Manufacturing of Herbal Extracts

Types, Techniques and Compliance

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Medicinal Plants - From Crop to Cure
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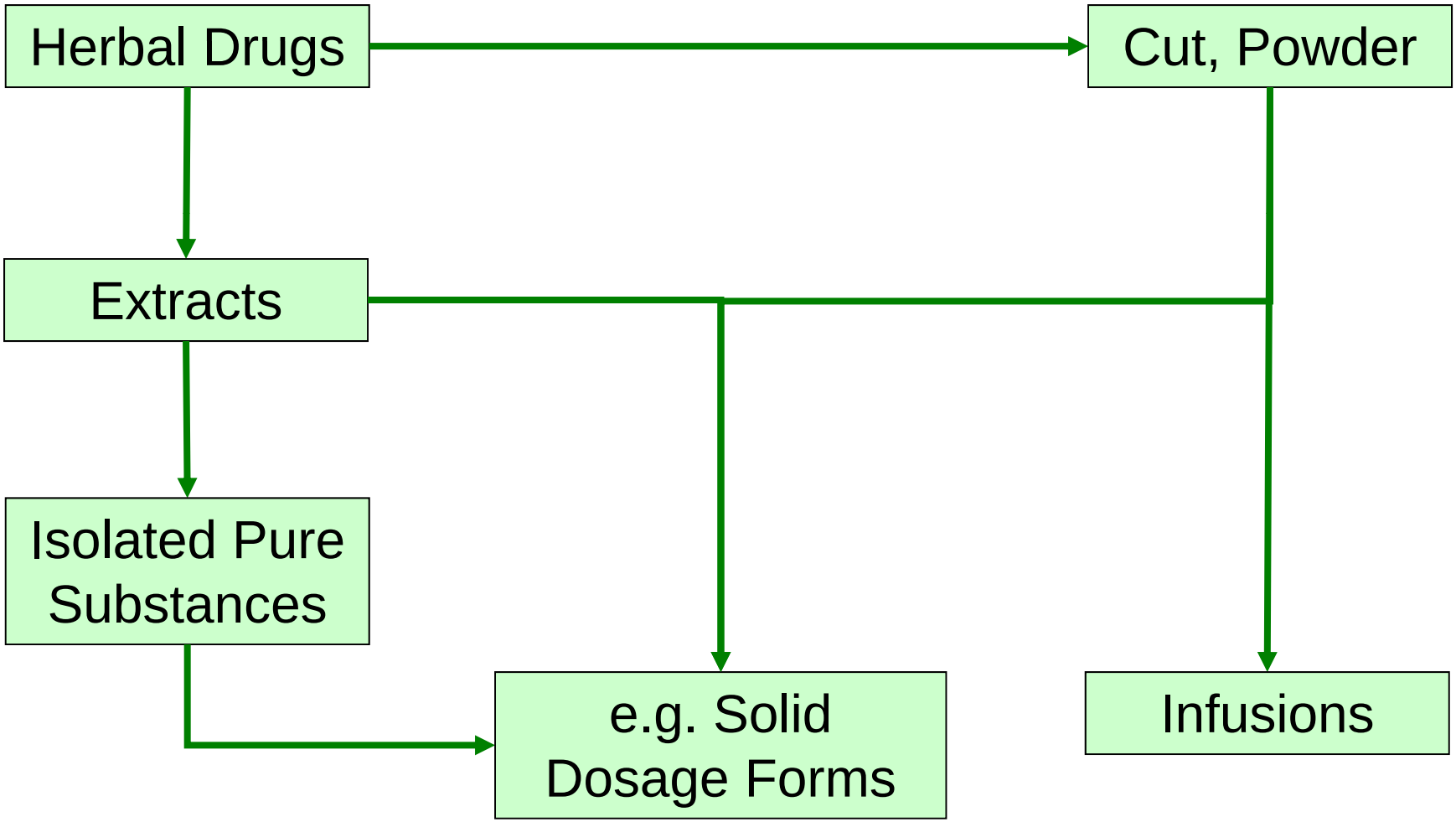
Herbals – Some Definitions



A Simple Example:

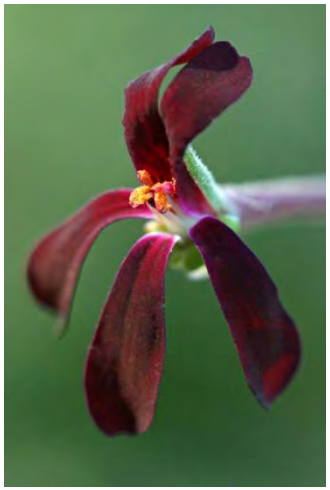
Equipment
Personnel

Product

Raw Material
Supplier

- Specifications
- Instructions
- Procedures
- Training
- Quality Control

A bit more complex:



- Specifications
- Instructions
- Procedures
- Training
- Quality Control

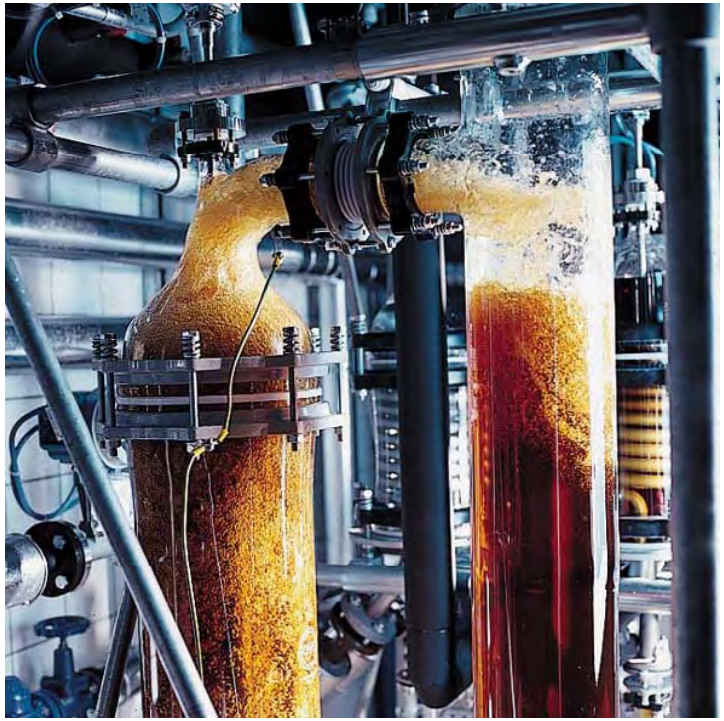
The key to success:

Control of the process from the beginning to the end

and

Quality assurance along the complete process chain.

