Well-established use
–
principles, requirements and case-studies

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Well-established use

„When an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. In such cases, application for marketing authorisation may be based on results from the scientific literature.“

- Directive 2001/83/EC – Article 10a

By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature.

Directive 2001/83/EC, Annex 1:

Factors taken into account in order to establish a well-established medicinal use of constituents of medicinal products:

- the time over which a substance has been used,
- quantitative aspects of the use of the substance,
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature)
- the coherence of scientific assessments

Whilst data concerning use in clinical trials, compassionate use, named patient supply may be submitted, this cannot replace the requirement to demonstrate a systematic and documented use for more that 10 year period in the Union.

Question: How to understand systematic and documented use?

Case study: applicant supported efficacy and safety of the product by series of published studies. All studies were published in 1990s, all of them were from one group of researchers. No other information concerning product efficacy or safety has been available dated before or after that period.

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Question: What does it mean more than 10 years?

- Medicinal products with multiple indications
- Date of when data were published, date of actual use of medicine
- Exploratory/ confirmatory trials
- Question of data exclusivity

Question: Well-established medicinal use within the Community?

- Study taking place outside the EU
- Example: EU use was demonstrated by imports into the EU from the USA

Question: What is appropriate scientific literature?

published scientific literature - the text must be freely available in the public domain and published by a reputable source, preferably peer-reviewed.

- Published clinical trials/studies that meet today´s standards
- Meta-analysis, systematic reviews

- Trials/studies not meeting today´s standards
- Guidelines

- Literature reviews
- Textbooks
- Databases
- postmarketing experience with medicinal products containing the same active substance (justification needed)

assessment reports, EPARs etc. – do not meet the requirements of Annex I of Directive 2001/83/EC. (intended for transparency reasons)

- Search strategy must be described

- **All documentation, both favourable and unfavourable, should be communicated**

- **If documentation is lacking, a justification should be given.**

- missing information - justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking

- Copies of the full text of the literature, including necessary translations must be submitted.

- Tabulated clinical and non-clinical summaries in Module 2 shall be provided. Tables may not be necessary for very old, well known substances, but a proper justification will be required. Overviews always have to be provided.

Question: Could be any of the data in the well-established use application supported by applicant´s own studies?

- yes, however, they should be only supportive, pivotal studies should be bibliographic

> „In certain cases, studies may be provided only to support the relevance of the literature (used to demonstrate safety and efficacy of the active substance(s)), to the product intended for marketing. These are considered on a case by case basis by the competent authorities.“

- Data proving the **bridge** between literature and proposed product, PK data for extension application

Directive 2001/83/EC, Annex 1: The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

Bridging presented data and proposed product

- How? (PK study, dissolution)
- Comparing to what? (multiple products used in the lit reference, or those products are not on the market anymore)

Referral according to Art. 29 – furosemide:

The applicant was asked to justify that the literature provided in support of this application was applicable to the product applied for and to demonstrate that the potentially lower or higher exposure to furosemide, compared to those described in literature, would not influence efficacy or safety

- applicant submitted dissolution profiles comparing the product to the products already present on the market – similar
- however, furosemide is BCS class IV – extrapolation of pharmaceutical data is not supported
- submission of PK data (of different products) showing highly variable absorption – not sufficient
- claim that there is no correlation between absorbed furosemide and diuresis

- result: applicant failed to establish the relevance of submitted literature data to demonstrate safety and efficacy of proposed product. The provided data do not show that proposed product is similar to the products described in the submitted literature.

Bridging presented data and proposed product

Referral according to Art. 29 – loratadine:

The same as furosemide, however, pharmacokinetic study was submitted comparing the proposed loratadine with reference medicinal product

- 90% CI for loratadine was not between 80-125%
- the sensitivity of the assay used was considered insufficient to detect low concentration of parent compound and main metabolite

- result: applicant failed to establish the relevance of submitted literature data to demonstrate safety and efficacy of proposed product. The provided data do not show that proposed product is similar to the products described in the submitted literature.

Well-established use of fixed combination:

- Active substanes are already used as monocomponents

- Scientific literature must concern the systematic and documented use of the active substances in combination

- It is possible to include information on the individual active substances in the application.

Assessment of well-established use application

- Strict interpretation

  → used only in cases where all aspects of the safety and efficacy are demonstrated by reference to published scientific literature

  → well-established use application does not lower the requirements of safety and efficacy that must be met

- Application based on full dossier – with scientific literature instead of preclinical tests and clinical trials

  → Can be used as reference medicinal product
  (Case C-104-13, ECJ 23/10/2014)

Assessment of well-established use application

- Applicant is expected to submit the same information as for application according to the Art. 8(3) – the difference is the form of submitted data, not the content

- For guidance about the requirements, the EMA clinical guidelines are used

- All the information in the SmPC must be supported by the documentation

- All the indications, age groups, special population use must be supported by literature data

- For a missing data, certain amount of extrapolation is acceptable, however, justification is needed

    - It is a difficult task to prepare high quality dossier for well-established use application

Common problems concerning well-established use application:

- No available data for „older“ active substances
- Submitted studies/trials do not meet today´s criteria
- Submitted studies/trials do not concern requested indication, they do not concern requested strength, they do not include requested population
- Extension application of older medicinal product
- Missing justification

To conclude:

- It is not easy to prepare high-quality well established use dossier

- The requirements are evolving with time and with encountered issues in different case-studies

- Critical analysis of the data and justification of missing data are the most common problems with well-established use application from the pre-clinical and clinical point of view

Thank you for your attention!

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