

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		Horizontal transfer of PA is not relevant for PA contamination. Please refer to a recent publication of Chmit et al. 2021. [2]. Mechanical weed control needs to remain a major mean of weed control. Depending on the crop and the possible toxic weeds it is not in all cases necessary, sensible or possible to remove all of them (e.g. emerging young weeds in tree crops). Therefore, the focus should be on relevant toxic weeds which should be removed as far as reasonably achievable. Please add "as far as reasonably achievable" Furthermore, depending on the farm management, the weeds themselves and the site conditions, composting should not be forbidden in general if there is no risk for contamination via toxic plants in the compost. Compost is generally considered a highly worthful material in farming. Therefore, please delete "….and not composted". Proposed change: During the cultivation season, any toxic weeds **that represent a risk of contamination** should be removed as far as reasonably achievable from the field ~~and not composted~~.	that represent a risk of contamination should be removed from the field as far as reasonably achievable and it should be considered not to compost them".
263-266		Comment: The use of pesticides is regulated by the local agricultural authorities. Therefore, the pesticide use must conform to the rules of the country of application. Proposed change: When necessary, approved plant protection products should be applied at the minimum effective level in accordance with the	Not agreed. It is retained herbicides and pesticides that are not allowed in the country of destination should be avoided.

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		recommendations from the manufacturer and approved by the authorities of the country of **application** ~~destination~~.	
266-267		Comment: There is already national legislation on the use of plant protection products. An agricultural business cannot carry out analyses on the retention time of the products in the plants. Proposed change: We recommend deletion of this sentence.	Not agreed. This sentence is only a consideration which should be taken into account.
268		From our point of view, it is not realistic and not necessary to use an **approved** equipment when applying pesticides or herbicides. Proposed change: "The application should be carried out only by qualified staff ~~using approved equipment~~."	Partial agreed. The sentence has been changed into "**suitable**" equipment, in line with section 6.
269 - 271		Comment: In any case, the preharvest intervals of used pesticides have to be in accordance with legal requirements, if available. Proposed change: Please change to: "The preharvest interval for a plant protection product application is based on official legal requirements or, if not available, on the recommendations of the pesticide manufacturer. The buyer can request a longer preharvest interval."	Agreed. The sentence has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
274 - 276		Comment: To make it more precise and practical, we suggest the following wording: Proposed change: In situations where the cultivation site is located in an area of other cultivation activities, the risk for possible contamination with pesticides <u>from neighbouring fields</u> should be assessed.	Agreed. The sentence has been modified accordingly.
278-279		Comment: We are wondering what "suitable rogueing" means in this context. Monitoring is already described in the first sentence, which seems sufficient from our point of view to maintain the plant in good growing conditions. Proposed change: We recommend deletion of "suitable rogueing should be carried out…".	Partially agreed. The sentence has been modified to "Suitable practices (e.g. rogueing) should be carried out to maintain the crop in good growing conditions". Please refer to the definition section for the meaning of "rogueing".
295-296		Comment: We suggest deleting "medicinal" and "herbal substance." Proposed change: "Designated individuals should supervise the collectors of the ~~medicinal~~ plants ~~/herbal substances~~ and also identify and verify the collected material (see 4.5, 4.6 and 4.7)."	Partially agreed. The word "medicinal plant" is already used in the current version of the guideline. A definition has been added, and the term herbal substance has been deleted here.

Section number and heading	Interested party	Comment and Rationale	Outcome
303-305		Comment: It will not be possible to implement this risk assessment in practice. There is already national legislation that must be complied with by collectors. An additional requirement for a risk assessment to be carried out by the collector increases the documentation effort without improving nature conservation. It would lead to the pharmaceutical industry being supplied with fewer collected plants. Proposed change: Please delete these sentences.	Agreed. Sentences deleted but reference to CITES and NAGOYA regulations have been included in section 2 Scope.
314-317		Comment: This is still GACP-Guideline and not GMP. The basics should be covered by national/regional legislation anyways. It is important that the maintenance of the cutting devices is food-compliant. Therefore, it is neither feasible nor does it contribute to patient safety or product quality. Proposed change (if any): *Change to: "Cutting devices or harvesters must be maintained according to the respective national/regional legislation and should be food-compliant."*	Agreed. The sentence has been modified accordingly.
318-320		Comment: Contact with soil or floor cannot be avoided in root harvest.	Agreed. The sentence has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Furthermore, if the floor was cleaned a direct contact with harvested plant material should be possible, e.g. in the unloading area before drying. Proposed change: "The harvested medicinal plant / herbal substance should not come into direct contact with the soil or uncleaned floor with exception of roots and rhizomes. "	
341-344		Comment: The criteria for "exceptional circumstances" are unclear. Proposed change: Please replace "exceptional", by "justified" and leave out the half sentence "which must …" The sentence should then read: "In justified circumstances, some of these steps …"	Not agreed. The exceptional circumstances are sufficiently described.
361-364		Comment: From our point of view, it is not realistic that an audit of small plants in the field is performed by the finished product manufacturer. In practice, audits or other options of suppliers' qualification can also be performed by other parties on behalf of the manufacturer. This is common practice also in case of chemical or biological APIs, where the API manufacturer and not the finished product manufacturer is responsible for the qualification including auditing the precursors of APIs. Moreover, the question of Intellectual Property of the API manufacturer is affected if the finished product manufacturer has to audit the	Partially agreed. The API manufacturer, or other parties on behalf of the API manufacturer is added. The part about inspections by the regulatory authority is deleted, because this is already in Annex 7 of the GMP Guideline.

Section number and heading	Interested party	Comment and Rationale	Outcome
		precursor of the API. Moreover, distillation in the field is already described in the respective table and explanations in Annex 7. Proposed change: We suggest deleting lines 361-364.	
368-370		Comment: The composting of plant material is common practice in agriculture. Proposed change (if any): The toxic waste plant material **may** ~~must~~ be segregated from growing media and the materials for the cultivation of plants.	Agreed. The sentence has been modified accordingly.
370		Comment: We agree that in some cases the waste plant material may require incineration for destruction. However, it should be specified under what circumstances the plant material should be incinerated. From our point of view, this should only be the case if the material is contaminated. Proposed change: In case the waste plant material is contaminated, incineration for destruction may be required.	Partially agreed. The sentence has been modified with additional reference to national/regional legislation.
38-59	Dagmar Honsbein	Comment: allowing for indoor cultivation opens the doors for biopiracy. Unless the GACP acknowledges the provisions of the NAGOYA Protocol and Global Biodiversity Framework (GBF)	Partially agreed. Indoor cultivation will be retained, and provisions are grouped within an annex. Agreed

