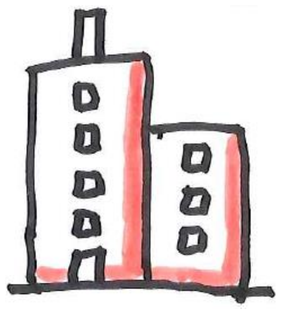
Dialogue between Members of the HMA-WG HMPWG and the Interested Parties AESGP, ECHAMP

Vienna - 17.10.2018

Determination of re-test dates of intermediate dilutions/triturations as a matter of GMP

DEFINITION OF THE PROBLEM

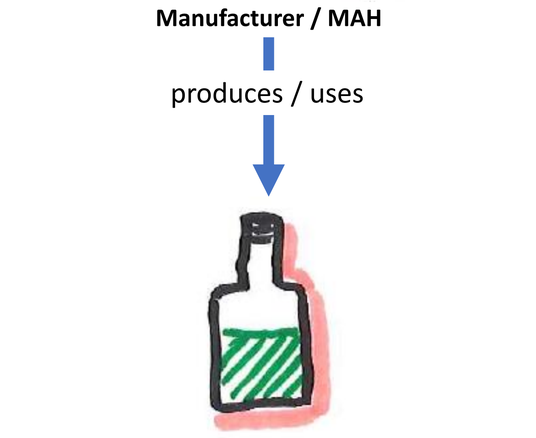


Manufacturer / MAH

produces / uses

1,000 stocks

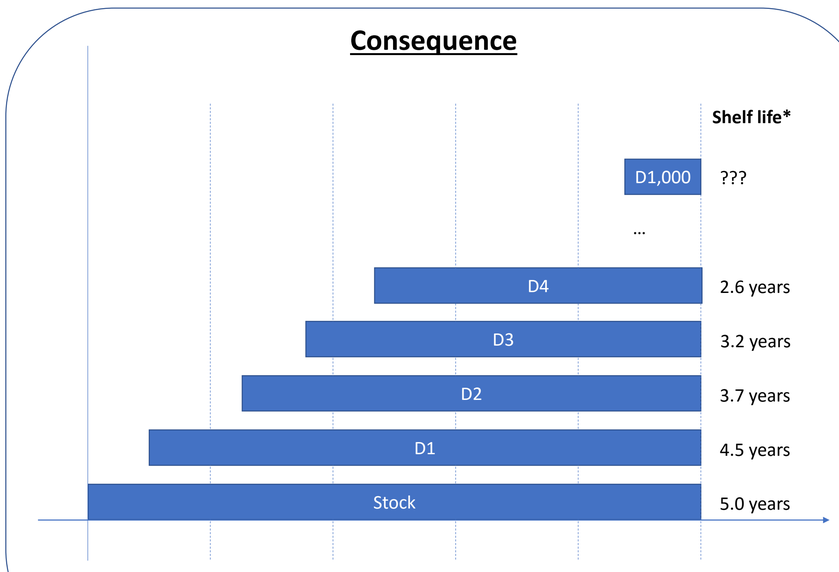
potentisation