Types of Extracts and Manufacturing



Extract Types of the European Pharmacopeia

Standardised Extracts

- are adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity; standardisation is achieved by adjustment of the extract with inert material or by blending batches of extracts.

Quantified Extracts

- are adjusted to a defined range of constituents; adjustments are made by blending batches of extracts.

Other Extracts

- are essentially defined by their production process (state of the herbal drug or animal matter to be extracted, solvent, extraction conditions) and their specifications.

„Purified“ Extracts in the European Pharmacopeia

- During Production of standardised and quantified extracts, purification procedures may be applied that increase these proportions with respect of the expected values; such extracts are referred to as ‘refined‘.

What makes a quantified extract work?

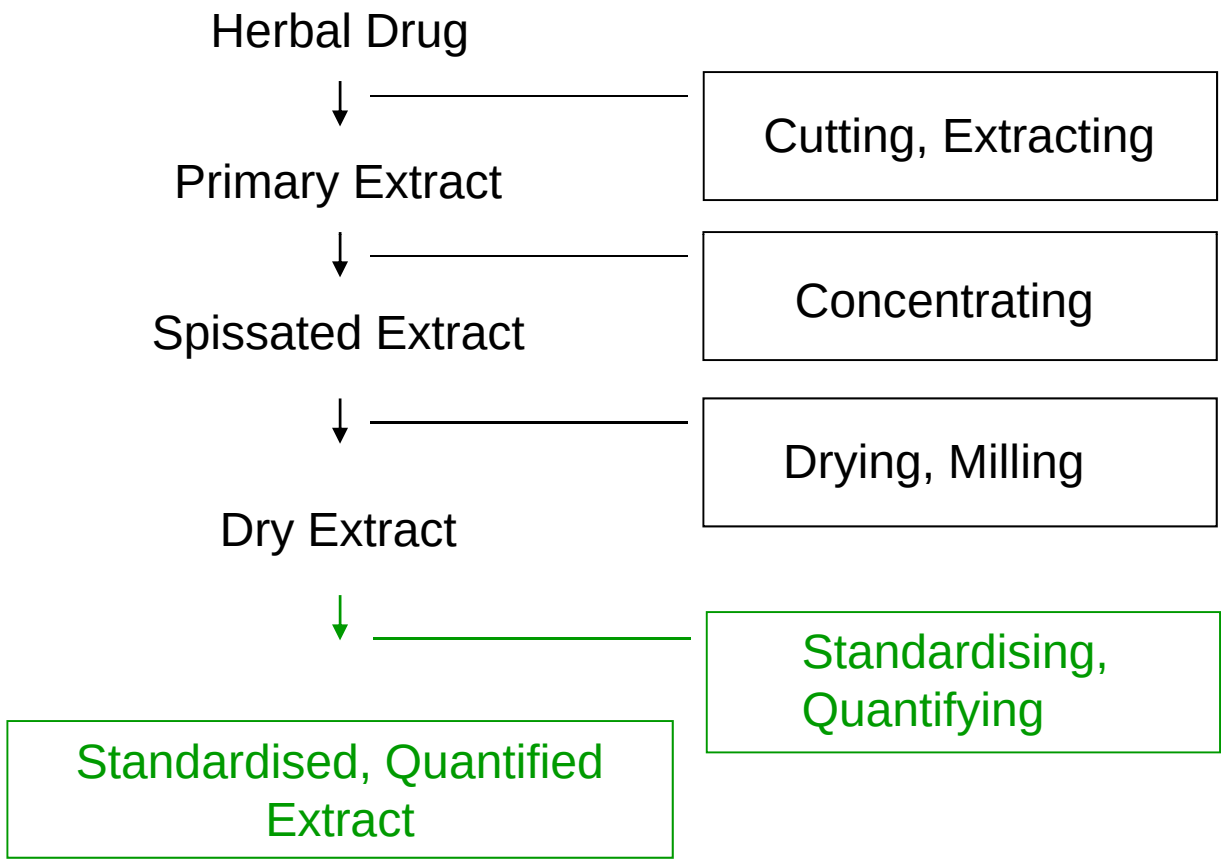
Example 1: St John‘s Wort Extract WS 5570

Pharmacological effect and pharmacological model	St. John’s Wort extract (WS 5570)	Hyperforin	Flavonoids	Hypericin
Antidepressant effect 1: model: Behavioural Despair Test after Porsolt	+	+	+	+/-
Antidepressant effect 2: model: acquired helplessness	+	-	-	-
Antidepressant effect 3: model: reserpine syndrome	+	+	-	-
Antidepressant effect 4: model: Behavioural Despair Test after Porsolt (rat) und tail suspension test (mice)	+	-	+	-
Re-uptake inhibition of neurotransmitters: model: synaptosomal uptake serotonin , noradrenalin, dopamine, GABA, l-glutamat	+	+	-	-
Increase of neurotransmitter concentration in brain: model: micro dialysis	+	+	+	-