Section number and heading	Interested party	Comment and Rationale	Outcome
		based on COP15, CITES is insufficient to protect the indigenous peoples and local communities rights holders of traditional, medicinal plants which Europe imports for multiple pharmaceutical applications. Proposed changed: (i) remove indoor cultivation from GACP and add such to the GAP provisions. *(ii)* The August 2006 GACP version refers to CITES only, which was OK, and the Nagoya Protocol and GBF was not as pertinent then. However, times have changed, and the GBF is a national legislation and needs to be considered first by producers. Therefore, strengthening the GACP by acknowledging the national legislations on biodiversity management is important.	to include references to Nagoya protocol and GBF under the section 2. Scope.
69-78		Comment: the change from "general" provisions of the GACP to "scope" makes the GACP enforceable. Producers of nature-based and indigenous plant materials will be forced out of market over time. Proposed change (if any): revert to GACP August 2006 provisions.	Not agreed. The headings have been updated according to the EMA template for guidelines. As note, at the beginning of the scope it is clearly mentioned that this guideline (not a regulation) that is intended to address the specific concerns related to the cultivation, collection, and primary processing of herbal substances that are used for the preparation of herbal medicinal products.
258-259		Comment: how will a grower in Cameroon be able to comply with "country of destination's" regional / national irrigation quality standards? If a producer / processor already has to comply with	Agreed. The sentence has been changed accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		GMP, the national standards prevail. So this provision contradicts itself. Proposed change (if any): revert to August 2006 version, remove "country of destination's"	
280-293		Comment: remove matters referring to indoor cultivation; these can be accommodated under the GAP standard Proposed change (if any):	Not agreed. Indoor cultivation will be retained, and provisions are be grouped within an annex.
300-305		Comment: acknowledge the provisions of the NAGOYA Protocol and the Global Biodiversity Framework. While some botanical material may not be a notifiable resource under CITES, they are protected under the biodiversity frameworks, and therefore require that national legislation is adhered to before cultivation and/or wild harvesting. Proposed change: add after (CITES … and provisions of the Nagoya Protocol and the Global Biodiversity Framework	Agreed. References to NAGOYA and GBF provisions have been included in section 2 Scope.
339-340, 344, 361,		Comment: how will a primary producer in South Africa who happens to be an indigenous person or member of a local community be able to adhere to the GMP provision (e.g. on Echinea, Buchu or Rooibos)? In many African countries, a standards bureau is not even set up to be able to verify adherence to GMP standards. Production will become extremely expensive, and delivery of natural input materials to the EU will be pushed out of the market, while EMA allows for 'indoor cultivation' and de facto biopiracy.	Not agreed. The API manufacturer is responsible for that the cultivation site and operations were audited and should ensure traceability of the raw material once it is procured.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change: this can be a provision under GAP but not GACP; revert to GACP August 2006 provisions	
421		Comment: harvesting must also refer to methods of natural collection, and acknowledge national legislation. It is an omission to only refer to 'cultivated sources'. Proposed change: add / acknowledge various harvesting/ collection methods.	Partially agreed. The following sentence has been included under section 10. 'Collection' to complement section 11. 'Harvesting': 'Provisions mentioned under section 11 ('Harvesting') must be taken into account, as long as they are applicable.'
38-39	EUROPAM	Comment: Let's consider this term(s) more relevant to the topic. Proposed change (if any): In most cases cultivation is performed **outdoors**, indoor**s** or in greenhouses.	Agreed. Sentence amended accordingly for clarification purposes.
50-52		Comment: Let's consider changing some terms and adding others to be useful. Proposed change (if any): Collection in wild habitats for instance, may present special problems, especially with regard to confusion with similar plants, ~~environmental *damage*~~, ***environment disturbance, lack of regional regulation and control and*** *poorly qualified personnel*	Agreed. Sentence amended accordingly.
54-55		Proposed change (if any): However, in situations where the agronomic requirements for a specific plant cannot be met by cultivation practices, **sourcing from wild collection is in general an acceptable option**. ~~manufacturers may opt for the collection of the specific herb from wild sources.~~	Agreed. The sentence has been reformulated.

Section number and heading	Interested party	Comment and Rationale	Outcome
74-81		Comment: we prefer to clarify better what is meant by standard or quality standard. Proposed change (if any): Manufacturers should ensure that all the steps are carried out in accordance with the marketing authorisation/registration and therefore establish an appropriate quality assurance system in different **source** ~~cultivation~~ circumstances. This Guideline provides additional **recommendations for good operating procedures** ~~standards~~ for the production and processing of medicinal plants/herbal substances insofar as they mainly focus on identifying those critical production steps that are needed to ensure good quality. The main aim is to ensure patient safety by establishing adequate ~~quality~~ **good operating procedu**res ~~standards~~ for obtaining medicinal plants and herbal substances, ensuring that they are handled appropriately throughout all stages of cultivation, collection, processing and storage.	Partially agreed. The text has modified adding 'recommendations for good agricultural and collection practices' and changing to 'adequate practices'.
82-87		Comment: we prefer to better clarify the danger and phrase the sentence regarding the inputs differently. Additionally, we have changed some terms to others that we find more relevant. Proposed change (if any): The handling of the herbal substance should be in accordance with good hygiene practices, to ensure microbiological load is kept to a minimum, **especially human pathogens**. Therefore, care should be taken **to** avoid **contamination with substances coming from agricultural practices.** ~~agricultural inputs. e.g.~~	Not agreed. Sentences retained as proposed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		~~fertilisers, growth media/promoters etc being a source of contamination.~~ 85 During ~~cultivation~~ **growth**, harvest, collection, and primary processing, medicinal plants, herbal substances and their preparations are exposed to a large number of environmental contaminants of both biotic and abiotic origin.	
99-103		Comment: we prefer to clarify here and in the definitions chapter the terms **buyer** and **producer** otherwise there is a high risk of confusion about roles within the supply chain. Proposed change (if any): Agreements between **producer of medicinal plants/herbal substances** ~~producers (cultivators, harvesters, collectors)~~ **and** ~~buyers manufacturers~~ **buyer/manufacturer of the medicinal product** ~~of medicinal~~ **(see definition)** ~~plants/herbal substances~~ should make reference to the GACP quality assurance system and should be laid down in written form. GACP quality assurance system compliance should be verified through regular audits of the cultivation or collection sites and processing facilities by expert representatives of producer~~s~~ **and/or buyer/manufacturer of the medicinal product.**	Agreed. Sentences amended accordingly and also definitions for buyer, manufacturer and producer have been included as proposed.
106-108		Comment: We suggest this reformulation of the sentence. Proposed change (if any): The personnel, **whether working in the field or collecting in the wild**, should be required to have a high degree of personal hygiene ~~(including personnel working in the field)~~ and have	Agreed. Sentence amended accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		received adequate training regarding their hygiene responsibilities.	
101		Comment: At this point, we would like to complete the definition of the quality system by including sustainability aspects. Proposed change: **The quality system include if possible a sustainable policy to describe the contribution of the producer to reduce his impact in the environmental (preserve the biodiversity, reduce the quantity of trashes, manage the use of water and energy,…) and to share value with his own suppliers** **The no conformity detected by buyer/manufacturer of the medicinal products are managed by the quality system of the producer to explain the no conformity and improve the quality system.**	Not agreed. The guideline is already covering the concerned aspects.
		Comment: the reason for the change is always to clarify the subject of the supply chain. Proposed change (if any): Records of training should be maintained, as required by the ~~manufacturer~~ **buyer/manufacturer** of the medicinal product.	Agreed. Guideline amended accordingly.
129-133		Comment: We suggest different terms to be more precise and introduce the importance of training to avoid unwanted contaminations. Proposed change (if any):	Agreed. Text modified accordingly and additional paragraph has been added.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Collectors should have sufficient knowledge about the best time to harvest and harvesting technique, and the importance of ~~primary~~ **adequate post harvest practises** ~~processing~~ to guarantee the best possible quality. Collectors should be instructed on all issues relevant to the protection of the environment and conservation of plant species, including information on regulations related to protected species. **Collectors should be instructed on all local issues relevant to risks of contamination of medicinal plants/herbal substances by biotic or abiotic sources of the immediate environment of the plants (e.g. roads, heavy metal contaminated areas, presence of toxic weeds susceptible to diffuse natural toxins (e.g. pyrrolizidine alkaloids (PAs)/tropane alkaloids (TAs)), animal farming, etc.)**	
140-148		Comment: We suggest rephrasing the sentence differently and have changed some terms to ones we find more appropriate. Proposed change (if any): **Personnel must have sufficient knowledge about plant pests, in order to recognize significantly diseased plants /plant parts. This knowledge enables them to decide about harvest, taking into consideration the quality of the medicinal plants/ herbal substances.** ~~Personnel must have sufficient knowledge about the presentation of plant pests to recognize diseased plants/plant parts in order not to harvest them.~~ Harvesters should have sufficient knowledge about the best time to harvest**,** ~~and~~ **harvesting as well as post-harvesting**	Agreed. The sentences have been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		techniques ~~and the importance of primary processing~~ to guarantee the best possible quality. 7. Personnel should be trained in the maintenance and cleaning of equipment. ~~and~~ ~~s~~**S**chedules and procedures (including assignment of responsibility) should be established for ~~the~~ equipment**,** maintenance and cleaning as a preventive measure against contamination. 8. In general, personnel should be trained not to engage in activities such as smoking, **chewing tobacco**, ~~eating,~~ drinking, eating and storing food in the direct proximity of the plants to avoid contamination.	
160		Comment: Let's consider adding some term to be useful. Proposed change (if any): • with a sufficient distance from the from **the roof and** the wall;	Agreed. The sentence has been modified accordingly.
169		Comment: In this case, we don't understand if it refers to indoor or outdoor cultivation, but we have changed the term to one that is more appropriate for us. Moreover, protection against fire may be assigned if possible because of risk of this activity of storage of dried material Proposed change (if any): Designated areas for different ~~stages of cultivation~~ **processes may be assigned.** ***Protection against fire may be assigned.***	Agreed. Information has been included.