4,000 series of potencies = 100,000 stored intermediate potencies

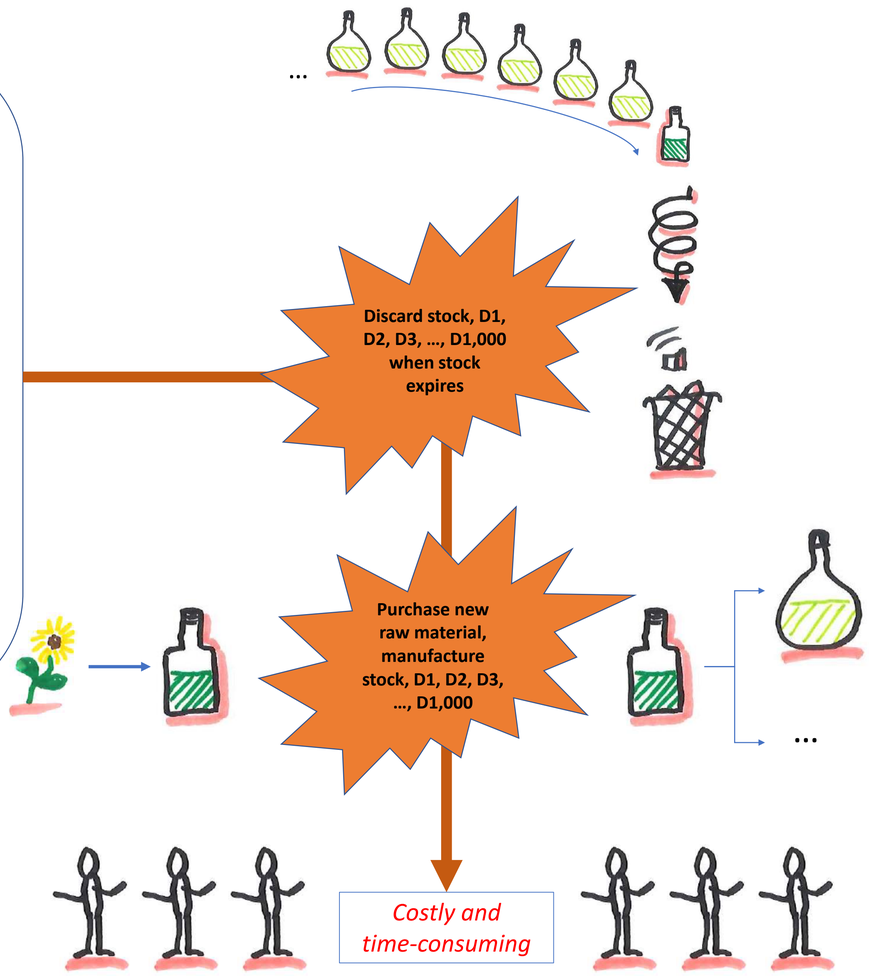
Finished products

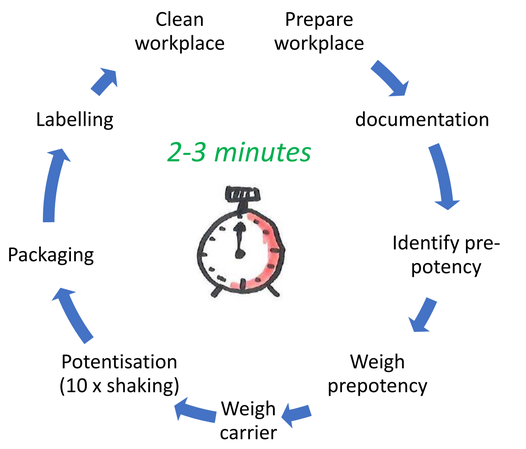
Consequence



*Note: These exemplary values base on the fact, that due to the enormous number of stocks intermediate potencies are usually manufactured only when actually needed for production.

Some agencies interpret the transfer of the expiry date of the stock <u>as an obligation and not as an option</u>

