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A Consideration of the Analytical Requirements for Fresh Herbal Drugs used to produce Herbal Drug Preparations

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Currently, there is one herbal drug monograph based on fresh plant material (other than those specified for homeopathic use) described in the European Pharmacopoeia (Ph. Eur.), this being the monograph for Fresh bilberry fruit (1602) [1]. However, after harvesting, the fresh bilberry fruits are frozen and stored in this condition until required for use. Samples are taken from the frozen bulk and subjected to analysis against the Ph. Eur. monograph, the frozen bulk being amenable to medium to long term storage, as is the case with herbal drugs in a dried state – the usual presentation of herbal drugs which are the subject of Ph. Eur. monographs.

A Ph. Eur. monograph for purple coneflower expressed juice is under elaboration, the manufacture of which necessitates that the juice must be expressed from the fresh herbal drug (the flowering aerial parts of *Echinacea purpurea* (L). Moench) within a specified time after harvesting. The elaboration of this monograph has led to the question as to whether or not a monograph is also required for the fresh herbal drug from the aerial parts of purple coneflower and the quality control parameters which may be applicable to such a material.

A similar situation exists for the production of essential oils from fresh plant materials. Essential oils, although herbal drug preparations, were considered, from a Good Manufacturing Practice (GMP) perspective, as primary starting materials. As a result, for the majority of Ph. Eur. monographs on essential oils, reference is made to the plant(s) from which the essential oil must be derived without any stated analytical requirements for that plant, for example: Citronella oil (1609) [2], defined as : *'Oil obtained by steam distillation from the fresh or partially dried aerial parts of Cymbopogon winterianus* Jowitt'. However, the regulatory requirements applied to the use of herbal drug preparations, such as essential oils, as active substances in

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medicinal products have been progressively adjusted such that the quality control parameters for the herbal drug from which the herbal drug preparation is derived are required to be detailed in any application for a marketing authorisation where an herbal drug preparation is an active substance. This has led a section of the industry which manufactures and supplies essential oils for use as active substances to approach the Ph. Eur. with a request that the pharmacopoeia examines the possibility of introducing monographs for those fresh herbal drugs from which essential oils to be used as active substances are derived.

The European Medicines Agency (EMA) *Guideline on quality of herbal medicinal products/ traditional herbal medicinal products* (EMA/CPMP/QWP/2819/00 Rev. 2 – 31 March 2011) [3] states the following under section ***5. Control of starting materials***:

> '***5.1 Control of herbal substances and of herbal preparations***
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> *This section should be in accordance with the 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/ QWP/2820/00 and EMA/CVMP/815/00 as revised).*
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> ***Control of herbal substances***
>
> *A comprehensive specification for each herbal substance must be submitted. This also applies if the applicant is not the manufacturer of the herbal substance. If the starting material is a herbal preparation, e.g., in the case of fatty or essential oils used as active substances of herbal medicinal products, a specification for the herbal substance is required, unless fully justified (...).*
>
> *If no monograph for the herbal substance is given in a Pharmacopoeia referred to in Annex 1 of Directives 2001/83/EC or 2001/82/EC as amended, a comprehensive specification for the herbal substance must be supplied and should be set out in the same way where practicable, as the monographs on herbal substance in the European Pharmacopoeia (...).'*

The guideline EMA/CPMP/QWP/2820/00 Rev.2 – 31 March 2011 [4] states, under ***3.2. Universal tests/criteria*** and ***3.2.1. Herbal Substances***: *'The following tests and acceptance criteria are considered generally applicable to all herbal* substances (...)'. This is followed by a list composed mainly of the quality parameters applied to herbal drugs in the Ph. Eur.

As no differentiation is made in either of these guidelines between fresh and dried herbal drugs, it must be assumed that the criteria given are applicable to all herbal drugs. However, the quality parameters for herbal drugs as described in the Ph. Eur. were selected because of their applicability to dried herbal drugs and the methodology given in the Ph. Eur. was neither intended nor optimised for fresh herbal drugs.

