EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Translating benefit-risk information into product information

PCWP and HCPWP joint meeting
Workshop on regulatory and methodological standards to improve benefit/risk evaluation of medicines

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EU product information

Package Leaflet

Assessment report

Summary of Product Characteristics

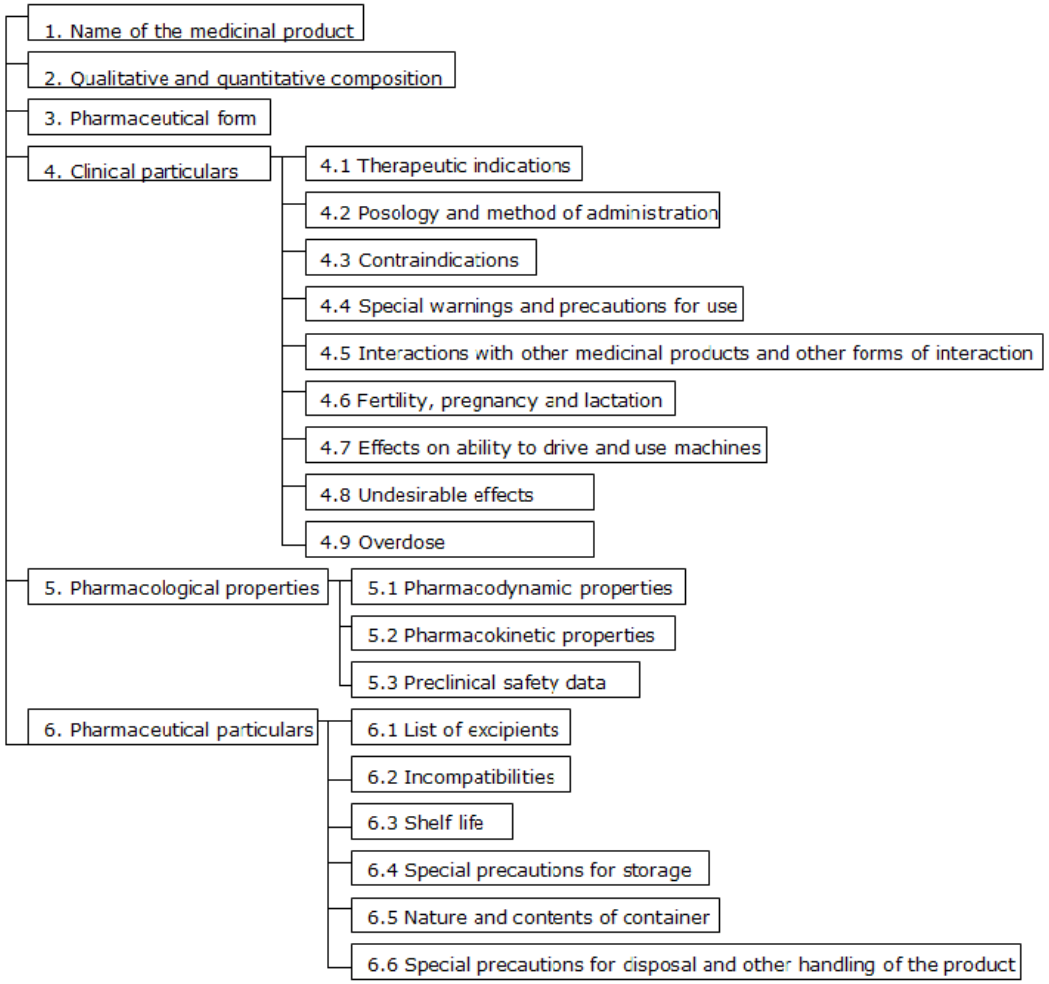
EMEA/PCWP/HCP WG report on information on benefit-risk of medicines *(23 June 2009, EMEA/40926/2009)*

❖ Assessment at population level *vs* individual use

- ➢ Always communicate benefits and risks together
- ➢ Clear information to help choose most appropriate treatment
- ➢ Clear description of benefits and risks, both qualitative and quantitative
- ➢ Factors which may influence a benefit or a risk in an individual should be clearly described

❑ Concise information + detailed data

Summary of product characteristics (SmPC) - What is it and what does it contain?



