Comparison and differentiation between clinical trials with medicinal products and scientific studies with nutritional products

The XIX. Int. Congress “Phytopharm 2015”
RFW-University, Bonn
20th - 24th July 2015
Herbal Medicinal Product

Definition according to Art. 1 of Directive 2001/83/EC:
Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Important impact of Directive 2004/24/EC:
All Member States may refer to one unique set of information on a herbal substance or herbal preparation when evaluating marketing applications for herbal medicinal products from companies. This reference information includes
- the therapeutic uses and
- a set of recommended safe conditions of use.
## Categories of Herbal Medicinal Products

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<th>Category regarding market access</th>
<th>Traditional medicinal use</th>
<th>Well-established use</th>
<th>Full/Mixed data application</th>
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<td>Basis and source of data</td>
<td>Sufficient safety data and plausible efficacy, mostly from <strong>bibliographic information</strong></td>
<td><strong>Scientific literature</strong> for recognised efficacy and an acceptable level of safety</td>
<td>Safety and efficacy data gained from (combination of) own clinical studies (and bibliographic data)</td>
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<tr>
<td>Characteristic</td>
<td>Traditional indications used for at least 30 years, including at least 15 years within the EU</td>
<td>Demonstration of similarity with literature for at least 10 years within the EU</td>
<td>Safety and efficacy data from the company’s own development (stand-alone application) combined with bibliography (<strong>mixed appl.</strong>)</td>
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<tr>
<td>Registration/Marketing Authorisation (MA)</td>
<td><strong>Simplified registration procedure</strong>: traditional use registration by a Member State</td>
<td>MA usually granted by a Member State or by the European Medicines Agency (EMA)</td>
<td>Granting of MA via the <strong>centralised procedure</strong>, if all conditions are met</td>
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Provisions according to Art. 16a(1) of Directive 2001/83/EC

1. **indications exclusively appropriate to traditional herbal medicinal products** which, by virtue of their composition and purpose, are intended and designed for use **without the supervision of a medical practitioner** for diagnostic purposes or for prescription or monitoring of treatment;

2. exclusively for administration in accordance with a **specified strength and posology**;

3. way of administration: oral, external and/or inhalation preparation;

4. **period of traditional use has elapsed**, i.e. herbal medicinal product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the EU;

5. **data on the traditional use** are sufficient: in particular the **product proves not to be harmful in the specified conditions of use** and the **pharmacological effects or efficacy** of the medicinal product are **plausible on the basis of long-standing use and experience**.
Submission of data and documents according to Art. 16c of Directive 2001/83/EC:

- **Information for Marketing Authorisation application** (e.g.,
  - Qualitative and quantitative particulars of all the constituents of the medicinal product,
  - Description of the manufacturing method,
  - Description of the control methods employed by the manufacturer,
  - Manufacturing license)

- **Results of pharmaceutical (physico-chemical, biological or microbiological) tests**

- **Summary of Product characteristics (SMPc)**

- Any authorisation or registration obtained by the applicant in another Member State, or in a third country/ details of any decision to refuse to grant an authorisation or registration

- **Bibliographical or expert evidence** to the effect that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years preceding the date of the application, incl. at least 15 years within the EU

- **Bibliographic review of safety data together with an expert report**, and where required by the competent authority, data necessary for assessing the safety of the medicinal product

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24/07/2015
Use of EU Herbal monographs

Herbal monographs contain the view of the Committee on Herbal Medicinal Products (HMPC) on all information necessary for the use of a medicinal product containing the herbal substance or preparations described in the monograph:

- Use
- Intention
- Safety information

A final European Union monograph can be used in application reference material by a marketing-authorisation applicant and by a traditional-use-registration applicant.

**well-established-use part:** demonstrated with sufficient safety and efficacy data

**traditional-use part:** accepted on the basis of sufficient safety data and plausible efficacy
Definition according to Art. 2 of Directive 2001/20/EC:

Any investigation in human subjects intended to

– discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of one or more investigational medicinal product(s), and/or

– to identify any adverse reactions to one or more investigational medicinal product(s) and/or

– to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s)

– with the object of ascertaining its (their) safety and/or efficacy
Novel Food:
Food that has not been consumed to a significant degree by humans in the EU prior to 1997, when the first Regulation on novel food came into force (Regulation (EC) No. 258/97).

Dietary Food for special medical purposes:
Food intended for the exclusive or partial feeding of people whose nutritional requirements cannot be met by normal foods.