Section number and heading	Interested party	Comment and Rationale	Outcome
182		Comment: We have reformulated the sentence. We do not consider it necessary to document the appropriateness of the machines used. This is evident from the quality of the product. Proposed change (if any): Equipment and other supportive systems used in the critical steps of cultivation, processing, packaging and storage, should be appropriate for the intended use. ~~*shown to be appropriate for the intended use, and this process should be documented.*~~	Partially agreed. The sentence has been rephrased.
186		Comment: the reason for the change is always to clarify the subject of the supply chain. Proposed change (if any): The following should be documented as agreed ~~with the~~ **between** ~~manufacturer~~ producer of medicinal plant/herbal substance and buyer/manufacturer of the medicinal product:	Agreed. The sentence has been changed accordingly.
187-189		Comment: We suggest not using the term 'all' but 'relevant,' as 'all' is exaggerated and does not impose any limits on the processes to be described. Additionally, we have reformulated the sentence. Proposed change (if any): ~~All~~ **Relevant** processes and procedures that may impact the quality of the product e.g. training **on good practices and hygiene**, ~~personal hygiene~~, cleaning and maintenance activities, **cultivation/wild collection steps**, ~~irrigation, fertilisation, applications of pesticides and herbicides~~, ~~harvesting,~~ **post**	Not agreed. The paragraph was retained as it is, with a minor addition.

Section number and heading	Interested party	Comment and Rationale	Outcome
		harvest handling ~~processing, packaging, residual plant material and management (if relevant).~~	
191		Comment: We prefer these terms because we are referring not only to cultivation but also to wild harvesting. Proposed change (if any): • Any extraordinary circumstances occurring during the ~~cultivation period~~ **growing season** that may influence the chemical composition of the medicinal plant, e.g., extreme weather conditions, pests and plant diseases (particularly in the harvest period).	Partially agreed. "Cultivation period" has been changed to "growing period".
194-197		Comment: We prefer that the term 'exact' not be used because in many cases both cultivated and wild harvesting cover extensive areas that cannot be easily defined. In our opinion, country, region, and province already provide very precise indications. Harvesting often occurs not on specific days but over a period of time. We also want to introduce the concept of field record, which contains all the information about what happened in the field (see definition). Proposed change (if any): For cultivated medicinal plants: the geographical location i.e. ~~exact~~ country and region~~/~~, area~~/~~ **or** province. The type, quantity, and the date**/period** of harvest as well as **relevant information of from the field record** ~~the chemicals and other~~, **which may affect the ~~stable~~ quality and safety of the product.** ~~substances used during production~~. ~~Site records~~	Partially agreed. The paragraph was amended accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		~~showing previous crops, varieties and/ or cultivars and plant protection products used.~~ • For wild collection of medicinal plants: the geographic location i.e. ~~exact~~ country and region~~/~~, area~~/~~ **or** province. The type, quantity, and the date**/period** of collection.	
205-206		Comment: We suggest this sentence, which we find more understandable. Proposed change (if any): • ~~Single and as well as~~ In case of combination batches of the same plant species: ~~information on the~~ ~~harvested from~~ **different** geographical **harvesting** location**s**~~,~~ i.e. ~~exact~~ country and region~~/~~, area~~/~~ **or** province, and/ or ~~subject to~~ differe~~nt~~**ing applied** cultivation conditions.	Partially agreed. The sentence has been rephrased.
208-209		Comment: the reason for the change is always to clarify the subject of the supply chain. Moreover, we suggest not using the word 'all' because it's unnecessary in this context. We prefer to define those that fall under the GACP prerogatives." Proposed change (if any): • ~~All~~ **A**~~a~~greements relevant to product quality and safety, between ~~each producer or collector and the manufacturer and~~ producers of medicinal plant/herbal substance and the buyer/manufacturer of the medicinal product ~~and buyers, e~~.g., production~~ direct manufacturer~~ guidelines, contracts,~~ ~~etc. should be in written form.	Partially agreed. The sentence has been rephrased.

Section number and heading	Interested party	Comment and Rationale	Outcome
211		Comment: Let's consider adding some term to be useful. Proposed change (if any): Copies of all documents, audit reports, **farm list**, analysis reports etc. should be stored (**physically or digitally**).	Partially agreed. The sentence was modified accordingly.
224		Comment: According to us, organic farming does not properly fall under GACP as it is already regulated at the European level. Proposed change (if any): ~~Seeds and/ or vegetatively propagated medicinal plants used in organic production must be certified as organic.~~	Partially agreed. A reference to this regulation has been introduced in the Guideline.
226		Comment: It is very difficult to determine if a variety is stable. Proposed change (if any): Where possible, ~~stable~~ varieties and cultivars naturally resistant or tolerant to disease should preferably be used.	Not agreed. For clarification a definition of stable varieties is given in the definition section. A stable variety is a variety for which relevant characteristics remain essentially the same after repeated propagation.
232-234		Comment: We consider supplier qualification and change control procedures more relevant to GMP. At the agricultural level, applying these concepts would become challenging, although important, and should be implemented further downstream in the supply chain. Proposed change (if any): Suppliers of **seeds and propagation** materials used in cultivation must be evaluated **regularly**.~~and qualified according to established procedures~~. **Along the supply chain there must be awareness about the fact that change in seeds and**	Agreed. The sentence has been changed accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		propagation material can affect the quality of the product and it is necessary to act responsibly ~~Changing the source of supply of materials should be handled through the Change Control~~ ~~procedure.~~	
240-241		Comment: We suggest including here which residues are involved. The term 'pesticides' should be clearly defined in the definitions chapter. Proposed change (if any): Medicinal plants should not be grown in soil or substrate contaminated with sludge, heavy metals, residues **of pesticides**, ~~plant protection products~~ or other chemicals.	Partially agreed. The sentence has been rephrased, and pesticides definition has been included.
248		Comment: we suggest this second option. Proposed change (if any): Manure should be thoroughly composted **or applied before the beginning of the crop** and should be void of human faeces.	Agreed. The sentence has been changed accordingly.
250-254		Comment: We suggest this version of the sentence Proposed change (if any): All other fertilising agents should be applied ~~sparingly and~~ in accordance with the needs of the particular plant species. Fertilisers should be applied in such a manner as to minimise leaching.	Partially agreed. Additional information was added given the context.

Section number and heading	Interested party	Comment and Rationale	Outcome
		o All fertilising agents should be **appropriate**~~d~~ in order to avoid contamination with heavy.	
258-259		Comment: just as in the case of pesticides, for irrigation too, the reference norms must primarily be those of the country where the herbal substance is cultivated and produced. Nothing prohibits, indeed it should be the norm, for the producer to agree with the buyer/manufacturer of the medicinal product to also comply with the regulations of the destination country. Proposed change (if any): o Water used in irrigation should comply with the country of ~~destination's~~ **origin's** regional/national quality standards.	Partially agreed. The sentence has been rephrased.
261-261		Comment: removing every single toxic plant from the field is almost impossible; consider, for example, small plants growing a few centimeters tall that would never be harvested. We suggest removing the word 'any'. We suggest not to hinder composting, but possibly allow it unless it poses problems for the cultivation of medicinal plants. Otherwise, the grower would only have the option to destroy by burning plants containing toxins, thereby producing pollution (see PAH). Proposed change (if any): Tillage should be adapted to plant growth and requirements. During the cultivation season, ~~any~~ **the** toxic weeds (e.g. plants containing PAs/TAs) should be removed **as far as rtoxieasonable achievable** from the field ~~and not composted~~.	Partially agreed. The sentence has been modified as follows: "During the cultivation season, toxic weeds that represent a risk of contamination should be removed from the field as far as reasonably achievable and it should be considered not to compost them".