SmPC information on benefits

Section 5.1 "**Pharmacodynamic properties**" summarises the benefits of the medicine in presenting:

- Its mechanism of action
- The main results of the clinical trials supporting the marketing authorisation
  - In giving the main characteristics of the patient population studied
  - And presenting the effects qualitatively and quantitatively
- Additional clinically relevant information in special populations:
  - In a balanced way (i.e. informing on uncertainties as appropriate)
  - Including study results in the paediatric population

SmPC information on risks

- Section 4.8 "**Undesirable effects**" provides:
  - A **summary of safety profile** (most serious and most frequently occurring adverse reactions)
  - A tabulated list of all adverse reactions with their respective frequency category
  - Information characterising specific adverse reaction
  - Information on clinically relevant differences in special population

- Information on a specific risk is also reflected in section 4.4 "Special warnings and precautions for use" when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk

SmPC information for individualised care

- SmPC information first addresses the recommendations that apply to the general population
- The SmPC also provides dedicated information for these groups of patients, when relevant information is available
- Information can be presented under specific subheading within each relevant section of the SmPC
  - Paediatric population, Elderly, Hepatic or renal impairment, Other concomitant diseases, Genomic factors, …
- Or in dedicated section;
  - e.g. Drug interaction, Pregnancy/Lactation, Driving, Overdose

Product information and older people:
how to assist informed prescription and safe therapeutic use

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Keywords
Older people; Product information; Summary of product characteristics (SmPC), Package leaflet; Co-morbidity; European Medicines Agency (EMA); Polypharmacy; Clinical trial; Adverse reaction reporting; Treatment adherence; Formulation; Packaging.

Abstract
Older people are the fastest growing population group and often the main users of medicines. Despite some challenges, it is possible to improve information on the use of medicines in older people, which will help in increasing safe and effective use, including treatment adherence. Provision of good information relies on collection of adequate data both before and after marketing authorisation. The summary of product characteristics (SmPC) should reflect the current knowledge and experience in older people, in particular any clinically relevant identified differences with the younger population. Because of the higher co-morbidity, clear information on risk factors and drug interactions will be of utmost value for older people. Consistent information should be presented in the package leaflet, which plays an important role in assisting patients to adhere and use the medicine safely. Attention should also be paid to older people's needs in term of formulation, packaging design and readability of the package leaflet. The European Medicines Agency's related initiatives are presented in this article.

Introduction

Worldwide, we are experiencing a demographic shift towards an older population, with the very old (>80 years) representing the fastest growing population group. In Europe, the old-age dependency ratio (the ratio of those over retirement age to those of working age) is projected to more than double, from 26.2% in 2011 to 52.6% by 2060.[1]

In many therapeutic areas, older people are the major users of medications, and polypharmacy plays an important role, with a mean of five medications per person.[2] How is the regulatory system adapting to the challenges posed by an ageing population?

In 2011, the European Medicines Agency (EMA) adopted its geriatric medicines strategy,[3] based on two main pillars:

- The demonstration of an appropriate benefit–risk balance in the population that will use the medication
- The appropriate reflection of these findings in the "product information" in order to assist informed prescription and safe use.

Drug development requirements in the elderly are addressed by the recent Question and Answers addition to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E7 guideline.[4]

In this article we explore challenges and possible solutions to the problem of providing concise, accurate, safety and efficacy data relevant to prescribing medicines for older people, and how the packaging and product information (SmPC, package leaflet and labels) could help in increasing treatment adherence.

Focusing on the needs of a real-life population

When developing and evaluating a medicine, we should keep in focus the people who will ultimately use it, and what their needs are. Chronic illness, complex medication regimens, and polypharmacy are significant risk factors for drug interactions and poor treatment adherence; in addition, changes in drug pharmacokinetics and pharmacodynamics put the older population at increased risk of adverse reactions. When significant use of a drug is expected in older patients, particular consideration of their specific needs should be integrated into the development and evaluation of medicines, which must take into account how medicines will be used in practice.

The ability to take or administer medicinal products as intended may be affected by a number of physical factors, such as poor hydration, poor dexterity, visual and cognitive impairment, swallowing difficulties and gastrointestinal changes. Reading labels or package leaflets, opening packaging, swallowing tablets – all seemingly simple tasks – can turn into barriers to correct use as one ages.

Medication non-adherence, which is due to numerous preventable factors, affects all age groups, but older adults face increased risk due to polypharmacy. Non-adherence impacts directly on the patient's clinical management and can lead to considerable disability, morbidity, increased numbers of emergency visits, prolonged hospital stays, re-admissions and even increased mortality.