Food Supplements:
Concentrated sources of nutrients (or other substances) with a nutritional or physiological effect.
Application to the European Food Safety Agency (EFSA)

Conditions to gain an Approval: Prove, that the novel food
- will not present a danger for the consumer,
- mislead the consumer or
- differ from foods or food ingredients, which they are intended to replace to such an extent that their normal consumption would be nutritionally disadvantageous for the consumer.

Assessment of wholesomeness of foods, incl. food ingredients: scientific challenges and alternative approaches

Information necessary to support an application for the placing on the market according to Commission Recommendation of 29 July 1997 (97/618/EC)

Excerpt of Key Issues for for the assessment of Novel Foods and Novel Food ingredients:
- Concept of „substantial equivalence“ with particular reference to foods produced by modern biotechnology: If a new food or food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety (approach to compare a potential new food with its conventional counterpart)
Key Issues (Cont.)

- **Compositional Analysis:**
  - prerequisite for nutritional and toxicological assessments
  - standardized and validated methods to ensure quality and consistency of the data
  - determination of the content of critical nutrients (both macro- and micronutrients) and any critical toxicants and anti-nutritional factors

- **Toxicological testing programme: Animal feeding studies**
  - the maximum level of dietary incorporation achievable without causing nutritional imbalance should be the highest dose level
  - the lowest dose level should be comparable to its anticipated role in the human diet

- **Allergenic potential:** the immunological reactivity of individuals who react to the traditional food counterpart should be tested in vitro and in vivo (e.g. skin prick tests or clinically supervised double blind placebo controlled challenges) against the Novel Food
Dietary food for special medical purposes

- **Directive 1999/21/EC, Art. 5 (1):**
  - Enable **efficient official monitoring** of dietary foods for special medical purposes: **Notification** of the manufacturer/importer to the **competent authority** of the Member States where the product is being marketed by **forwarding** to it a **model of the label used for the product**

- **Regulation (EC) 953/2009:**
  - Annex: List of nutritional substances that may be used in the manufacture of foods for special medical purposes
  - following requests submitted by interested parties, **new substances have been evaluated by the European Food Safety Authority (EFSA)** and added to the list of nutritional substances

- **New Regulation on Food for Specific Groups from 20 July 2016**
  - general compositional and labelling rules
  - specific compositional and labelling rules for foods for special medical purposes, including those for infants
• Directive 2002/46/EC:
  – **Protection of consumers against potential health risks** from those products and to ensure that they are not provided with misleading information
  – **Safety**: **Harmonised list** of vitamins and minerals that may be added for nutritional purposes in food supplements (Annex I)
  – **Art. 5 (1a)**: Maximum levels for intake of vitamins and minerals:
    o **upper safe levels** as established by **scientific risk assessment based on generally acceptable scientific data**
    o intakes of nutrients from the normal diet or other dietary sources (**reference intake amounts**)
  – **Art. 10**: Facilitation of **efficient monitoring of food supplements**: Member States may require the manufacturer or the person placing the product on the market in their territory to **notify the competent authority of that placing on the market** by forwarding it a **model of the label used for the product**
• Regulation (EC) 1924/2006 („Health Claims Regulation“):
  – **Objective:** To ensure that any claim made on a food’s labelling, presentation or advertising in the European Union is **clear, accurate and based on scientific evidence**
    o *nutrition* claims (such as "low fat", "high fibre")
    o *health* claims (such as "Vitamin D is needed for the normal growth and development of bone in children")
    o all permitted nutrition claims and
    o all authorised and non-authorised health claims
Authorisation Procedures:

- Establishing the EU list of permitted “Function” claims (“Article 13 list”):
  - Relating to the growth, development and functions of the body
  - Referring to psychological and behavioural functions
  - On slimming or weight-control

EU-countries provided national lists of approximately 44,000 health claims to the Commission. These were consolidated into a list of some 4600 claims and sent to the European Food Safety Authority (EFSA) for evaluation.

  - Adoption of the list of permitted “Article 13” health claims by European Commission

- Authorisation procedure for individual applications [Article 14 (1)(a) and 14 (1)(b)]:
  - Risk reduction claims and
  - Claims referring to children's development
  - Involvement of the applicant, the competent national authorities, the EFSA and the European Commission
• Health Claims Application: **Reporting of human studies** (e.g. design, methodology, statistics and results)

• **Missing information** may lead to **delays in the review process** (e.g. request of additional information to the originating source) or **preclude a complete scientific evaluation** (e.g. if the additional information requested is not available).

• “**Consistent reporting** of human studies submitted for the **scientific substantiation of health claims** in a **harmonised and standardised way** would **benefit both EFSA and its stakeholders**” (Info Session on Applications, Parma/Italy, 20th November 2013).
Thank you for your kind attention.

Do you have questions?