Dried herbal drugs are significantly different from fresh herbal drugs. In the case of dried herbal drugs, the drying process is intended to ensure that the herbal drugs can be stored for a period of time. In some cases, depending upon commercial demand for an herbal drug, this storage may be over many years and hence, there is a need to include quality parameters which are able to monitor the stability of dried herbal drugs. This includes chemical stability, requiring the monitoring of both qualitative (e.g. profiling, usually chromatographic methods) and quantitative (e.g. assay) parameters and microbiological stability where the water content (either by loss on drying or chemical determination) and the microbiological bioburden of the herbal drug are important. The eventual use of a dried herbal drug may be uncertain. It may be incorporated directly into a medicinal product when cut for use as an herbal tea or powdered for incorporation into tablets/capsules. Where an herbal drug is used directly in such medicinal products it is necessary to include quality parameters which ensure acceptable levels of

impurities which may be either harmful (e.g. heavy metals, pesticides, aflatoxins, ochratoxins, pathogenic micro-organisms) or undesirable, for example, other plant parts or species (foreign matter, specific exclusion tests) or sand and related contaminants (ash, acid insoluble ash, etc.). This is in addition to the requirement to correctly identify (macroscopy, microscopy and chemical profiling) the herbal drug.

A large proportion of dried herbal drugs are used in the manufacture of herbal drug preparations, mainly extracts. In this case, not all of the quality parameters applicable to a dried herbal drug for direct incorporation into a medicinal product have the same significance in defining the quality of a dried herbal drug for extraction. For example, during extract manufacture, the extraction process may eliminate or significantly reduce the levels of various contaminants, e.g. heavy metals, microbial bioburden, etc. However, despite the extensive analysis of a dried herbal drug against a significant number of quality parameters, the chemical composition of the majority of the herbal drug remains unknown.

The source of a dried herbal drug is a fresh herbal drug. It has never been suggested (and it would be ludicrous to do so) that it is necessary to have a comprehensive specification for each fresh herbal drug from which a dried herbal drug is produced. The accepted requirement for the fresh herbal drug is correct botanical identification, this being confirmed by subsequent analysis of the dried herbal drug. However, because of the changes which occur during the drying process, particularly when volatile and/or thermo-labile constituents are present in the fresh herbal drug, analytical data derived from the fresh herbal drug may not be a reliable indicator of the acceptability of the quality of the dried herbal drug, and *vice versa*, nor of the quality of the herbal drug preparation obtained from the herbal drug. For example, the composition of a distilled essential oil may differ significantly from that which exists in the plant. Thus, chamazulene, which gives the deep blue colour to matricaria oil, is not present in the plant and is derived from matricine during the distillation process; terpinen-4-ol, the most important component of marjoram oil, is produced from thujanyl acetate during distillation; some of the linalool in lavender and lavendin oils is derived, during distillation, from linalyl acetate, explaining the presence of up to 12 per cent (*S*)-linalool in the oils even though the flowers contain approximately 99 per cent (*R*)-linalool.

Fresh herbal drugs are not intended to be stored (unless dried or frozen), but to be processed, within a short time after harvesting, into an herbal drug preparation (e.g. essential oil, fatty oil, juice, tincture, etc.). The provenance of a fresh herbal drug will depend upon its geographical location and whether it is cultivated or wild crafted. The quality of an herbal drug preparation derived from a fresh herbal drug will depend not only on the origin, but also on the time of harvesting and methods of processing of the herbal drug, some of which may vary from region to region (e.g. there are significant differences in the chemical profiles of peppermint oils depending upon their origin).

Purple coneflower expressed juice will always be produced from cultivated, fresh purple coneflower aerial parts. As a result, the complete history of the crop should be available to the producer of the juice and hence, when required, to the manufacturers of the medicinal products into which the juice will be incorporated. Correct botanical identification will have been assured by the choice of seed and from observations and records derived during crop development. Harvesting of the aerial parts, expression and stabilisation of the juice will have taken place under controlled and validated conditions. If further quality parameters relevant to the fresh herbal drug are required, these will only be valid if they can be performed on the fresh herbal drug in the condition in which it exists at the time of pressing the juice. Other quality requirements should be applied to the expressed juice itself, for example, chemical profiling for identity of juice constituents, impurity profiles for heavy metal, pesticides, etc., microbiological quality, assay of marker constituents.

Essential oils produced from fresh herbal drugs originate from a diverse range of plant materials. Some (e.g. peppermint oil) originate from cultivated crops, as for purple coneflower expressed juice, whilst others (e.g. pine needle oil) originate from wild crafted materials. However, unlike dried herbal drugs or extracts or purple coneflower expressed juice, the majority of the chemical composition of an essential oil is known and is determined as its chromatographic profile. Such a chromatographic profile is usually species specific and is a useful method of indicating that the correct plant species, plant part and time of harvesting were used for the production of the essential oil. However, this does not obviate the need for suitable site documentation confirming that the requirements for specified plant material, time of harvesting, cleanliness of equipment and validated production methods have been satisfied.