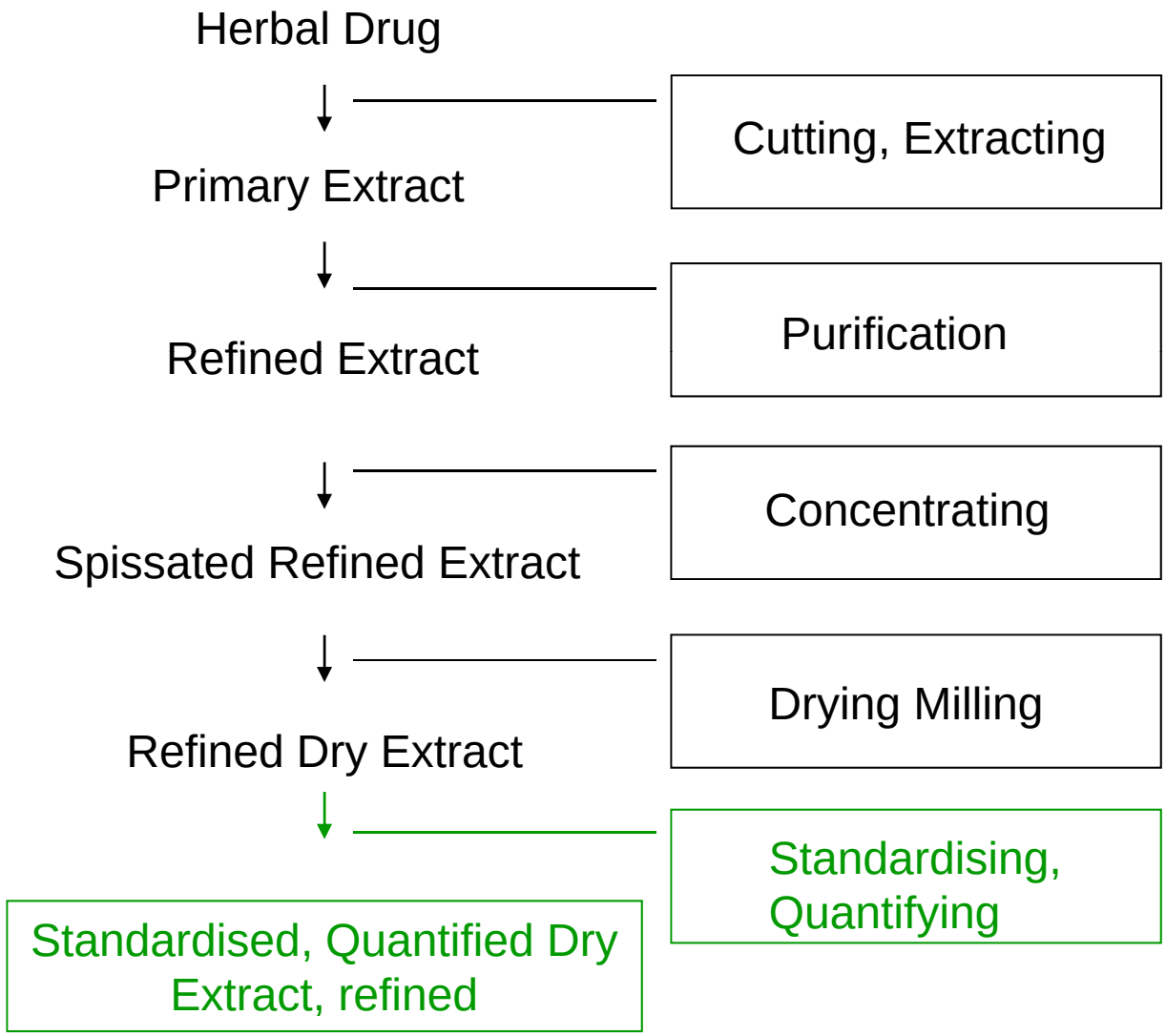
Example 2: Ginkgo biloba Extract EGB 761

Pharmacological effect and pharmacological model	Ginkgo biloba dry extract EGb761	Flavone & proanthocyanidin fraction	Bilobalide fraction	Ginkgolide fraction	remaining fraction
Protection against free radicals and antioxidant activities model: alloxan induced diabetes	+	+	-	-	+
Protection against ischemic damages and antihypoxic activity model: hypoxia and ischemia	+	-	+	+	-
Protective and curative effect on brain edema model: cytotoxic or postischemic brain edema	+	-	+	+	(+)
Influence on brain metabolism model: hypoxia	+	-	+	-	(+)
EDRF/NO-dependant vasorelaxation model: Saphenus artery and vein (rabbit)	+	+	-	-	-

Manufacturing of a Dry Extract



Manufacturing of a Purified Dry Extract



Techniques for Purification

- Precipitation
  - Temperature
  - Salt
  - Solvents
  - Reagents/ Chemical reaction
  - …
- Extraction
  - Pure solvents
  - Solvent Mixtures
  - CO_2
  - …
- Adsorption
  - Adsorption Chromatography
  - Ion exchanger
  - …