A wide range of erroneous medication-taking behaviours have been identified: omitting or multiplying doses; discontinuing medication prematurely; taking medication at the wrong time; or storing it inappropriately.

Appropriate product information, packaging and pharmaceutical drug design can and should assist in overcoming these problems.

The EMA has a strong working relationship with patients and healthcare professionals:[3] the agency's message is that it considers as a priority the provision of high quality information on medicines, tailored to the specific needs of the individual patient, and the need for relevant information on geriatric medicines was acknowledged at the March 2012 EMA workshop on medicines for older people.

Need for evidence-based information

In order to be able to provide accurate information to the patient and the prescriber, the first requirement is the establishment of the benefit–risk balance. This concept is meaningful only within the

SmPC challenges in practice

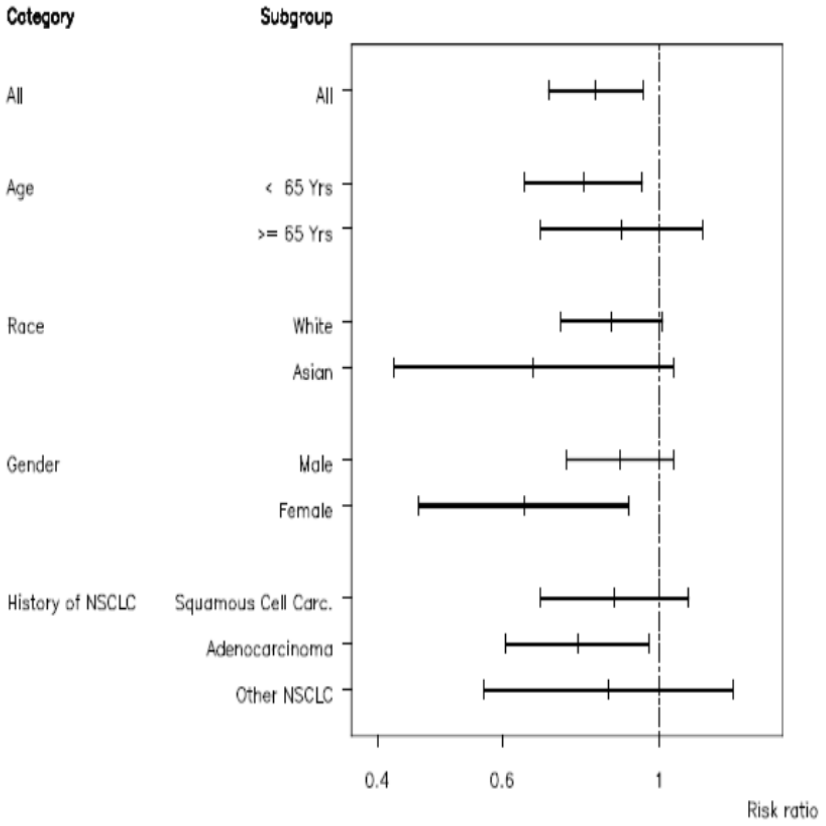
- Concise vs comprehensive information / Transparent vs unduly alarming
  - Efficacy - Main results (statistically compelling and clinically relevant)
  - Safety - Causal relationship – Frequency of adverse rections
  - Subpopulation with relevant clinical different efficacy or safety
  - Missing information
  - Drug interactions
- Consistency between products and with therapeutic guidelines

Which efficacy results?