Section number and heading	Interested party	Comment and Rationale	Outcome
263-279		Comment: With regard to the rule to follow for pesticide treatments, we have already clarified the position above. Firstly, it is the rule of the country of origin that must be followed. The definition of pesticide should be included; we suggest using the EP definition, see definitions. Proposed change (if any): Pesticide ~~and herbicide~~ applications should be avoided as far as possible. When necessary, approved ~~plant protection~~ products should be applied at the minimum effective level in accordance with **the country of origin's regulation and recommendations of the buyer/manufacturer of the medicinal product.** ~~the recommendations from the manufacturer and approved by the authorities of the country of destination.~~ Consideration should be given to exclude their application to those plants that rapidly uptake and retain them. The application should be carried out only by qualified staff using approved equipment. The minimum interval between such treatment and harvest time must be stipulated by the buyer**/manufacturer of the medicinal product** or be consistent with recommendations from the manufacturer of the ~~plant protection~~ product. Regional and/or national regulations on maximum residue limits in the European Pharmacopoeia, European Directives, Codex Alimentarius etc. should be complied with.	Partially agreed. The sentence has been modified and a definition for pesticides has been introduced.

Section number and heading	Interested party	Comment and Rationale	Outcome
		o In situations where the cultivation site is located in an area of other cultivation activities, the risk for possible contamination with pesticides *and herbicides* not approved for the concerned species should be assessed. The cultivated plant should be monitored for signs of defects, regardless of whether these are of biotic or abiotic origin. Suitable rogueing should be carried out to maintain the ~~plant~~ **crop** in good growing conditions.	
300-305		Comment: We have reformulated this very important but also complicated issue because it is already regulated by the CITES convention and national or regional rules. Therefore, we suggest this version that referring to the CITES convention for listed species (including cultivated species, for example), and raises awareness among producers and buyers about sustainable harvesting. Proposed change (if any): **For species included in the Appendices II or III of CITES (Convention on International Trade in Endangered Species of wild Fauna and Flora), the collection of wild plants or the exporting/importing of wild or cultivated plants must be carried out only after carefully verifying the requirements of CITES regulations and local CITES management and scientific authorities. Wild species listed in CITES Appendix I cannot be collected.** ~~Medicinal plants/herbal substances from species that are listed as endangered (CITES, Convention on International Trade in~~	Agreed. The text has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		~~Endangered Species of Wild Fauna and Flora) must not be collected unless the relevant competent authority has given its authorisation~~. **Species and habitats that are rare, threatened, or endangered require careful consideration. It is essential to be aware of the conservation status of the species and populations being targeted. Over-exploitation should be avoided.** ~~Medicinal plants/herbal substances from species that are not yet listed as endangered (section 10.3) should undergo a risk assessment prior to collection to ensure that the species is not pushed towards extinction~~	
318-319		Comment: We have made an exception for roots and rhizomes prior to washing. While in highly humid areas, transporting them in dry conditions could be a problem. Proposed change (if any): • The harvested medicinal plant / herbal substance should not come into direct contact with the soil or floor **with exception of roots and rhizomas but only before washing them.** It must be promptly collected in suitable containers and transported **in clean and the driest possible** conditions.	Agreed. The text has been modified accordingly.
321-322		Comment: comment similar to a previous one. Proposed change (if any): Care should be taken to ensure that ~~no~~ **the** toxic weeds (e.g. plants containing PAs/TAs) are not co-harvested **as far as**	Agreed. The text has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		reasonable achievable with medicinal plants/herbal substances.	
323-324		Comment: added a possibility Proposed change (if any): All containers used during harvesting must be clean and free of contamination from previous harvests **and other uses**.	Agreed. The text has been modified accordingly.
330		Comment: added a possibility Proposed change (if any): O **bulk height in case of loose transport.**	Agreed. The text has been modified accordingly.
336-344		Comment: Cutting can sometimes be done after drying, always remaining within the scope of GACP. Proposed change (if any): Primary processing may include washing, cutting <u>before drying</u>, microbial decontamination, freezing, distillation, primary and secondary drying, etc. Where applicable, all these processes must conform to the competent authority regulations. **Primary processing as washing, drying, freezing or, distillation** ~~and~~ should be carried out as soon as possible after harvesting. In some circumstances drying and cutting should be performed according to EudraLex Volume 4 GMP part I or II (refer the GMP Table5 340 in Annex 7). In exceptional circumstances, which must be justified in the marketing authorisation/registration, some of these steps, like expression and distillation, may be performed in the field, **but** only if it is	Agreed. The text has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		necessary for these activities to be an integral part of harvesting in order to maintain the quality of the product within the approved specification (see note to the Table of GMP Annex 7).	
346-352		Comment: Not only insects can come into contact with the material, but also other animals, as well as fumes, etc. In some cases, exposure to the sun greatly accelerates drying, preventing the formation of mold and therefore potentially micotoxins. Additionally, there are cases where the quality is not affected. Proposed change (if any): Prior to processing, the material should not be exposed directly to the sun (except in cases where there is a specific need) and must be protected from rainfall, ~~insect infestation~~ **animals, smoke** etc. • In the case of natural open-air drying, the medicinal plant/herbal substance must be spread out in a thin layer. To secure adequate air circulation, the drying frames must be located at a sufficient distance from the ground. Drying directly on the ground **should be avoided**. **Drying under direct exposure to the sunlight should be avoided unless specifically required or if there is no negative influence to the quality**. ~~or under direct exposure to~~ ~~the sunlight should be avoided unless specifically required.~~	Partially agreed. First paragraph has modified also including "other unfavourable conditions".
355-360		Comment: In some cases, active ingredients are not known but rather simple markers. It should be specified that the drying parameters do not apply to natural drying. Regarding the fuel used to generate heat, we believe it is not appropriate to give	Partially agreed. Text modified accordingly except for the sentence referring to artificial drying.

Section number and heading	Interested party	Comment and Rationale	Outcome
		specific recommendations in this document on which to use, but rather to recommend indirect drying (direct drying is the main cause of PAH contamination) and in any case, to pay attention to the issue. Proposed change: The drying conditions such as maximum temperature, duration and air circulation must be selected taking into consideration the medicinal plant part to be dried, such as root, leaf or flower, and the nature of its active constituent **or quality markers,** such as essential oils. **This is not applicable for natural open air drying.** Individual conditions must be recorded ~~in detail~~ **(e.g. drying temperature, duration, method).** In case of artificial drying **measures should be taken to avoid contamination with**, ~~gas or electrical ovens should be~~ ~~considered, and the use of wood and petrol ovens minimised, to reduce to possible contamination~~ with polycyclic aromatic hydrocarbons (PAHs). **Indirect drying is always recommended.**	
361-364		Comment: Europam has always considered distillation done in the field for logistical or quality reasons to be under the GACP, as it is a practice sometimes carried out by small producers who would not have the capacity or competence to work in accordance with GMP anyway. Proposed change: In case of distillation in the field (refer the GMP Table 5 in Annex 7), this can be performed at a ~~small~~ **suitable** plant in the field **or**	Not agreed. Reference to GMP principles is kept.

