Equivalence and Quality Principles for Herbal Medicines

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The concept of “generics” i.e. products with the same active ingredient used for the same indication with the same dosage and formulation cannot apply to natural/herbal medicines. For natural medicines, starting product and process defines the product. Therefore, it is essential that a product which makes health claims derived from a clinical trial is the same or equivalent to the product used in that trial (or ‘essentially the same’).

Herbal medicines possess unique challenges with respect to showing equivalence. They contain complex compounds comprising multiple biologically active components, of which only a subset may have been identified and can be directly measured via Quality Assurance (QA) processes. Therefore, the manufacturing steps of the herbal medicine (e.g. sourcing, extraction and production), and validated testing of the material throughout production, must be uniform and homogenous in order to maintain consistency of both the known and unknown active components in the finished medicine.

Equivalence and Quality Principles (EQP) capture the fundamentals of product consistency that need to be met, in conjunction with the QA methods currently in use in GMP manufacturing processes. These principles aim to ensure that a product consistently delivers the required clinical outcomes claimed. Clinical outcomes should only be ascribed to products that have been assessed and found to be fundamentally equivalent through the application of the EQP process. Healthcare professionals and patients can then be assured that the benefits demonstrated in the clinical trials will be delivered in clinical practice.

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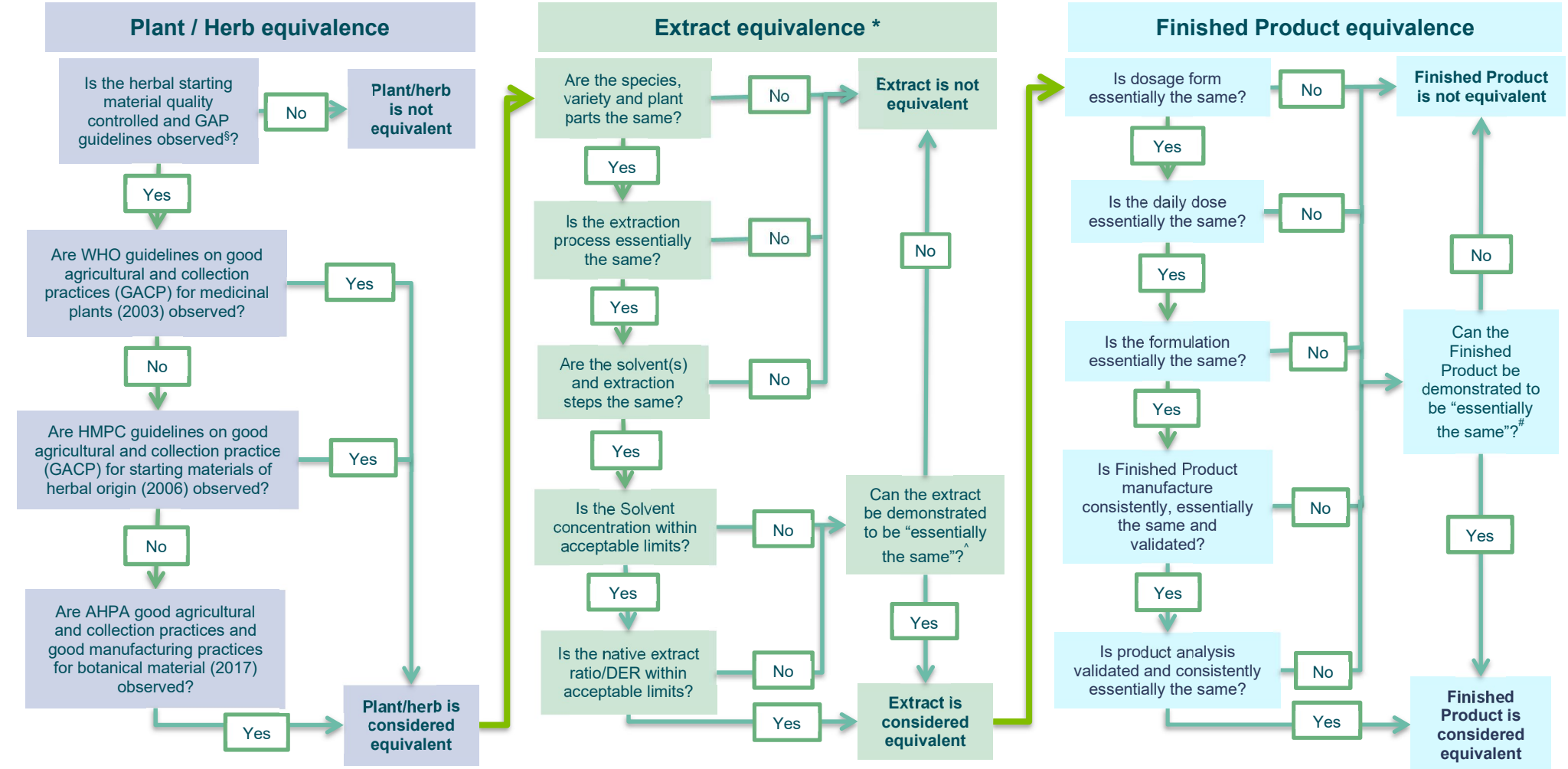
Figure 1 Equivalence and Quality Guidelines Flowchart