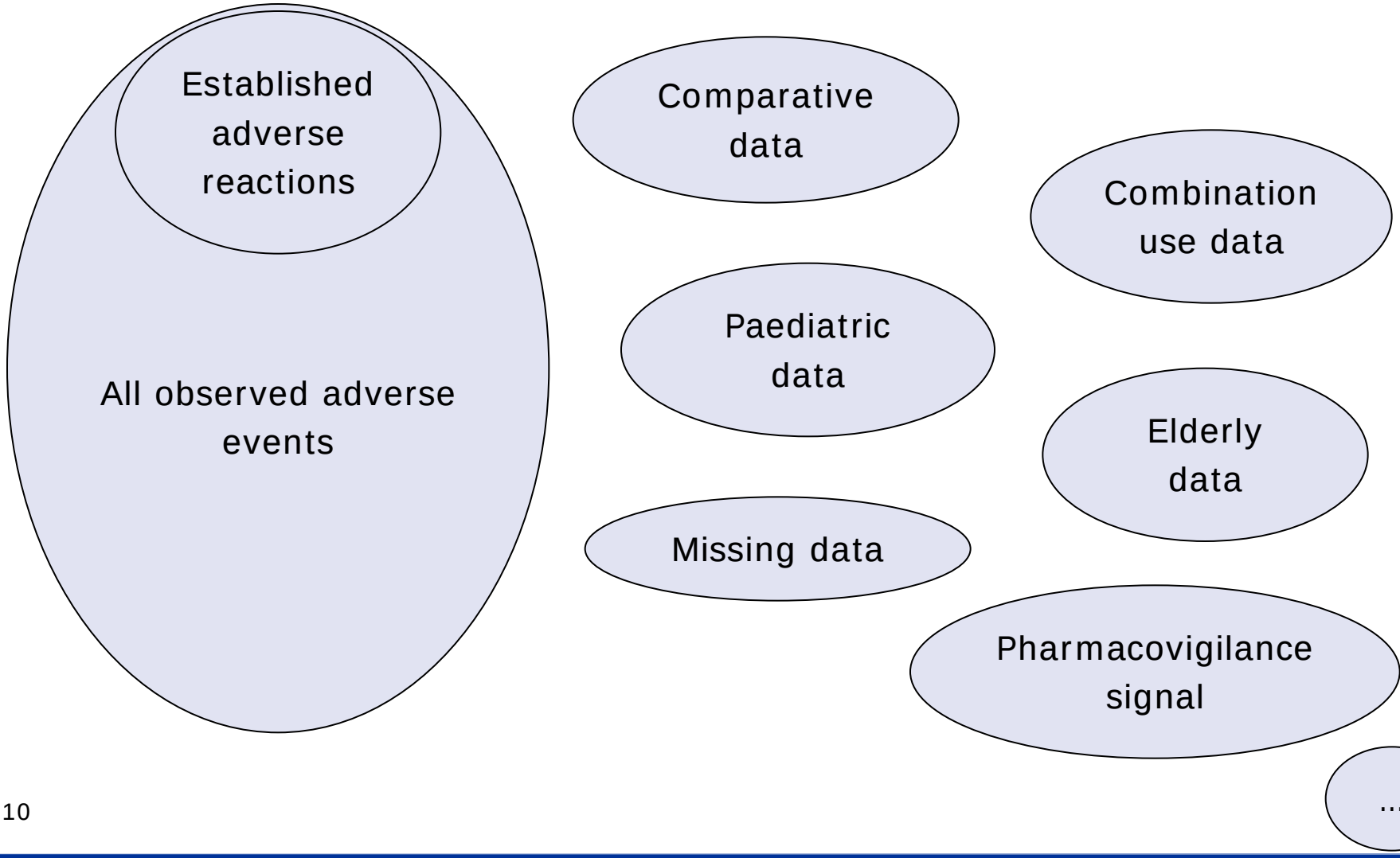
Examples of endpoints in Rheumatoid Arthritis

- ACR20 (50, 70) response criteria
- DAS28
- swollen joint count
- tender joint count
- Patient pain
- physical function (e.g. HAQ, AIMS)
- patient global assessment of disease
- physician global assessment of disease
- Clinical remission
- radiographic evidence
- acute phase reactants (e.g. erythrocyte sedimentation rate, C-reactive protein)
- ...

Example of analyses



Which safety information?

