Safety Measures in the new Pharmacovigilance System

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Antworten, auf die es ankommt.

Documentation and reporting requirements: Centralisation

Regulation Art. 24

The Agency … shall set up and maintain the Eudravigilance database … to allow competent authorities to access the information at the same time and to share it.

Directive Art. 107 and 107 a

MAHs shall be required to submit information electronically to Eudravigilance….

Member States shall … submit the reports electronically to the Eudravigilance database. MAHs shall access those reports through Eudravigilance.

Assessment

- Simplified reporting rules for MAH.
- Only 1 safety database as data source and working tool for ALL CA: data and IT quality ?
- Is it possible to avoid additional national requirements ?

Documentation and reporting requirements: Centralisation

Regulation Art. 28a

Regarding medicinal products authorised in accordance with this Regulation, the Agency and MAHs shall take the following measures: …

1c) monitor the data in the Eudravigilance database to determine whether there are new or changed risks or whether there are changes to the risk benefit balance.

3. The Agency and MAHs shall inform each other in the event of new or changed risks or changes to the risk benefit balance being detected.

Assessment:

- Expanded role for EMEA: search/monitor signals
- Role of nat. CA ?

Documentation and reporting requirements: Expansion

Directive Art. 107
MAHs shall record all suspected adverse reactions in the Community or in 3rd countries brought to their attention, whether reported spontaneously by patients or HCP or in PASS.

(CT cases acc. CT-Directive)

Assessment:

- Consumer assessment regarded as equivalent to HCP-assessment !
  ➔ All Consumer-Reports reportable like HCP-Reports

- Case WITHOUT Consumer assessment also reportable, if causal relationship „cannot be excluded“ ? (by whom ?)
  ➔ Event = „reaction“: „Event-Reporting“ ⇔ suspected cases
  ➔ Follow-Up at treating physician without patient consent ?

Documentation and reporting requirements: Expansion

Directive Art. 107

- MAHs shall submit electronically to Eudravigilance, no later than 15 days following the receipt of the report, all serious suspected adverse reactions that occur in the Community and in 3rd countries; 90 d for non-serious reports from within Community.
- These reports will be made available to the MS through Eudravigilance.
- MS report all cases directly reported to them to Eudravigilance within 15 d

Assessment:

- ALL serious cases (listed/unlisted, Consumer/HCP) from EU and non-EU
- ALL non-serious, listed/unlisted, consumer/HCP from EU in 90 d
  - Includes non-interventional studies ! (Exceeds CT requirements!)
  - Transition period ? None
- ALL reports DIRECTLY to EMEA, NOT to national authority (Not even for purely nationally approved products !)!
- CA: Concern about domestic reports and Rapp/RMS role !
- No individual scientific case assessment any more !

Our objective ....

But instead of ……

Documentation and reporting requirements

Directive Art. 107

- The MAH shall accept reports of adverse reactions electronically. These reports shall be collated at one point within the Community.

Assessment:

- Electronic „reporting form“ on company websites or by e-mail to company accounts.
- No transitional period (as for EMEA).
- Paper reports must still be accepted by companies

Documentation and reporting requirements

Directive Art. 107a

1. MS to record all suspected adverse reactions that occur in their territory which are brought to their attention from HCPs and patients.
   Suspected adverse reactions" from patients ? (Definition ?)

   MS shall ensure that reports of such reactions are submitted by means of the national medicines safety web-portals. Paper reports ?
2. MS shall, within 15 days … submit the reports electronically to Eudravigilance. MAHs to access reports through Eudravigilance.
   No more cases on BfArM Website, but Eudravigilance access for MAH.
3. MS shall ensure that reports of medication errors brought to their attention in the framework of suspected adverse reaction reporting for medicinal products are made available to Eudravigilance and to any authorities responsible for patient safety within that MS.
   MS (only ?) responsible for „medication errors" (Definition ?)