§GAP guidelines include, but not limited to:
WHO 2003 http://apps.who.int/medicinedocs/pdf/s4928e/s4928e.pdf
AHPA 2017 http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Documents/AHPA_Good_Agricultural_Collection_Practices_Good_Manufacturing_Practices_Botanical_Materials.pdf

* Adapted from TGA Guidance on Equivalence of Herbal Extracts in Complementary Medicines Version 1.0 February 2011 accessed September 2017
^ Profile Chromatogram

Pharmacokinetics ADME, release profile and dissolution. Daily dose is quantifiable. GMP principles, technical quality review audit.

Equivalence and Quality Principles for Herbal Medicines

Introduction

Natural medicines usually contain a profile of pharmacologically active components. This multi-active character of herbal medicines (in particular) lends itself to the view that the entire herbal extract is the active compound. The composition of the active compound and finished product must be essentially the same as that used in clinical efficacy trials to ensure that the medicine containing the active compound available to the consumer is clinically demonstrated as efficacious.

An added complication is that there is a degree of natural variation in the spectrum of the composition of the active compound due to seasonal variations including time of sourcing/ harvesting, climatic conditions and geographical situations. Therefore any variance must be assessed for impact to the degree of equivalence to the marketed product.

In addition, the extract may contain unidentified compounds that are not part of the spectrum of composition of the active compound that are not detected using the conventional analytical techniques in quality control. These undetected compounds may influence the solubility, absorption process and other pharmacokinetic properties of known (and also unknown) extract components, potentially contributing to the pharmacodynamic effect(s). This implies the limitations of specifications, that even extensive specifications with numerous different physical and chemical parameters are not sufficient to guarantee that a herbal extract can be referred to as “essentially the same”. A designation of “essentially the same “ can only be granted if key steps, including from the plant origin (e.g. species and variety) to a fully characterised and well-defined manufacturing process which includes extensively validated in process controls, are implemented in acknowledgment that the process defines the product.

If the plant /herb starting material is not quality controlled and therefore not equivalent, or if the extract cannot be demonstrated as equivalent, or if the finished product cannot be demonstrated as equivalent, as described in Figure 1, then the evidence used to support any efficacy claims can only be matched at the level of equivalence achieved (either plant or extract or finished product level).

Plant / Herb Equivalence

The traceability of herbal raw materials for use in herbal medicines is essential to avoid the risk of adulteration and to deliver consistent quality in products to the consumer. The production and primary processing of the plant / herb has a direct impact on the quality of the active components. A robust quality assurance system for the collection, harvest and primary processing of the plant material is essential as a foundation to ensure consistent composition of the active compound. There are a number of Good Agricultural Practice guidelines that should be complied with, including but not limited to:

- American Herbal Products Association. March 2017. Good Agricultural and Collection Practices and Good Manufacturing Practices for Botanical Materials http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Documents/AHPA_Good_Agricultural_Collection_Practices_Good_Manufacturing_Practices_Botanical_Materials.pdf*

- European Medicines Agency's Committee on Herbal Medicinal Products Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin, (2006) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003362.pdf*

- WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants. (2003) http://apps.who.int/medicinedocs/pdf/s4928e/s4928e.pdf*

*Accessed September 2017.