The diagram illustrates some of the routes by which fresh herbal drugs may be processed as the source materials for active substances in medicinal products. Thus, an essential oil obtained by distillation from a fresh herbal drug will, in most cases, represent less than 2 per cent of that fresh herbal drug with the remaining 98+ per cent of the herbal drug being discarded after distillation of the essential oil.

The only realistic quality requirements for the fresh herbal drug prior to distillation are: (i) correct botanical identification of the plant and the parts of the plant to be processed, and (ii) a check for acceptable levels of other plant components whether derived from other plant species or non-specified parts from the correct species. Tests for quality parameters on the herbal drug which are nullified by the distillation process, for example, heavy metals, ash, microbiological contaminants, etc. should not be required. Since the essential oil is composed of a narrow range of the constituents from the fresh plant and because the gas chromatographic profile determines the majority of these constituents and hence characterises the composition of the majority of the essential oil, the focus should be on applying quality parameters to the essential oil with the only quality parameters relating to the fresh herbal drug being those related to the macroscopy of the herbal drug and/or foreign matter.
Note: a similar rationale can be developed for essential oils obtained by means other than distillation; for fatty oils (e.g. olive oil) and for essential oils obtained from dried herbal drugs (e.g. clove oil).

Herbal drug preparations, other than essential oils and fixed oils, which are obtained from fresh herbal drugs, for example, juices and tinctures, where the applied quality parameters are only able to determine a small percentage of the overall chemical composition of the herbal drug preparation, need to be considered on a case by case basis. However, the following general principles are proposed:

a. The primary differentiation should be on the basis of whether or not the herbal drug has been cultivated or wild crafted.

b. Where the herbal drug has been cultivated from seed which was supplied from a source whose business is the production of commercial seed and whose quality systems can demonstrate origin and traceability of the seed and where the complete history of the herbal drug from planting of the seed to harvesting is documented, it should be acceptable to process the fresh herbal drug using only the following botanical/physical quality parameters:

    i. correct macroscopial identification of the plant and the parts of the plant to be processed;

    ii. a check for acceptable levels of other plant components, whether derived from other plant species or non-specified parts from the correct species;

    iii. a check for acceptable levels of extraneous matter (stones, soil, etc.);

and the statement of:

iv. a maximum storage period between harvesting and processing in order to ensure the absence of unwanted fermentation, the presence of which may lead to an alteration in the quality of the herbal drug preparation and/or to mycotoxin production.

Quality control parameters for chemical identity and contaminant profiling, microbiological quality and assay would be performed on the herbal drug preparation.

c. Where the herbal drug has been cultivated but the requirements stated above for seed origin and traceability and/or history of the cultivation of the herbal drug from seed planting to harvesting are incomplete, processing would be allowed on the same basis as above, but there would be a requirement for further testing, as determined to be necessary, depending upon the plant material to be processed and potential or known quality issues.

d. The processing of fresh herbal drug from wild crafted origin for the manufacture of herbal drug preparations such as juices and tinctures could be justified by 100 per cent examination/identification of the plant material by a suitably qualified person or by other methods as agreed with regulatory authorities.

In order to bring clarity and understanding with regard to the quality parameters to be applied to herbal drugs, it is proposed that the Ph. Eur. general monograph on Herbal drugs (1433) [5] should be re-examined with a view to differentiating the analytical requirements for herbal drugs on the basis of: (i) whether or not they are conserved (e.g. dried, frozen, etc.) and/or (ii) the quantified percentage composition of their herbal drug preparations (e.g. where a high percentage composition of the herbal drug preparation is known, e.g. an essential oil, the analytical requirements for the herbal drug from which it was derived would be less stringent than those for a herbal drug used to produce, for example, a non-refined extract). In addition, consideration should be given to the inclusion of a macroscopical description of the fresh herbal drug in the Production section of all Ph. Eur. monographs for herbal drug preparations processed from fresh herbal drugs.

REFERENCES

[1] Fresh bilberry fruit, monograph 1602. Ph. Eur. 7th Edition. Strasbourg, France: Council of Europe; 2010(vol 1).

[2] Citronella oil, monograph 1609. Ph. Eur. 7th Edition. Strasbourg, France: Council of Europe; 2010(vol 1).

[3] Guideline on quality of herbal medicinal products/traditional herbal medicinal products. Ref: CPMP/QWP/2819/00 Rev. 2. EMA; 2011 March [guideline].

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[5] Herbal drugs, general monograph 1433. Ph. Eur. Suppl.7.3. Strasbourg, France: Council of Europe; 2011.