Section number and heading	Interested party	Comment and Rationale	Outcome
		close by.~~which should be audited by the finished product manufacturer and validated according to GMP principles, and may be subject to inspections by Regulatory~~ ~~Authorities to assess compliance.~~	
366-370		Comment: We have clarified the operations to be performed for screening and removed the incineration of toxic plants, which we consider a challenging operation that could even be detrimental due to PAH contamination." Proposed change: Sieves must be **regularly cleaned and** maintained ~~in a clean state and should be serviced regularly~~.**Cleaning of sieves before product change is mandatory, to avoid mixing of products or cross contamination.** • Clearly marked waste-bins **for waste plant material** should be available, emptied daily and cleaned. ~~The~~ Toxic waste plant material must be segregated from growing media and the materials for the cultivation of plants. ~~The waste plant material may require incineration for destruction.~~	Agreed. Sentence has been changed accordingly. Sentence on cleaning of sieves was also included.
371-379		Comment: We reformulated the sentence by adding the need to consult, if possible, the buyer/manufacturer of the MP. Proposed change: Fumigation should be limited as far as possible and only be used when a real need is identified **and after consultation with the buyer/manufacturer of the medicinal product.**	Partially agreed. Consultation with buyer/manufacturer has been included.

Section number and heading	Interested party	Comment and Rationale	Outcome
		In such cases, treatment**s** should be carried out at the earliest possible stage, **and must be carried out only by licensed personnel** ~~according to the~~ ~~specific recommendations for use~~ • ~~Fumigation against pest attack should be carried out only where necessary and must be carried out exclusively by licensed personnel.~~ **Only registered chemicals must be used according to the specific recommendations for use.** The use of ethylene oxide and 1,3-dichloropropene is prohibited. Any fumigation against pests must be documented (see section 7). • For fumigation of warehouses, only substances permitted by the regional and/or national regulations should be used ~~and~~ documented **and in accordance with the buyer/manufacturer of the medicinal product** (see section 7).	
394-381		Comment: We think the term 'boxes' is more appropriate than 'cases'. Additionally, we are adding a warning about the use of ink on labels, which in some cases may penetrate and come into contact with the raw vegetable material. There are also minor spelling changes. Proposed change: Following processing monitored by in-process controls, the product should be packaged in clean and dry, preferably new sacks, bags or **boxes** ~~cases~~. The labels must be clear, permanently fixed and made from non-toxic material. **Attention should be paid to solvents, and chemicals used in the inks.**	Agreed. Text has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		(see also lines 391-392). Information must conform with regional and/or labelling regulations of the country of destination. Reusable packaging material should be well cleaned and properly dried prior to use. No contamination should occur through **the** reusing of bags. Packaging materials must be stored in a clean and dry place**, which** that is free of pests and inaccessible to livestock and domestic animals.	
396-399		Comment: In certain productions in countries with high humidity, measures should be taken to prevent the product from becoming damp during storage in warehouses or during transport. During transportation, care must be taken to prevent smoke from coming into contact with the material to avoid contamination. Proposed change: **In humid environments storage in air tight rooms/containers/bags could should be suitable to avoid unwanted moisture absorption of the product.** In the case of bulk transport, it is important to secure dry conditions. Furthermore, to reduce the risk if mould formation or fermentation it is advisable to use aerated containers. As a substitute, the use of sufficiently aerated transport vehicles and other aerated facilities is recommended, **whereby special care should be taken to avoid contamination through exhaust gases, smoke, etc. When using air tight containers/bags in humid conditions the packed medicinal plants/herbal**	Agreed. Text has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		substance have to be dried sufficiently to avoid mould formation during transport.	
401		Comment: We think it would be useful to include the following points. Proposed change: • **Before shipment, a control of the quality and hygiene of truck before loading is done and recorded.** • **For every batch send to buyer/manufacturer of medicinal product a representative sample could be stored during 3 years to control the quality in case of no conformity detected by buyer/manufacturer of medicinal product.**	Agreed. Text has been modified accordingly.
402		Comment: We think it would be useful to include the following definitions, mostly taken from the EP. Proposed change: **Batch (or Lot): A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous (EudraLex, Volume 4: EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use. Annex 7: Manufacture of Herbal Medicinal products.).** **Batch number (or Lot number): A distinctive combination of numbers and/or letters, which specifically identifies a**	Agreed. Definitions included with exception of tropane alkaloids which is not mentioned in the main text.

Section number and heading	Interested party	Comment and Rationale	Outcome
		batch (EudraLex, Volume 4: EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use. Annex 7: Manufacture of Herbal Medicinal products.). **Producers: someone or a company that produces the medicinal plant/herbal substance (by our definition this would be the (direct) supplier (?)) these definitions could also be left like that, but then the text needs to be adjusted** **Buyer/manufacturer of the medicinal product: someone or a company that purchases the herbal substance.** **Field record: a document (also digital) that gather any information about the cultivation such as: previous crop, seed used, name of the plant cultivated, exact location of the field, any treatment with pesticide, fertilizer and growth regulator or any chemical plant protection (specified as: name of the product, date, quantity and reason of the treatments), person performing the work.** **Pesticide: any substance or mixture of substances intended for preventing, destroying, or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals, causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances that may be administered to animals for the control of insects, arachnids, or other**	

Section number and heading	Interested party	Comment and Rationale	Outcome
		pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant, or agent for thinning fruit or preventing the premature fall of fruit. Also used as substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport (International Code of Conduct on the Distribution and Use of Pesticides. Rome: FAO 2002). **Tropane alkaloids: are a class of bicyclic alkaloids and secondary metabolites that contain a tropane ring in their chemical structure.**	
430-431		Comment: We think it would be useful to change the following definitions. Proposed change: These include comminuted **(it describes a herbal drug that has been either cut or powdered)** or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.	Agreed. Definition has been included with reference to the Ph. Eur.
456		Comment: the old version of the GACP Guideline should be mentioned here too. Proposed change: reference to GACP old version (2006)	Not agreed. The document is a revision (not a new one).
463		Comment: reference to Herbal drug preparation should be added here. Proposed change:	Agreed. Reference has been added.

Section number and heading	Interested party	Comment and Rationale	Outcome
		European Pharmacopoeia General Monograph "Herbal Drug Preparations" n° 07/2010:1434	
Line 38-41	German committee on medi aromatic and spice plants	Comment: I would adjust the order and add a separate sentence for indoor farming. I would question whether Indoor farming is really already being used on a larger scale. Therefore I would rephrase the sentence. It exists no clear definition for indoor farming. Sometimes greenhouses are also considered as indoor farming. I would therefore consistently write indoor vertical farming systems (IVFS) or just vertical farming (VF). Then it is clear that a cultivation under artificial light and closed cultivation systems is meant. Proposed change (if any): In most cases cultivation is performed in open field or in greenhouses. Cultivation in indoor vertical farming systems, where environmental factors such as light, temperature, and humidity can be controlled, is gaining increasing interest for herbal medicinal plants due to standardized production conditions.	Partially agreed. The sentence has been modified accordingly except inclusion of references to vertical farming.
Line 63-65		Comment: Proposed change (if any): It addresses specific issues associated with outdoor, greenhouse and vertical farming cultivation, collection of medicinal plants/herbal substances in the wild and production facilities for the primary processing of medicinal plants/herbal substances.	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
Line 164-165		Comment: Proposed change (if any): Indoor cultivation facilities should contain adequate systems for air, climate and humidity control, light, water treatment, ventilation and air filtration systems. They are designed to:	Agreed. The sentence has been modified accordingly
Line 166-168		Comment: Proposed change (if any): • minimize potential contamination; • facilitate cleaning, maintenance and other operations; • be impermeable to cleaning and disinfecting agents; and a hygiene lock for access would be advisable.	Agreed. The text has been modified accordingly.
Line 212-213		Comment: What is meant by fully documented? Perhaps a distinction should be made here between climatic conditions (light, humidity, temperature, CO2) which should be monitored regularly (eg by climate computer) and cultivation measures at/after implementation. Proposed change (if any): For indoor cultivation (and greenhouse, if applicable) the climatic and light conditions should be monitored regularly (e.g. by a climate computer) and all materials used or cultivation measures should be documented at/after implementation	Not agreed. The meaning of "Fully documented" is explained afterwards.
Line 213-215		Comment:	Agreed. The text has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		At present, there is probably little experience in defining acceptance criteria. Rather, one might ask that such criteria be developed and made generally available. Proposed change (if any): If possible, acceptance criteria for all cultivation conditions to obtain the specified quality should be developed and documented for each batch.	
Line 215-216		Comment: What do written procedures mean - does this refer to the originally documented climatic conditions and cultivation methods? It is not entirely clear to me what is required here. Proposed change (if any): All documents related to the cultivation and production should be prepared, reviewed, approved and distributed according to written procedures.	Agreed. The sentence has been clarified (standard operating procedures replaces written procedures).
		Comment: In my opinion, this part (documentation management) is not specific to vertical farming but is relevant for all farmers. Proposed change (if any): A procedure should be established for retaining all appropriate documents.	Agreed. The sentence has been added in the documentation chapter.
Line 216-217		Comment: Proposed change (if any):	Not agreed. Vertical farming is considered to be included in the indoor cultivation.