Extract Equivalence

Extract Equivalence has been described in detail in the TGA Guidance on Equivalence of Herbal Extracts in Complementary Medicines Version 1.0 February 2011 (https://www.tga.gov.au/publication/guidance-equivalence-herbal-extracts-complementary-medicines accessed September 2017). Parameters that influence the quantity and change the composition of the spectrum of components extracted from a herbal material can result in an extract that is not equivalent and is a separate and distinct good. It may be possible to demonstrate that extracts are essentially the same by quantitative assessment as well as qualitative assessment of the chromatographic profiles, when the change in parameters does not significantly affect the quality or spectrum of extract components. The spectrum of components that have been extracted may not necessarily be affected by factors which affect the quantity of the native extract obtained (a change in the native extract ratio/drug extract ratio-DER). It is expected, however, that a change in plant part, species or variety, extraction process or solvents used will have a profound effect on the spectrum of components, which may be reflected in the expression of the native extract ratio / DER and create a separate and distinct good that cannot be demonstrated to be essentially the same.

Demonstration of equivalence, 'essentially the same', from extracts to finished products

For a native extract to demonstrate a bridge to a finished product, the equivalence must be shown via comparability of the pharmacokinetic and pharmacodynamics properties of the two native extracts. This is appropriate for such studies that use a component/marker or metabolite in blood that has been directly demonstrated to correlate with the biological effects of the product and no other component is considered relevant to therapeutic action as shown in the original clinical trials that underpin the claim to efficacy.

Finished Product Equivalence

Natural medicines can be regarded as therapeutically equivalent if they have the same active compounds, meeting the same applicable standards (concentration, quality, purity and identity), the same dose and the same dosage form without relevant differences. Essentially the same/equivalent finished products should be standardised with sufficient quality controls to ensure consistent composition, safety and potency.

The medicines are considered essentially equivalent if they can demonstrate and possess comparable pharmacodynamics and pharmacokinetic properties, and safety profile.

Dosage Form

The dosage form is the format in which the medicine is presented to the patient. The format can impact the pharmacokinetics and bioavailability of the medicine and as a result, may impact the

final dose delivered to the patient. For example, a solid dose form requires dissolution before it can be absorbed, whereas a liquid does not. For oral dosage forms, the dynamics of the transit process will be different for various dosage forms. The rate and degree of dissolution vary between solid dose forms e.g. between a chewable tablet and a gelatine capsule. A delay in dissolution can impact the absorption influencing bioavailability and mechanism of action which may impact clinical outcomes.

For a natural medicine to be considered 'essentially the same' the dosage form must be the same as the original, or data must be provided to demonstrate that rate and extent of bioavailability after administration is similar to such a degree that the effects can be expected to be essentially the same. For solid dosage forms using the same route of administration, dissolution must be significantly similar, and for different dosage forms (e.g. liquid compared to solid) or different routes of administration (e.g. suppository vs oral) appropriate pharmacokinetics and pharmacodynamics profiles should be demonstrated *in vivo* to support therapeutic equivalence.

As outlined below, the different dosage forms will also have different ingredient formulations which may result in different physical, chemical and biological profiles, which may also impact not only stability profiles but also pharmacokinetics and pharmacodynamics of the finished product.

Daily Dose

The daily dose is the total amount and concentration of active component delivered in a 24 hour period to produce a therapeutic effect and is obtained through delivery of the dosage form containing the appropriate active compounds at the appropriate concentrations.

If a daily dose has been tested in clinical trials to deliver a certain efficacy with a demonstrated safety profile, then only an equivalent daily dose will deliver this same efficacy without changing the safety profile.

To be considered 'essentially the same' the natural medicine needs to show that it delivers the same daily dose as that measured in the clinical trials. Variation may be allowed for the individual dose and frequency, as long as the total daily dose is achieved (not exceeded or under delivered) and any variations to dosage form have been addressed, including adherence to dosage directions applied in the clinical trial (e.g. take with fat containing food or snacks, do not take with meals).