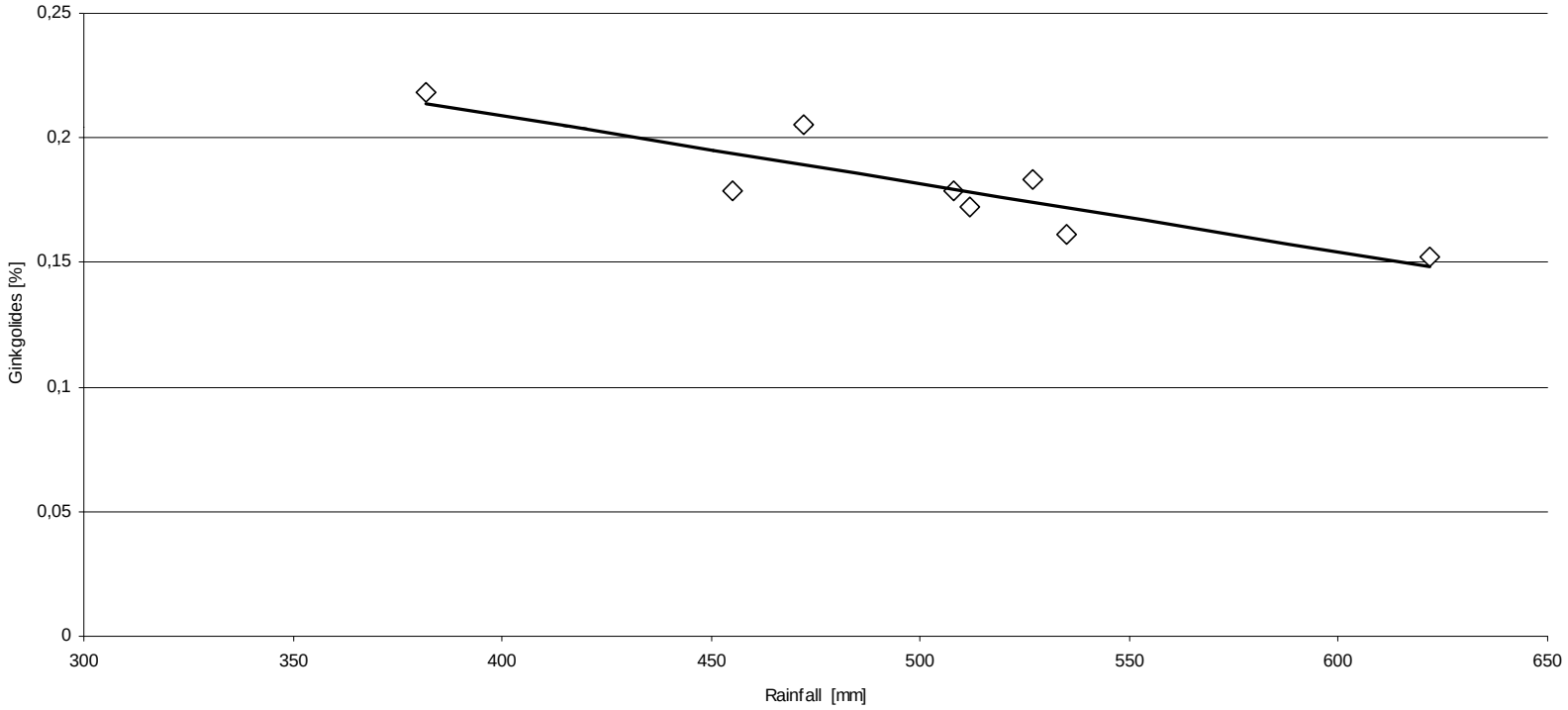
Reasons for a Refined Extract

- Enrichment of pharmacologically active constituents
- Depletion of ballast
- Depletion of toxicologically dubious components
- Equalisation of variable starting material

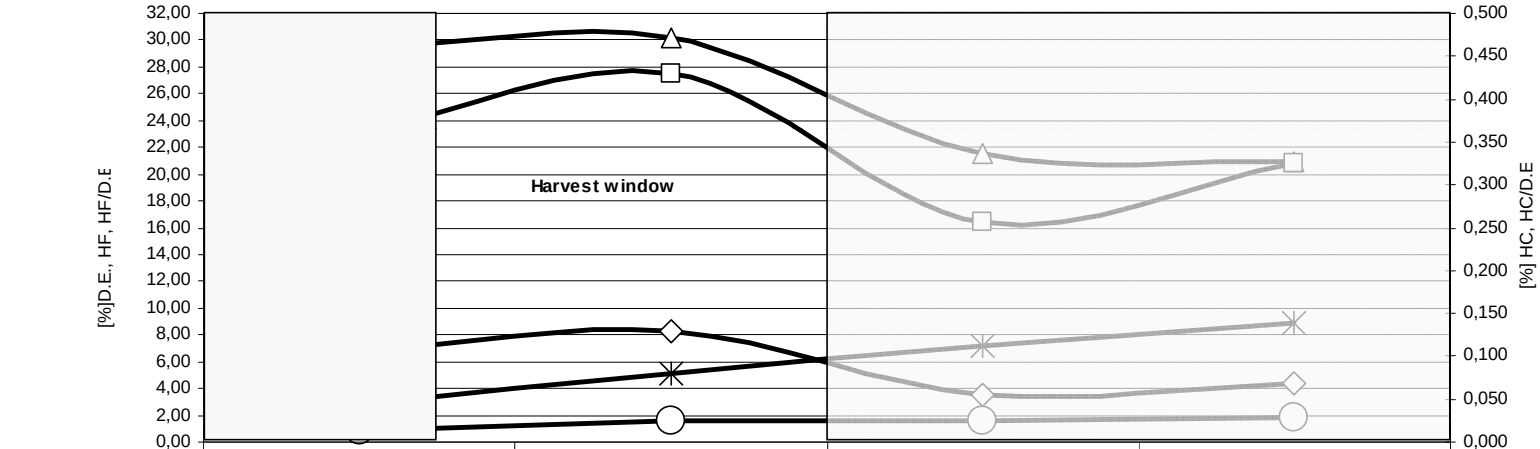
Critical Parameters for the Manufacturing of (Refined) Extracts