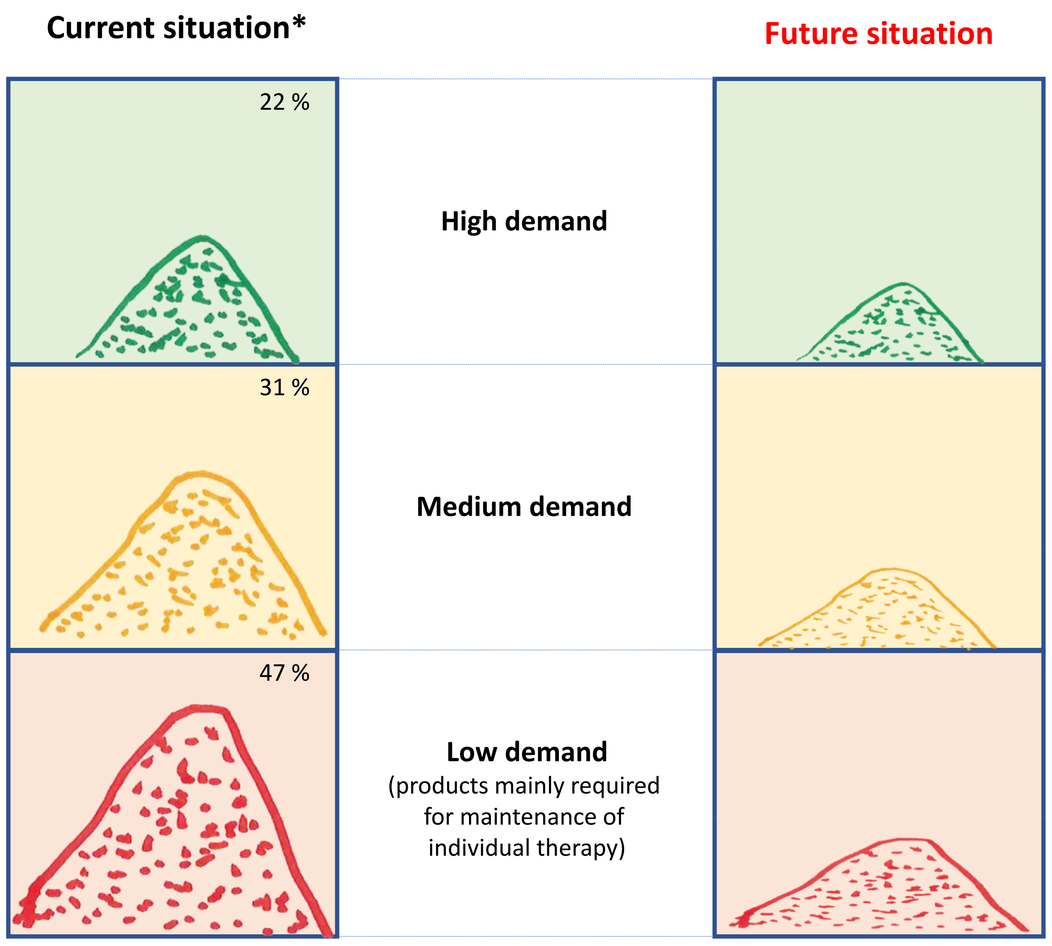




Manufacturing time for	D10	D30	D100	D1000
one product	0.5 h	1.2 h	1 day = 8 h	1 week = 40 h
ten products	5 h	12 h = 1.5 days	2 weeks	10 weeks
100 products	50 h ≈ 12 days	120 h = 3 weeks	20 weeks ≈ 4.5 months	100 weeks ≈ 2 years
1,000 products	500 h ≈ 4 months	1,200 h ≈ 7 months	200 weeks ≈ 4 years	1,000 weeks ≈ 19 years

Time needed for one person

IMPACT ON AVAILABILITY OF FINISHED PRODUCTS



* Average of ECHAMP-Members

PRINCIPLES FOR DISCUSSION

Directive 2001/83/EC, Annex I, PART III PARTICULAR MEDICINAL PRODUCTS, 3. Homeopathic Medicinal Products, Module 3, d) Stability tests:

Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof.

If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

HMPWG "Points to Consider on Stability Testing of Homeopathic Medicinal Products": *"According to Annex I of Directive 2001/83/EC stability data from homeopathic stocks are generally transferable to dilutions / triturations obtained thereof.* ***The expiry date of the dilutions / triturations may not exceed that of the homeopathic stock[4].***"

[4] *or the first possible homeopathic preparation according to the monograph, if required.*
(3.1 "Homeopathic stock" b))

Guidance on module 3 of the Homeopathic Medicinal Product Dossier (HMPWG, 2007): *Stability data or re-testing may also be required for all dilutions or triturations,* ***if the stability is not linked to the expiry date of the stock*** *and that are not processed immediately after testing.* (3.2.S.7.3 Stability Data)

This means:

- **The transfer of the expiry date and / or stability data is an option as a matter of convention if no individual stability data are available. These refer to the lowest preparations (stock or potency), for which stability data exist.**
- **Re-test of intermediate potencies before further processing is always possible. The definition of re-test dates based on stability data is possible for every intermediate potency.**

Further principles:

- **General guidance on stability testing is accepted and may be applied (e.g. stability testing of existing active substances and related finished products CPMP/QWP/122/02 Rev. 1 Corr. and ICH Q1D bracketing and matrixing designs for stability testing of drug substances and drug products CPMP/ICH/4104/00).**
- **Generally, all concepts shall be based on reasonable, pharmaceutically and scientifically meaningful approaches. They may vary as the companies´ assortments are different.**

→ Suchwise, the required quality of the used intermediate potencies is ensured.

Is data on re-test-dates for intermediate potencies a matter of the dossier or a matter of GMP?

- Not required according to Directive 2001/83/EC
  - Article 15
  - Annex I
- Intention of simplified registration was to give the possiblity to register under simplified requirements
- New requirement! ~1990 – 2010 never required in a dossier in any country.