Formulation

For finished products to be equivalent they must contain the same active compound with no added active ingredients to enhance the overall finished product efficacy. In other words, if supportive clinical data was generated with a single herbal component, the data should not be used to support multi-herbal medicine formulations.

During the production of a medicinal product, excipients are added to the pharmacologically active compound/s of the product to render it in suitable dosage form to deliver efficacy to the patient. Excipients have no therapeutic actions, however their actions include facilitating manufacture of the finished product, aiding lubricity, flowability, disintegration, solubility, taste and stability, and facilitating the physiological absorption of the active compounds. Common dosage forms include oral (tablet, capsule, caplets, solutions, suspensions, syrups, elixirs, tinctures, powders, and lozenges), suppositories, topical creams, and parenteral (intravenous, subcutaneous injections). Solid dosage forms are complex to formulate and contain the greatest number of excipients while parenteral dosage forms contain the least. The selection of appropriate excipients depends upon factors including the route of administration, the active compound characteristics and the manufacturing process.

It is important that any product claiming to be essentially the same as a clinically tested product, is able to exhibit the same stability and pharmacokinetic/dynamic parameters and any physical/ chemical change to excipients in a formulation poses the risk that these parameters will change.

Limited changes to excipient type or amount should only be allowed where it can be shown that the stability and key pharmacokinetic/dynamic parameters are maintained once the changes have been made.

Manufacturing Process

The manufacturing process involves a series of quality controlled steps (using validated processes) to develop the active compound and then produce a finished product in dosage form ready to be administered to a patient, e.g. tablets are made via a process which follows certain steps such as milling, granulation, tablet compression and coating. Manufacturing should be supported by complete manufacturing and testing documentation to appropriate Good Manufacturing Practice (GMP).

Due to the fact each of the manufacturing steps in the process can be achieved utilising different machinery and methodology, any differences could subject the pharmacologically active component/s in the formulation to different damaging physical challenges, forces and stresses including temperature and pressure, which could affect the pharmacological outcomes derived from the resulting dosage form.

Limited changes to the manufacturing process should only be allowed where it can be shown and validated that the stability and key pharmacokinetic/dynamic parameters are maintained once the changes have been made.

Product Analysis

Physical, chemical and biological determinations of natural medicines, both qualitative and quantitative, are integral to ensuring that the manufactured finished product is validated to its label claim and composition. To that end, testing must be accurate, validated and specific to the finished product. Analyses can include testing to finished product specification for identity, strength, quality and purity. Quality control analyses may include microscopic, physical, chemical and biological parameters.

Natural medicine products claiming to be ‘essentially the same’ as a clinically tested product must be analysed and validated using the same analytical tests to demonstrate equivalence.

Demonstration of equivalence ‘essentially the same’ to a Finished Product

In the event that comparability of the source material cannot be established to substantiate that a product is ‘essentially the same’ as the finished product used in clinical trials, then a clinical trial is required that demonstrates statistically significant effects on the clinical endpoint for which a health claim is made.

In the event that comparability of the dosage form or formulation cannot be established to substantiate that a product is “essentially the same” as the finished product used in clinical trials, then it is required to demonstrate comparability of the pharmacokinetic and pharmacodynamics properties.

The changes in parameters that trigger the extent of demonstration of equivalence are summarised in Table 1.

Table 1. Changes in parameters and equivalence requirements.

Changed parameter of Finished Product	Pharmacokinetics/pharmacodynamics Sufficient if	Repeat Clinical Trial needed if
Dosage Form	No new active ingredients / components	New active ingredients / components
Dosage of active	No new active ingredients / components	ADME profile is not retained at new dose
Formulation changed	No new active ingredients / components	Excipient modifies ADME profile of the active ingredient changed or a new active ingredients
Manufacturing method changed	No modification to active components as tested in QA process and no new active ingredient	Change to or modification of active component in manufacturing method or new active ingredients / components
Analytical Methods changed	Analytical QA methods test for same active components and validated as equivalent	Analytical QA methods assay for a new marker or active component