- Starting Material
- Manufacturing Process
- Final Adjustment by Blending

Correlation between amount of ginkgolides in ginkgo leaves and rainfall



Concentration of constituents in St. John's Wort in the course of flowering



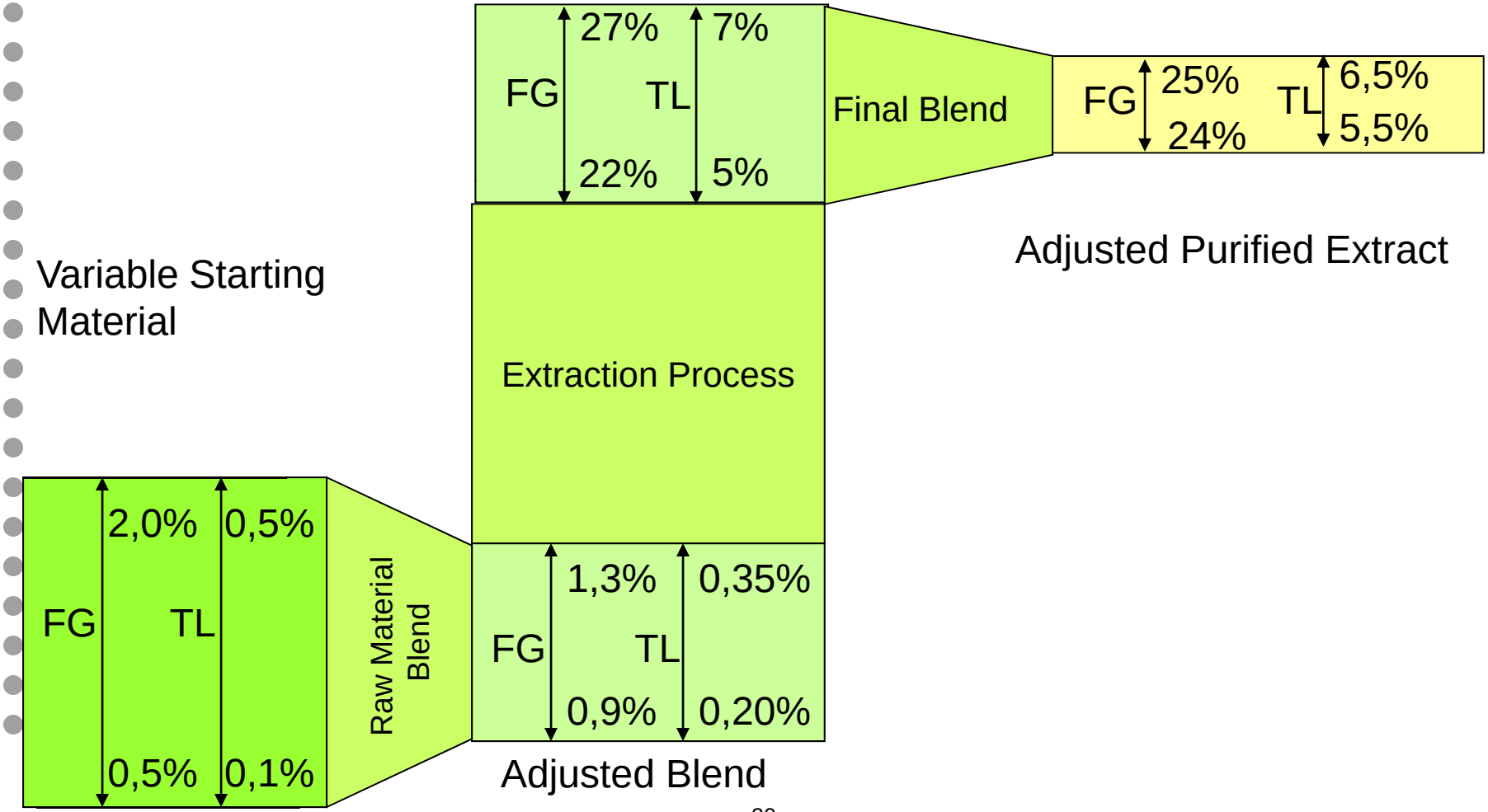
	Flowering (Start)	Flowering (Full)	Flowering (End)	Ripeness
Hyperforin (HF)	0,81	1,56	1,54	1,86
Dry extract (D.E.)	29,3	30,2	21,5	20,9
HF/D.E.	2,76	5,17	7,16	8,90
Hypericin (HC)	0,106	0,130	0,055	0,068
HC/D.E.	0,362	0,430	0,256	0,325

Blühzyklus

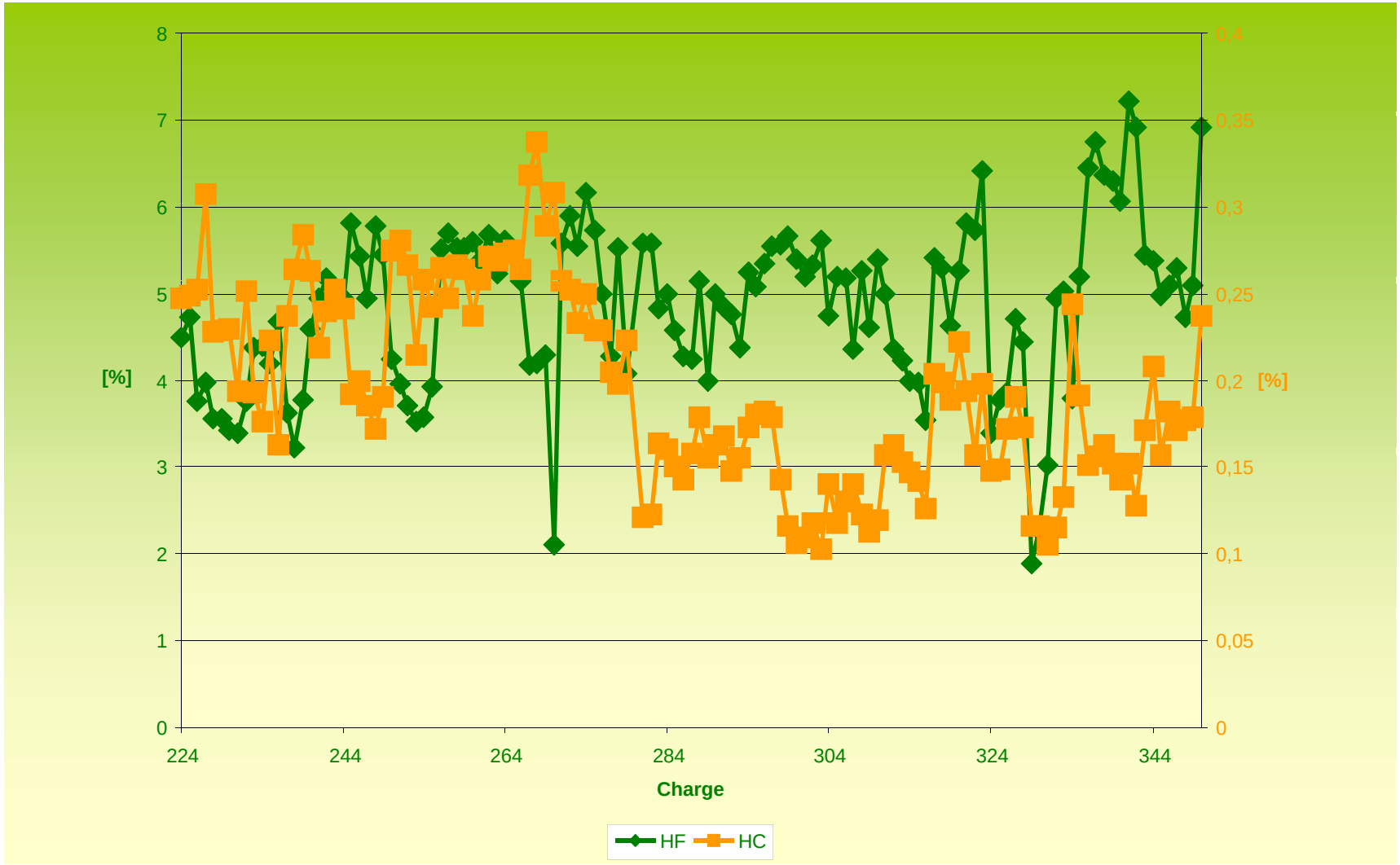
Blending of the Starting Material Hawthorn Leaves and Flowers