Section number and heading	Interested party	Comment and Rationale	Outcome
		For vertical farming cultivation daily records of critical process parameters must be kept and reviewed.	
Line 286		Comment: Not all equipment can be calibrated. Proposed change (if any): All the measuring devices involved in the cultivation process must be calibrated according to the established procedure and schedule.	Partially agreed. Sentence complemented with "where applicable".
Line 290-293		Comment: Does this paragraph refer to the climatic conditions, the composition of the nutrient solution, pH, EC, etc.? It would be good to specify what is meant and what is expected. Proposed change (if any):	Not agreed. It is not possible to specify any parameters at this general level.
Line 291-292		Comment: I am afraid that clear criteria only exist for a few parameters at the moment. So perhaps "should be established" would be better. Proposed change (if any): Appropriate in-process acceptance criteria and controls should be established.	Agreed. The sentence has been modified accordingly.
Line 291		Comment:	Not agreed. Indoor cultivation should have standardised conditions.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Standardization is certainly desirable. However, since vertical farming is very energy-intensive, methods that dynamically adapt the climatic conditions depending on the renewable energy supply could also become established in practice. So I am not sure whether standardization should be mandatory or desirable. There are no standardized conditions in the field or in the greenhouse. Proposed change (if any):	
Line 432-433		Comment: Proposed change (if any): Cultivation in a closed environment with artificial light and equipped with air filtration and water treatment to avoid cross-pollination, pollutants, insects etc.	Agreed.
102 - 103	Parceval Pty	Comment: The introduction of regular QA system audits poses a grave burden on the cultivator / collector. The cost can be substantial – having to include expert time, (international / intercontinental travel and accommodation, evaluation, etc. – and it needs to be clear who carries this cost. It promotes "audit tourism" and adds substantial cost to the raw material. As stated above, these costs can be absorbed easier by large commodities or companies but are an unfair burden on smaller crops and smaller companies or individuals. It therefore exacerbates uneven playing fields and disfavours smaller producers and crops.	Not agreed. GACP compliance should be verified by regular audits of the cultivation and/or collection sites and processing facilities by expert representatives of the buyer/manufacturer of medicinal plants/herbal substances. Alternative compliance checks may be performed and should be justified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): Leave the current version as is	
303 - 305		Comment: There need to be clear guidelines on what is meant with "not yet threatened". Proposed change (if any): Introduce the IUCN classification and clarify at what level a risk assessment should be conducted.	Partially agreed. Explanation on CITES has been added.
341 - 344		Comment: The reference to Table of GMP Annex 7 is of course very convenient to use and relevant. However, it could be worded more openly so as to allow for more leniency in what requirements may really be necessary. E.g. in essential oils, the quality of the oil complying with the expected specifications and being void of contaminants should be more of a guiding principle than ticking a long list of first world GMP concepts and auditing. Making exemptions should not be exceptional but more commonplace. To rope in Regulatory Authorities for compliance inspections is asking for further complications. In developing nations, there is a severe lack of inspection capacity for GMP in the first place – and an understanding of applying GMP to such processes as envisaged here is likely not available. It is simply not practical. Proposed change (if any): "In case of distillation in the field (refer the GMP Table5 in Annex 7), this can be performed at a ~~small~~ plant in the field, which should be audited by the finished product manufacturer <u>from time to time</u> and validated according to GMP principles, ~~and may be subject to inspections by Regulatory Authorities to assess compliance.~~	Partially agreed. Reference to GMP Annex 7 remains. Audition by the API manufacturer or the finished product manufacturer has been added.

Section number and heading	Interested party	Comment and Rationale	Outcome
Line 140	PharmaRolly DOOEL	Comment: The word "presentation" is not suitable. Proposed change (if any): We suggest the term "appearance"	Agreed. The term appearance has been added.
Line 173, 174, 175		Comment: The phrase "equipment used in fertiliser and pesticide application, or other operations must be qualified and regularly calibrated." if read in connection with Eudralex Volume 4 GMP guidelines creates a very demanding process for the producer to qualify all equipment that is used. Especially, in the case of agricultural production it is very difficult to be implement. Proposed change (if any): We suggest one of the following: 1) The word "qualified" can be deleted since in line 183 the phrase "be appropriate for the intended use" would describe a need of this process. 2) The addition of the definition of qualification. The qualification process should be linked to the Operational Qualification and/or Performance Qualification. In this case more details on the process of qualification and documentation needed for verifying this is needed.	Partially agreed. The sentence has been modified accordingly.
Line 258, 259		Comment: The phrase "Water used in irrigation should comply with the country of destination's regional/national quality standards." refers to a significant problem of irrigation water. However, there in many cases there is neither regional or national quality standard for the irrigation water. Proposed change (if any): At the end of the phrase a reference to international standards can be added for the applicability of the	Agreed. The sentence has been modified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		specific requirement for those countries that do not have their own standards on irrigation water quality.	
Line 264. 265, 266		Comments: The following phrase"…approved plant protection products should be applied at the minimum effective level in accordance with the recommendations from the manufacturer and approved by the authorities of the country of destination." sets two major requirements that can hinder the use of any plant protection product. First, many of the herbal/medicinal plants are cultivated in many countries as minor crops. That means a very limited, if non-existing, list of active ingredients and commercially produced Plant Protection Products (PPPs) available per crop. Especially in the European Union, according to the legislation, the PPPs to be used shall be licenced per crop and be target specific. Moreover, there are many countries where the legislation is not highly descriptive but on the contrary is very generic, leaving the interpretation to the producers regarding the correct use of PPPs. In addition to that, acquiring the approval of the authorities of the country of destination is a major challenge. Although, the approach of including the concept of COD in the Guideline is well-accepted, a more explicit requirement has to be drawn regarding the use of PPPs, since even tracking down the respective authority for the PPPs in the COD, could be impossible. Proposed change (if any): We suggest the following amendment of the requirement (based on the EU Regulations and more specifically on the Organic Production):	Partially agreed. The sentence has been modified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		"All the plant protection products applied shall be registered in the country of application (COA). The approved plant protection product should be applied at the minimum effective level in accordance with the recommendations from the manufacturer and/or authorities. If there is an official registration system, but the pesticide/biocide is not registered for the crop (and for the enemy target to be used), then extrapolated use is permitted, when the authority allows it.	
Line 329, 330		Comment: There are other containers used for harvesting besides sacks. Proposed change (if any): We suggest the use of a more generic term instead of sacks, to include more types of containers e,g. "harvesting containers"	Partially agreed. *'Containers'* replaces *'sacks'* in the guideline.
Line 283, 284, 285, 286.		Comment: The requirement described here, regarding the need of validation of production etc, just for the production in Indoor and possibly in the Greenhouse, creates a huge discrimination for the cases where the same species is cultivated outdoors as well. This comment applies to all the requirements set throughout the document (eg Line 290, 291, 292 and 293), which create a clear distinction between the outdoor production and the indoor /GH cultivation of the same crop. Proposed change (if any): Outdoor production of Medicinal Cannabis shouldn't be allowed at all. There are many factors that can affect the quality of the product and that cannot be controlled (bird excretes for example) which might happen on one or two plants that will be a part of the same batch that goes	Not agreed. The proposed sentence can't be accepted because it is a general guideline without any reference to a specific medicinal plant cultivation. Furthermore, outdoor cultivation cannot be prohibited.