Documentation and reporting requirements: Transparency

Regulation Art. 24

- Eudravigilance to be fully accessible to MS, EMEA and Commission. Also accessible to MAHs to the extent necessary for them to comply with their pharmacovigilance obligations.
- HCPs and the public have appropriate levels of access to Eudravigilance, with personal data protection being guaranteed.
- The data held on Eudravigilance shall be made publicly accessible in an aggregated format together with an explanation of how to interpret the data.
- Individual adverse reaction reports may be requested by the public. Reports to be provided by EMEA or MS within 90 days.

➔ Individual cases public: Resources at EMEA / nat. authorities ?

- Also public (Dir. Art. 107m): the recommendations, opinions and decisions referred to in Articles 107b to 107l (e.g. PSUR assessments)

List of „intensively monitored products”

Regulation Art. 23

- EMEA to establish and publish a list of medicinal products for human use under intensive monitoring.
- The list contains names and active ingredients of products authorised under conditions or special requirements.
- EMEA removes product from list, when the Commission, on the basis of an opinion of the Agency, concludes that the conditions have been fulfilled and that the risk-benefit balance remains positive (Art. 14a).

Rationale:

“To increase the proportionality between ADR reporting and the level of knowledge about the safety of a product and to allow a differentiated view of important new medicines.”

Statement in PIL and SmPC

Directive Artikel 11:

"This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web -address of the national competent authority>."

- Reference on outer packaging (similar to „black triangle" in UK) not proposed any longer.

Assessment

- Products not listed might be mistaken as „entirely safe“
- Reduced compliance for products included in list
- What‘s the benefit for patients to know that their product is „intensively monitored“ ?
- Current PIL already asks patients to report side effects
- Better: Statement in SmPC (similar to old §49 AMG)
- Each new product listed for approx. 10 years ?
- Plus all older active ingredients with existing RMP ?

➔ Politically motivated labelling as „new = dangerous“ ?

New section in PIL & SmPC

Rationale for Commission proposal

Why

The current organisation of product information makes it difficult to identify the most important safety warnings: this results in a risk that key safety measures / warnings may be missed.

Impact

Major benefit to public health by ensuring that key safety information is highlighted maximising the chances of it being read, understood and leading to risk minimisation.

„Black box summary“ (Dir. Art. 11, 59)

- New summary of the essential information necessary to use the medicine safely and effectively (formerly called: „key safety information“) in PIL & SmPC.
- Text to be presented in a box surrounded by a black border.
- New or amended text be presented in bold text and preceded by the symbol *⁎* and text “new Information“ for 1 year.
- Plus: “This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority>“, if applicable.
- “Black box for all products (not only “intensively monitored”)
- Implementation at renewal, max. after 3 years

Assessment

- “Key safety information about the medicinal product and how to minimise risks” means:
  - Summary of the most important warnings ? (redundant from 4.4 ?)
  - Summary of the most important side effects (redundant from 4.8 ?)
  - How to define „most important“ ? ?
  - Patient‘s perception: New = intensively monitored = warning (!)
- „Key information“ must be defined for each product
- Might lead to focus on this section ONLY => Negative impact on compliance?
- Length of „Black Box“ during the product life cycle ?
- New info highlighted for 1 year: yearly PIL revision
- IMPORTANT: General revision of PIL / SmPC guidelines with appropriate balance of BENEFIT/RISK

Internal audit reports (Art. 104)

„… the Marketing Authorisation holder shall:

- perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and followed.“

Assessment

- Those reports are internal reports.
- Audits aim at improvements of PhV systems
- Open identification of shortfalls must be possible

➔ Audit reports should remain internal; PhV system faster file might include date and agenda of audit

Guidelines for the conduct of NIS PASS

Why

Studies are often of poor quality and frequently promotional. Currently there are no guiding principles and there is no oversight in EU legislation of non-interventional safety studies. There is an EU guideline but it does not ensure harmonised practice. Therefore there are divergent national measures (including legislation in some Member States) that interfere with the single market and make the conduct of these studies difficult.