Lot	OPC/D.E. [%]	Amount [kg]	Bales
W102200	17,52	2.000	40
W100657	21,14	2.500	50
W104092	14,28	500	10
Sum Blend		5.000	100
OPC/D.E. Blend	19,01		
Yield 98 %	18,63		

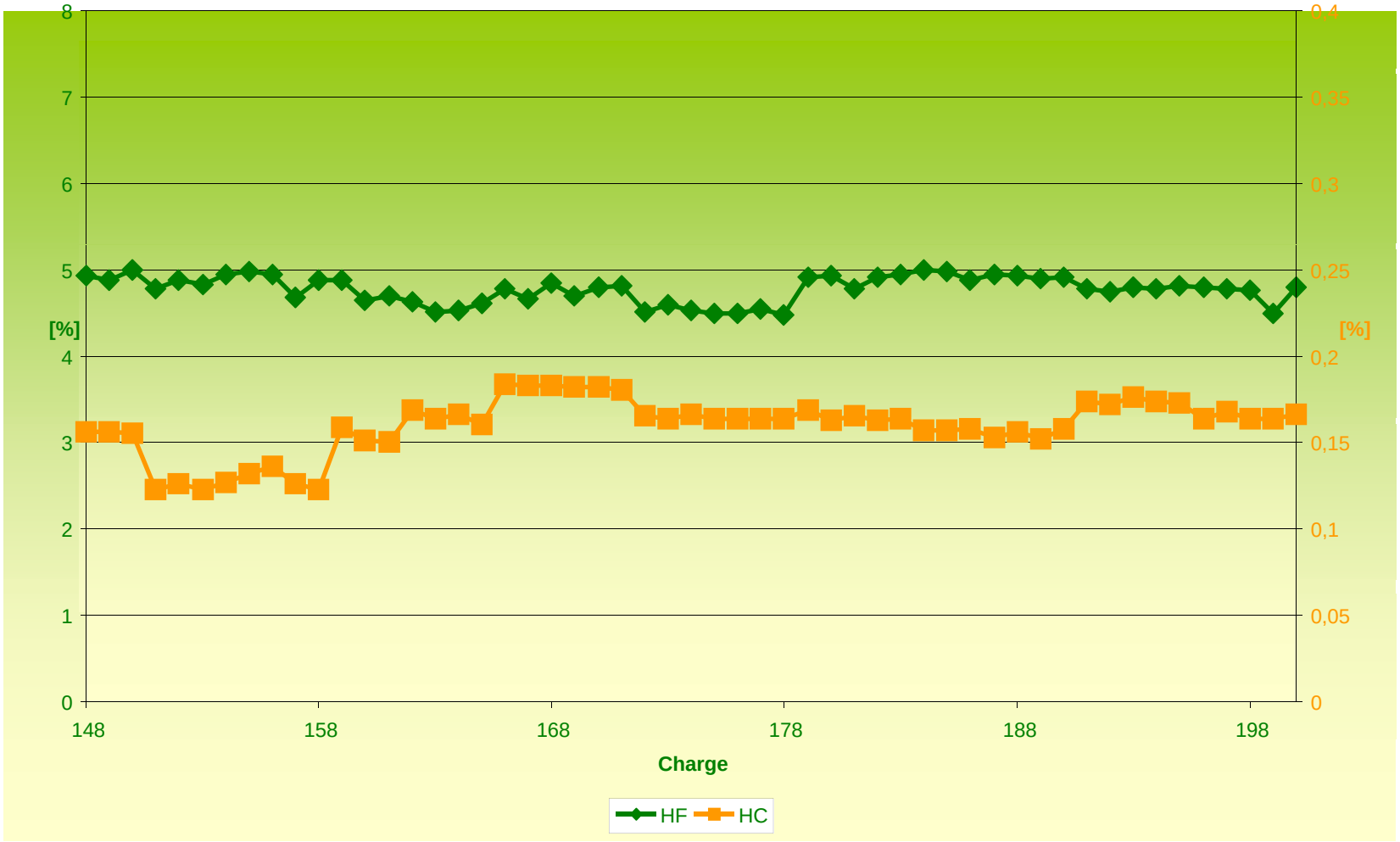
Scheme of Purification of Ginkgo Dry Extract



Contents of Hypericin und Hyperforin in St. Johns Wort Extract directly out of the Process



Contents of Hypericin und Hyperforin in St. Johns Wort Extract after Final Blending



Compliance and Quality Assurance

EU-GMP Guideline Part II (since 2005)

- Transfer of ICH Q7A (2000)
- Detailed Description of GMP requirements for active pharmaceutical ingredients
- Herbal API is especially mentioned.
- Special requirements (start of GMP requirements) are defined.