Section number and heading	Interested party	Comment and Rationale	Outcome
		on market at the end. Quality assurance principles cannot be applicable for the outdoor production at all.	
Line 83	Q-CERT S.A.	**Comment**: The following phrase "Therefore, care should be taken avoid agricultural inputs" does not make sense **Proposed change (if any):** Probably the word "to" is missing	Agreed. The sentence has been modified accordingly.
Line 103		**Comment:** The audits can also be performed by independent entities, such as Certification Bodies (third party audits) **Proposed change (if any):** add the phrase "and/or Certification Bodies"	Partially agreed. The term "Expert representatives" includes the possibility of a third-party contractor.
Line 123		**Comment:** The following phrase "As required by the manufacturer", is limiting. The text should also define what are the requirements when there is no contact of requirement from a manufacturer (e.g. before a contract is signed). **Proposed change (if any):** An amendment to the phrase should made: "Records of training should be maintained, including at least: topic, date, name of participants and trainer. Where there are additional requirements by the manufacturer, regarding training records, those also have to be taken into account."	Partially agreed. The sentence has been modified.
Line 138		**Comment:** The following phrase "or beneficial arthropods and microorganisms" refers to a very technical part of the Integrated Pest Management method. We believe, that a more generic comment shall be included instead.	Agreed. The sentence has been modified accordingly.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): The phrase could be replaced by the following "or the implementation of Integrated Pest Management techniques (IPM)"	
Line 140		**Comment:** The word "presentation" is not suitable. **Proposed change (if any):** We suggest the term "appearance"	Agreed.
Line 159		**Comment:** In a lot of cases, the product is stored on racks. **Proposed change (if any):** We suggest the addition of the phrase "and/or racks" after the "pallets"	Agreed.
Line 173, 174, 175		**Comment:** The phrase "equipment used in fertiliser and pesticide application, or other operations must be qualified and regularly calibrated." if read in connection with Eudralex Volume 4 GMP guidelines creates a very demanding process for the producer to qualify all equipment that is used. Especially, in the case of agricultural production it is very difficult to be implement. **Proposed change (if any):** We suggest one of the following: 1) The word "qualified" can be deleted since in line 183 the phrase "be appropriate for the intended use" would describe a need of this process. 2) The addition of the definition of qualification. The qualification process should be linked to the Operational Qualification and/or Performance Qualification. In this case more details on the process of qualification and documentation needed for verifying this is needed.	Partially agreed. The sentence has been modified.
Line 183-184		**Comment:** The phrase "should be sown to be appropriate for the intended use and this process should be documented." could	Partially agreed. The sentence has been modified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		create huge discrepancies on the understanding of the method used to "saw" the appropriateness. **Proposed change (if any):** Since this phrase is of major importance for the appropriateness of the used equipment, we suggest the phrase to be amended as follows "should be sown to be appropriate for the intended use and this process should be documented. Records may also include the manufacturer's operation manuals, confirmation letters by the manufacturer, and/or results of in-house calibration and testing of operation where applicable"	
Line 186		**Comment:** The phrase "as agreed with the manufacturer" is limiting the applicability of the specific chapter to the case where there is an agreement with a manufacturer. The production and primary processing usually begin before any agreement is signed, so this and every other requirement referring to a manufacturer agreement shall be revised to include a generic requirement of the Guideline itself. **Proposed change (if any):** We suggest that the whole document should be revised regarding the manufacturers' requirements. The manufacturers' requirements (where applicable) could be an addition on top of those described in the current Guideline. The producer shall align with the strictest of them (where applicable).	Partially agreed. The sentence has been modified.
Line 217		**Comment:** The phrase "All the specifications related to the process" is not self-explanatory.	Agreed. The sentence has been modified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): We suggest including the name of the process e.g. cultivation and production process	
Line 226		**Comment:** The phrase "stable varieties" is not self-explanatory. Please revise or give more information on the word stable **Proposed change (if any):** -	Agreed. The definition for "stable variety" has been added in the definition section.
Line 240		**Comment:** The term "should not" in the phrase "Medicinal plants should not be grown in soil or substrate contaminated with sludge, heavy metals, residues, plant protection products or other chemicals" is weak. It is of major importance for the product safety to avoid sources of contamination which are correctly described in this point. **Proposed change (if any):** Use of "shall not" instead of "should not"	Not agreed.
Line 248		**Comment:** The term "should not" in the phrase "Manure should be thoroughly composted and should be void of human faeces." is weak. **Proposed change (if any):** Use of "shall not" instead of "should not"	Not agreed.
Line 258, 259		**Comment:** The phrase "Water used in irrigation should comply with the country of destination's regional/national quality standards." refers to a significant problem of irrigation water. However, there in many cases there is neither regional or national quality standard for the irrigation water. Proposed change (if any): **At the end of the phrase a reference to international standards can be added for the**	Agreed. The sentence has been modified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		applicability of the specific requirement for those countries that do not have their own standards on irrigation water quality. E.g. "FAO Irrigation and Drainage Paper 29 (Rev. 1): Water Quality for Agriculture", " Guidelines for the Safe Use of Wastewater, Excreta, and Greywater, Volume 2", "EU Regulation 2020/741 on Minimum Requirements for Water Reuse" etc	
Line 264. 265, 266		**Comments:** The following phrase"…approved plant protection products should be applied at the minimum effective level in accordance with the recommendations from the manufacturer and approved by the authorities of the country of destination." sets two major requirements that can hinder the use of any plant protection product. First, many of the herbal/medicinal plants are cultivated in many countries as minor crops. That means a very limited, if non-existing, list of active ingredients and commercially produced Plant Protection Products (PPPs) available per crop. Especially in the European Union, according to the legislation, the PPPs to be used shall be licenced per crop and be target specific. Moreover, there are many countries where the legislation is not highly descriptive but on the contrary is very generic, leaving the interpretation to the producers regarding the correct use of PPPs. In addition to that, acquiring the approval of the authorities of the country of destination is a major challenge. Although, the approach of including the concept of COD in the Guideline is well-accepted, a more explicit requirement has to be drawn regarding the use of PPPs, since even tracking down the respective authority for the PPPs in the COD, could be impossible.	Partially agreed. The sentence has been modified acknowledging both national regulations in the country of application and leaving room to request the use of plant protection products that are allowed in the EU.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): We suggest the following amendment of the requirement (based on the EU Regulations and more specifically on the Organic Production): **"**All the plant protection products applied shall be registered in the country of application (COA). The approved plant protection product should be applied at the minimum effective level in accordance with the recommendations from the manufacturer and/or authorities. If there is no official registration system, then the safe use criteria of PPPs must be according to the 'International Code of Conduct on the Distribution and Use of Pesticides' by FAO (Rome, 2002) or other national/international protocol for the safe use of pesticides. Extrapolated uses are allowed if the active ingredient is allowed in Organic Agriculture according to the EU regulation (based on the principle of minimum effective level). If there is an official registration system, but the pesticide/biocide is not registered for the crop (and for the enemy target to be used), then extrapolated use is permitted, when the authority allows it. **For products that are exported, the producer shall be able to demonstrate documented information of any limitations on the ingredients in the Country of Destination (COD), as well as the MRLs of the COD (where applicable)"**.	
Line 269, 270, 271		**Comment:** Regarding the interval between plant protection products and harvest time, the phrase allows the buyer to agree	Partially agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		with the producer on the interval even stipulating against the manufacturers' description. Proposed change (if any): **We suggest the addition of the phrase "whichever is higher" at the end of the sentence.**	
Line 280, 281		**Comment:** It is not clear what the phrase "and if the following aspects should also be considered." means. Please clarify in which cases the "following aspects" need tote be considered? Proposed change (if any): -	Agreed.
Line 283, 284, 285, 286.		**Comment:** The requirement described here, regarding the need of validation of production etc, just for the production in Indoor and possibly in the Greenhouse, creates a huge discrimination for the cases where the same species is cultivated outdoors as well. This comment applies to all the requirements set throughout the document (eg Line 290, 291, 292 and 293), which create a clear distinction between the outdoor production and the indoor /GH cultivation of the same crop. **Proposed change (if any): -**	Not agreed. It is not possible to prohibit outdoor cultivation.
Line 308		**Comment:** The phrase "The following should be noted", could create confusion as far as the necessity and the importance of the following requirements. Proposed change (if any): **We suggest the use of a different phrase, eg. "The following requirements apply"**	Agreed.
Line 329, 330		**Comment**: There are other containers used for harvesting besides sacks.	Agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): **We suggest the use of a more generic term instead of sacks, to include more types of containers e,g. ”harvesting containers”**	
Line 391, 392		**Comment:** There is no reference to the suitability of the packaging material. Proposed change (if any): We suggest adding the requirement of the packaging materials to be suitable for coming in contact with food.	Agreed. The reference has been added.
Line 395		**Comment:** The phrase “…in which daily temperature fluctuations are defined…” is confusing. At the storage area, you usually monitor and where applicable you limit the daily temperature fluctuation by using HVAC system etc. Proposed change (if any): **We suggest using the word “monitored” instead of “defined”**.	Agreed.
42	RQC Partners	Comment: Not consistent with lines 61, 64, 81 – missing "production" Proposed change (if any):	Agreed.
66		Comment: The document should also include assessment for ICH Q7A specific to APIs from plant sources. Proposed change (if any):	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		These considerations should be read in connection with EudraLex Volume 4 GMP guidelines Part II for APIs, Annex 7 Manufacture of Herbal Medicinal Products, and ICH Q7A…	
75		Comment: Cannabis products are not registered, flexibility for "any marketing authorisation" be added. Proposed change (if any):	Not agreed.
83		Comment: Avoid "untreated agricultural inputs." And add consideration for treated fertilisers (blood and bone, manure). Risk Organic system impacts Proposed change (if any):	Partially agreed. It's been corrected.
100 & 102		Comment: That language for quality system be considerate of other regulated material types, (e.g., remove "assurance"), keep quality system or add production quality system. Proposed change (if any):	Not agreed.
116		Comment: Consideration for personnel operating where "open" plant processing or processing occurs. Proposed change (if any):	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
134		Comment: Guarantee could be replaced with "verify and approve." Proposed change (if any): …a local supervisor should verify and approve the training, supervision, and documentation.	Agreed. The sentence has been modified.
148		Comment: Add storage of personal medicines to listing Proposed change (if any):	Agreed.
155		Comment: Include provision for locally trained operators. Proposed change (if any):	Not agreed.
159		Comment: Add consideration for "Treated" pallets. Proposed change (if any): It is recommended that the packaged medicinal plant/herbal substance be stored: • in buildings with concrete or similar easy to clean floors; • on treated pallets;	Not agreed.
164		Comment: Consider "climate control and humidity management."	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): Indoor cultivation facilities should contain adequate systems for air, climate and humidity control, light…	
222		Comment: Add consideration for seeds and propagation material (such as cuttings), and for provision for those plants that have not yet achieved Variety/ Cultivar/ Chemotype designation (e.g., materials such as cannabis) Proposed change (if any):	Not agreed.
227		Comment: Add consideration for seeds and propagation material (e.g., cuttings) Proposed change (if any): Seeds and propagation material should be free from…	Agreed. The sentence has been modified.
231		Comment: Add consideration for seeds or propagation material (e.g., cuttings) Proposed change (if any): The use of genetically modified medicinal plants, seeds, or propagation material must comply with regional and/or national regulations.	Agreed. The sentence has been modified.
240		Comment:	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Add consideration for transformed materials (e.g., heat-activated compost) Proposed change (if any):	
246		Comment: Verification of cultivation conditions and key inputs (e.g., irrigation water quality) shall be conducted by the responsible person (e.g., master grower) Proposed change (if any):	Not agreed.
248		Comment: Thoroughly composted, transformed to be free from gross microbial contamination. Proposed change (if any): Manure should be thoroughly composted, transformed to be free from gross microbial contamination, and should be void of human faeces.	Agreed. The sentence has been modified.
253		Comment: Consider addition of "fertilising agents should be substantially free from heavy metals and organic contaminants." Proposed change (if any): All fertilising agents should be substantially free from heavy metals and organic contaminants…	Not agreed.
271		Comment:	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Reduce the potential for differences in country level standards, and make reference to the tightest limit when multiple countries are involved (e.g., supply country, sale country) Proposed change (if any):	
283		Comment: Add "considerate of regional and national regulations." Proposed change (if any): Considerate of regional and national regulations, the company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.	Not agreed. This is out of scope for this guideline.
287		Comment: Align with language for regulated products, verified and approved. Proposed change (if any): Before a new cultivation cycle, all materials used should be verified and approved by the person responsible for quality.	Agreed. The sentence has been modified.
290		Comment: Allow flexibility for critical elements, "Any critical quality attributes…" Proposed change (if any):	Agreed. The sentence has been modified.