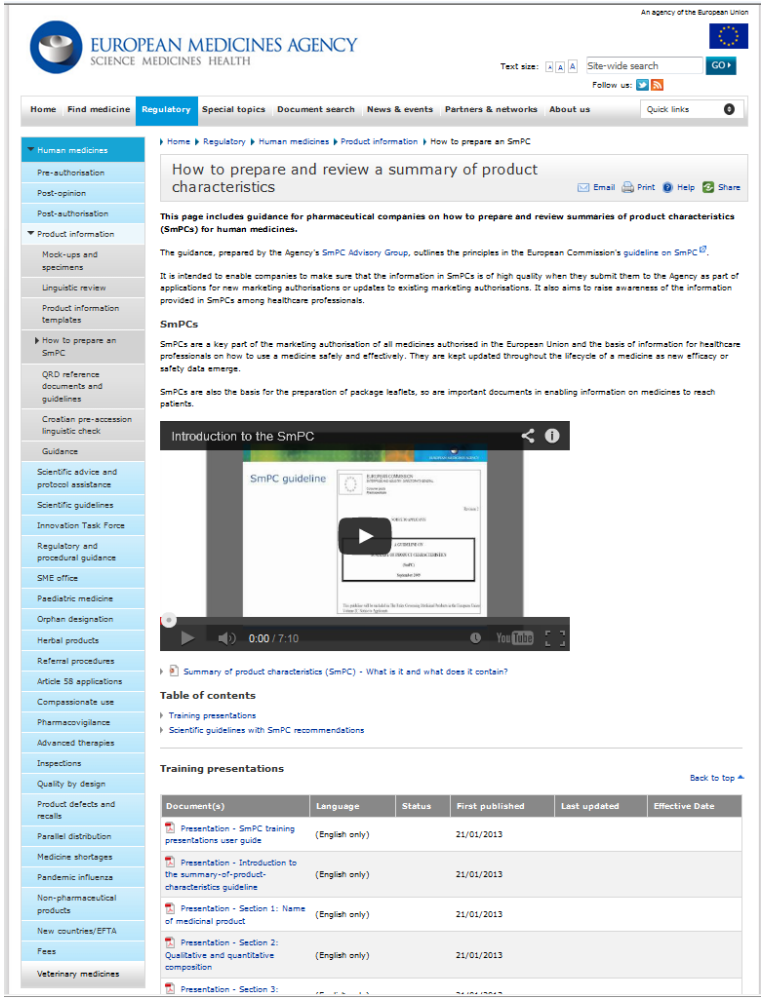


Consistency between products and with therapeutic guidelines

- Products developed at different times
- Different developments (endpoints, standard of care, populations, vs placebo or active comparator, in monotherapy or in combination, …)
- Different companies and marketing authorisation procedures
- Different standards of care
- Science is evolving

Promoting compliance and consistency

SmPC Advisory Group



Package leaflet

- Information on benefit-risk of medicines: patients', consumers' and healthcare professionals' expectations - EMEA/40926/2009
  - *"the package leaflet could progress from a document on the use of the medicine (which may create fear in patients when reading the warnings and list of undesirable effects) toward an "information tool". It should provide more information on benefits in understandable terms."*
- To help supporting adherence to treatment

QRD product information annotated template (from July 2011) - benefits

[Information on the benefits of using this medicine]

[On a case-by-case basis, information on the benefits of the treatment could be included in this section, as long as it is compatible with the SmPC, useful for the patient, and to the exclusion of any element of a promotional nature (in accordance with art 62 of Directive 2001/83/EC). This could be included under a separate subheading, e.g. entitled "How X works".

The information should be depicted in a clear and condensed way. For example, information could relate to:

- signs and symptoms of the target disease, in particular for non-prescription medicines, but also for medicines to be taken "on-demand" (e.g. treatment of migraine);
- the benefit(s) of taking the medicine could be summarised (e.g. "this medicine reduces pain associated with arthritis", "this medicine has been shown to reduce blood sugar, which helps to prevent complications from your diabetes"). This would be particularly important to encourage adherence to the treatment, e.g. for long-term and prevention treatment. Benefit may be described in terms of prevention of disease complications (e.g. anti-diabetic), if established. The timing of the effect may also be described if useful. In any case, information must be compatible with the SmPC, in particular section 5.1;
- information on the amount of time the medicine usually takes to work may be presented if relevant for the patient (pain-killer, antidepressant, etc).

<You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.>.]

Information on benefit in the PL

- Clinical trials data should be interpreted in their context
- How far can results be presented qualitatively and quantitatively in the PL in lay language?
- Are quantitative measures suitable in the PL or should information be presented semi-quantitatively (e.g. delay, reduce, improve, prevent)?
- Could comparative benefit information be presented?
  - vs placebo?
  - vs active comparator?

Is information robust, evidence-based, clinically relevant and patient-oriented?

QRD product information annotated template
4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

[The section should generally be divided into two sections bearing in mind that there should be sufficient patient-friendly description of the overt clinical signs and symptoms to enable the patient to recognise all side effects which may occur as set out in section 4.8 of the SmPC:

1) the most serious side effects need to be listed prominently first with clear instructions to the patients on what action to take (e.g. to stop taking the medicine and/or seek urgent medical advice. The use of the words "straight away" or "immediately" may be helpful in this context).

2) then a list of all other side effects, listed by frequency and starting with the most frequent (without repeating the most serious included above).