Impact

Benefit to public health by ensuring that non-interventional safety studies are high-quality and non-promotional. Possible cost reduction for industry as this will simplify the current divergences between Member States.

Conditions for NIS PASS (Art. 107n – 107r)

(CHAPTER 4 Supervision of post-authorisation safety studies)

- Draft study protocol to national authority (for single MS PASS) or PRAAC (for multi-country PASS).
- After max. 60 days: approval by nat. authority or PRAAC.

  Reasons for rejection:

  (i) Study is considered as clinical trial according to Directive 2001/20/EC;

  (ii) Study is considered as promoting the use of a medicinal product;

  (iii) design of the study does not fulfil the study objectives;
- Implicit approval after 60 days.
  BUT: In case of rejection written approval needed (NO deadline !)
- major amendments to the protocol require approval
- Payments to physicians restricted to compensation of time and expenses
- During NIS: ongoing benefit/risk assessment by MAH.
- Final report max. 12 mo; assessment of findings and possible effects on label.
- Abstract to PRAAC, possibly published.
- PRAAC publishes its assessment of effect on label.

Assessment

- Process too complex; approval procedures too long;
- Definition of PASS not clearly in line with Vol. 9A; open to interpretation
  - Vol. 9A acknowledges that there are NIS which are no PASS
  - For NIS, which are PAS (post authorisation studies), information to CA and publication on website should be sufficient
    - ➔Requirements for “other NIS” ? (e.g. health outcomes ?)
- How many national PASS will be accepted ?
- Assessment criteria unclear, such as
  - “the act of conducting the study promotes the use of a medicinal product“
  - „Payments … shall be restricted to compensation of time“
- Terminology for NIS should be different from CTs.
  - E.g. instead „study protocol“ ←➔ „observational plan“

PSURs (Dir. Art. 107 b -h)

1. Marketing authorisation holders shall submit PSURs to the Agency
2. Summaries of relevant data, not line listings of individual cases.
3. The frequency and dates of submission of the PSURs shall be laid down in the MA.
   (Community reference dates and current timelines apply.)
4. Reports shall be submitted electronically.
5. … the requirements shall not apply to products authorised in accordance with Articles 10, 10a, 10c, *(generics)* 13 to 16 *(homoeopathic products*) or 16a to 16i *(traditional herbal products),* unless other requirements have been laid down in the MA.
6. EMEA distributes to PRAAC, CHMP and CMD(h)
   Rapporteur/RMS to assess in 90 d to PRAAC.
   MAH 30 d for comment.
   PRAAC to report to CHMP; CHMP to pass opinion in 30 d;
   Commission to issue CD.

Assessment

- Positive: fully electronic submission
- Convoluted submission and assessment procedure (time loss)
- Why exceptions for generics ?
  - Small market share of original,
  - Possibly vanished from market
  - Generics regarded as “established and safe” ?
- Answer from EU Commission: „based on a judgement of the Pharmacovigilance Committee of the risk posed, including the need for product information to be updated, PSURs covering a specified period of time would be required to be submitted by a deadline for all products containing a particular active substance.”

Summary

Proposals defined by

- Centralisation at EMEA
- Marginalisation of national competent authorities
- Strong belief in the power of databases
- Increased reporting requirements (‘haystack’)
- Focus on aggregate data (instead of indiv. cases)
- Transparency (access to indiv. cases, hearings, etc.)
- Politically intended emphasis on “established products”

Perspective

- PhV proposal not discussed controversially
- Possible area of further changes (?)
  - PRAAC membership and scope
  - Audit reports
- „Pharma package“ parts progressed individually ?
- Timetable unclear.
  Best guess:
  ➔ EU parliament early 2010 ?
  ➔ 18 month transition period
  ➔ in force end 2011 or early 2012 ?

Thank you for your attention