Section number and heading	Interested party	Comment and Rationale	Outcome
		For indoor cultivation, any critical quality attributes and critical process parameters should be identified.	
280-293		Comment: Considerate of GMP boundary in ICH Q7, any qualification/ validation should be included in steps following primary processing. Proposed change (if any):	Not agreed.
329-330		Comment: Consider replacing "sacks" with "containers." Proposed change (if any): …attention must be paid to: o overfilling of the containers; o stacking up of containers.	Agreed.
339-340		Comment: Consistency between Annex 7 and ICH Q7A to be made. Annex 7 table refers to both GACP and GMP for cutting and drying steps. Proposed change (if any):	Not agreed.
341		Comment: There may not be marketing authorisation/registration associated with medicinal products, this statement could reflect processing steps based on risks and market/ country regulations.	Not agreed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any):	
391		Comment: Potentially use terms "verified and approved." Proposed change (if any):	Agreed.
395		Comment: Consider addition of environmental conditions controlled and limited. Proposed change (if any):	Agreed. The sentence has been modified.
98-103	Tillotts Pharma AG	Comment: we as a pharma company don`t have direct relationships and contracts with single farmers growing peppermint and doing harvesting and steam distillation. Also the intermediate buyer (from farmers) and seller (to us) is dealing with the needed pharma quality only for a small percentage of the full volume. Therefore, the quality management of both farmers and intermediate company can`t be ruled and judged by GACP (or even GMP). Proposed change (if any): a quality management system must be in place that has similar policies and SOPs in place, e.g. ISO 9001 or regulations from food industries, GACP principles have to be followed by the cultivators/harvesters. Audits must be possible and take place regularly. Quality agreements should be in place between the pharma company and the intermediate company (buyer/seller).	Not agreed. This guidance refers to plants of a medicinal grade therefore GACP and GMP are mandatory.

Section number and heading	Interested party	Comment and Rationale	Outcome
335-381		Comment: Peppermint as example is not planted solely as medicinal plant. Primary processing on the field (drying of cut material) and at the farmers sites (steam distillation) can`t be performed under full GMP or GACP. For example, it is not necessary that adept farmers record the drying conditions of peppermint in detail (cf. lines 357, 358). Solitarily for economic reasons they will avoid e.g. underdrying (too high energy consumption during steam distillation) or overdrying (unnecessary loss of material when picking the plants up into the trailers used for steam distillation). Proposed change (if any): processes can be done according to the needs to obtain a product (e.g. peppermint oil) that fulfils the Ph. Eur. Monograph (Mentha piperita) and additional specifications (if needed). Relevant GACP principles have to be followed and checked during audits.	Not agreed. See above.

References:

AESGP:

[1] Raiser M, Hofmann W, Stekly G, Tegtmeier M, Torres Londono P, Steinhoff B. Qualification of Suppliers of Cultivated and Wild Collected Medicinal Plants. Pharm Ind 2017; 79(1):66-70

[2] Chmit M SMS, Horn G, Dübecke A, Beuerle T. Pyrrolizidine Alkaloids in the Food Chain: Is Horizontal Transfer of Natural Products of Relevance? Foods 2021; 10:1827