Scheme of the EU GMP- Guideline

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology : fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

GACP

European Medicines Agency
Evaluation of Medicines for Human Use

London, 20 February 2006
Doc. Ref. EMEA/HMPC/246816/2005

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

GUIDELINE ON GOOD AGRICULTURAL AND COLLECTION PRACTICE (GACP) FOR STARTING MATERIALS OF HERBAL ORIGIN

ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	July 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 October 2005
AGREED BY HMPC QUALITY DRAFTING GROUP	January 2006
ADOPTION BY HMPC	12 January 2006
DATE FOR COMING INTO EFFECT	1 August 2006

Note: the previous Herbal Medicinal Products Working Party Points to consider on GACP is now reintroduced as a HMPC Guideline. Only minor changes have been made to its contents further to the public consultation.

GACP

- GACP regulates handling with medicinal plants during cultivation, collection, storage and…

- „Primary Processing“
  (Cutting, Pressing, Distillation…)

Annex 7 – The confusion begins…

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products.

Activity	**Good Agricultural and Collection Practice**	**Part II of the GMP Guide†**	**Part I of the GMP Guide†**
Collection, Cultivation and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates			
Expression from plants and Distillation *			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

This table replaces the herbal section of Table 1 in part II of the GMP Guide.

Common Sense is needed

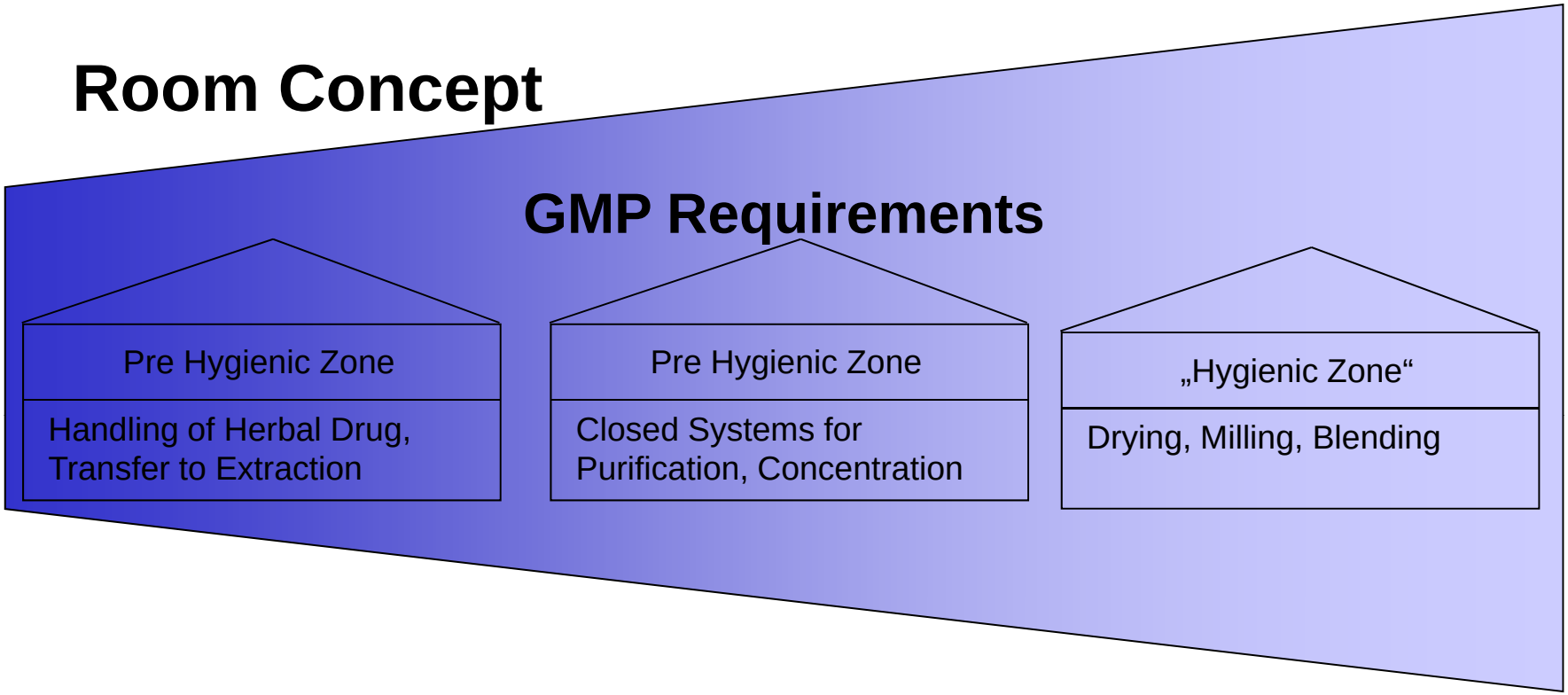
The manufacturer should designate and document the rationale for the
point at which production of the active substance begins.

For synthetic processes, this is known as the point at which
"Active Substance Starting Materials" are entered into the process.

For other processes (e.g. fermentation, extraction, purification, etc.),
this rationale should be established on a case-by-case basis.

… From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps.