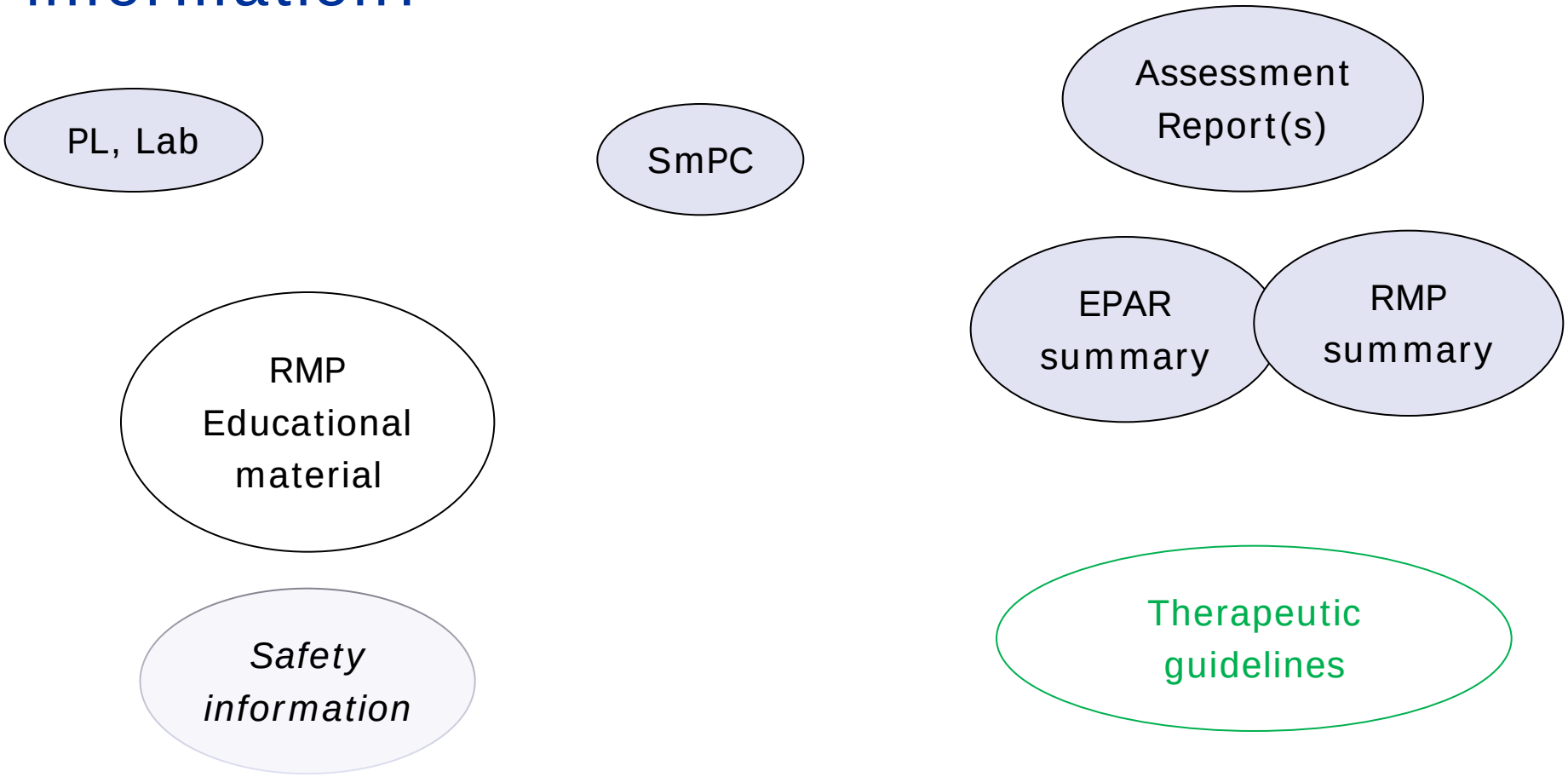
Within each section mentioned above, side effects should be arranged by frequency. The following frequency convention is recommended:

Reporting of side effects

Area for future discussion?

- More information?
  - Comparative data?
  - Reference to therapeutic guideline?
- Abstract?
- Link to other documents (assessment reports, RMP, PL, …)?
- Increased granularity?
- More involvement of stakeholders in SmPC review (two-way communication + value judgement)?
- … *eHealth (e-prescribing tools) context?*

Strengthening the link between the different information?



Strengthening the link between the different information?