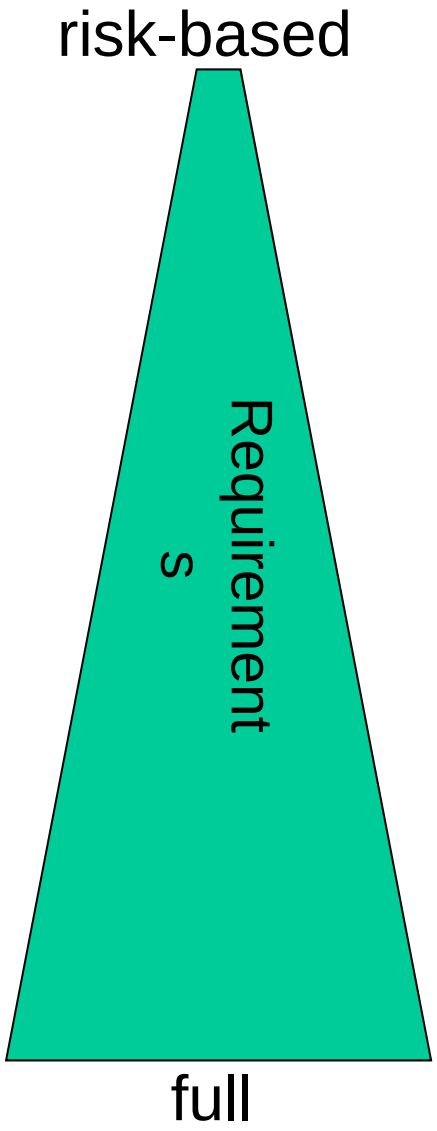
Room Concept



Herbal API	Collection of plants	Cutting and initial extraction	Further extraction		Physical processing and packaging

GMP

Risk Based Approach for Qualification and Validation



Herbal Drug

↓ — Cutting, Extracting

Primary Extract

↓ — Purification

Purified Extract

↓ — Concentrating

Spissated Purified Extract

↓ — Drying Milling

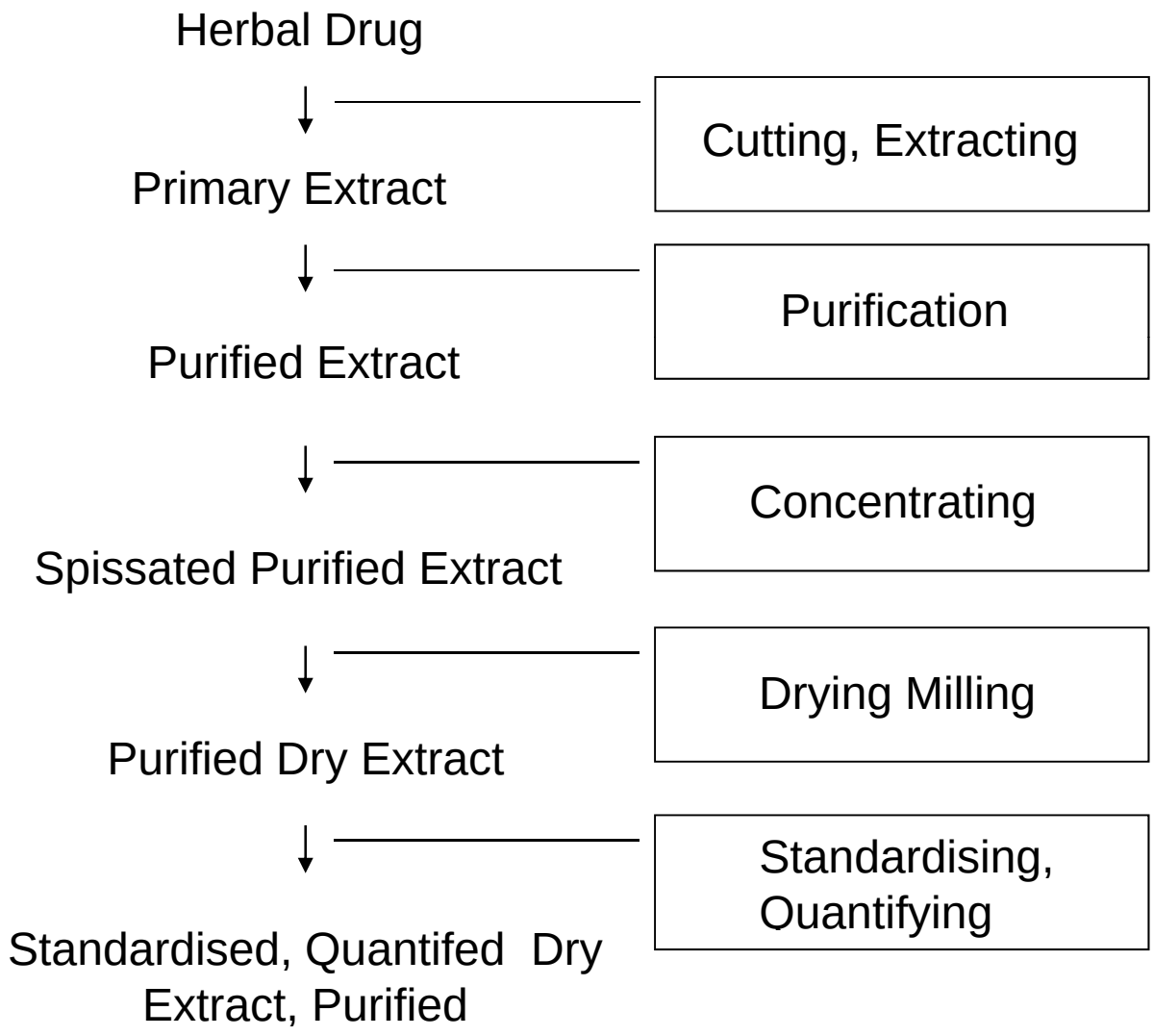
Purified Dry Extract

↓ — Standardising, Quantifying

Standardised, Quantified Dry Extract, Purified

Documentation

Complete Manufacturing and Testing Documentation




Thank you
very much for
your attention!