PRAC Experience

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The legal framework

- The Pharmacovigilance legislation (Regulation No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council in December 2010.
- The legislation is the biggest change to the human medicines legislation EU since 1995
- Major implications for
  - Applicants for new drugs
  - **Holders of European Union marketing authorizations**

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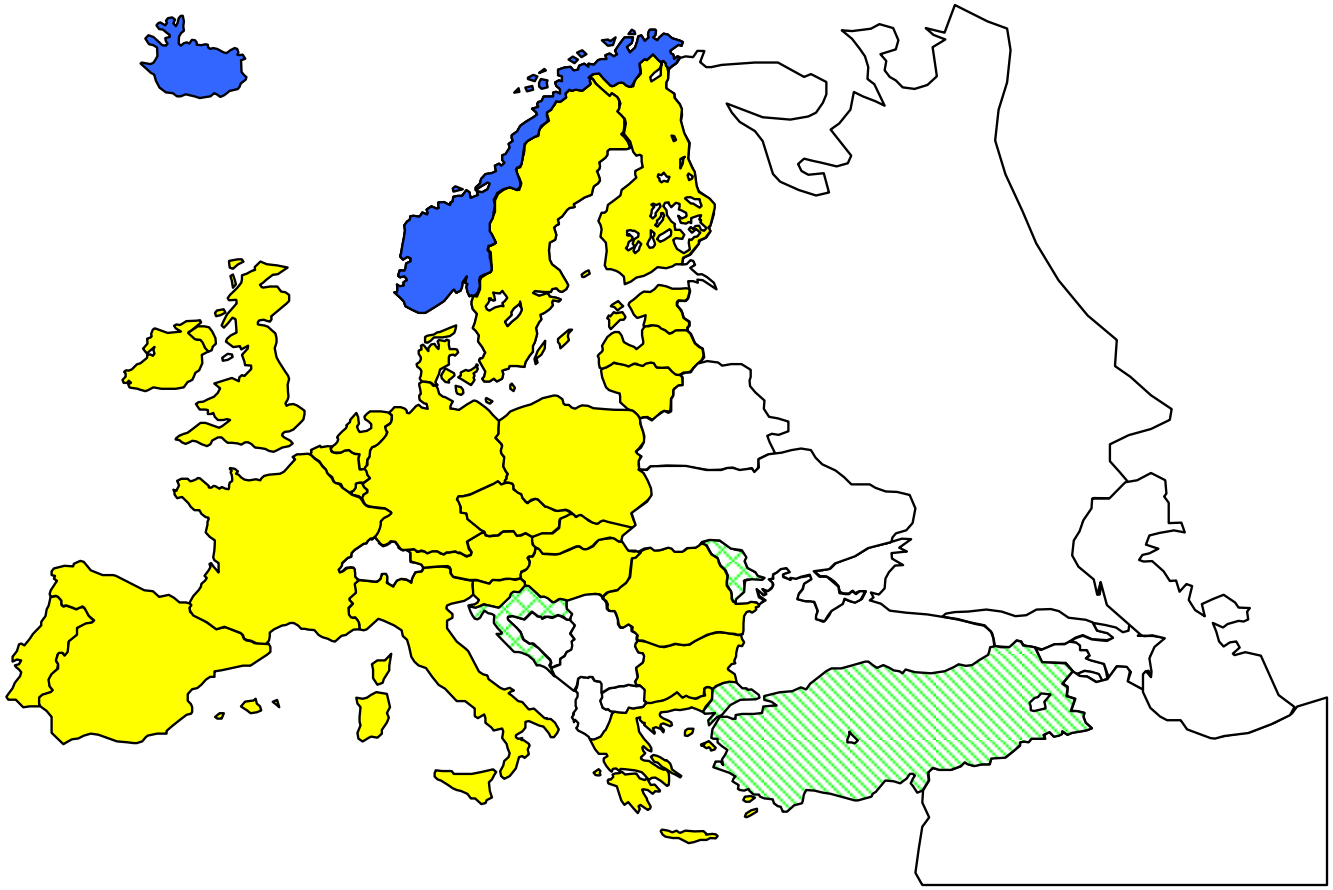
Valid throughout the EU from July 1st, 2012



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Overview – what has changed?

- **Adverse Drug Reaction reporting**
  - **After a successful audit (no critical or major findings) of a marketing authorization holder**
    - ADR reports only electronically into eudravigilance database at EMA. This includes reporting of medication errors that result in an adverse reaction
    - “The Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) evaluate signals from EudraVigilance and may recommend regulatory action as a result” (EMA homepage)

PSUR's

- **Periodic Safety Update Reports (PSURs) with single assessment for the same active substance or a combination of active substances**
  - **One assessment over ALL indications:**
    - Synchronization of activities
    - Improvement in knowledge
    - One indication AE described in all data sheets/for all indications
    - Need for qualifiers
- **Routine PSUR reporting is no longer necessary for products with low risk or for old or established products (if without particular concerns)**

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Differences

- Electronic PSUR reporting
- PSURs are sent directly to the European Medicines Agency only (no submission to single national agencies anymore)
- Legal basis strengthened for requesting post-authorization safety and efficacy studies (PASS/PAES): Makes it easier for authorities to ask for these post approval studies

Differences

- **Risk-management systems required for all newly authorized medicines**
  - **New line extensions of established products**
  - **Definition to be provided on what is a “new medicine” by EMA – Tecfidera (Dimethylfumarate), see also Fumaderm**
  - **Some examples**
    - Generics
    - Established products from a new applicant
    - New pharmaceutical forms from a new applicant (e.g. a patch where an oral drug exists)

Differences/News

- **Pharmacovigilance Master File to be kept by MA holder**
  - **“Inspectable at any time”, inspections will be performed regularly without announcement**
  - **Contains PV system**
  - **Contains all PV measures to be taken for new molecules**
  - **Contains all other PV information of relevance and how it is maintained/updated**

Pharmacovigilance referrals

- Most significant change!
- All PV referrals will be discussed by the new Pharmacovigilance Risk Assessment Committee (PRAC) and
- Committee for Medicinal Products for Human Use (CHMP)

or

- the Co-ordination Group for Mutual Recognition and Decentralized Procedures (CMDh)
- Always with opinions

(Opinions are to be ratified by the EU Commission and will lead to EU decisions, which are binding to all, marketing authorization holders and authorities)

Referrals

- Definition
- How “to get into it”? Reasons
- Potential outcome
- How to maneuver through such a situation

Referral – When is it invoked

- A referral is a procedure used to resolve disagreements and address concerns on the benefit to risk ratio of a certain medicinal product or a class of medicinal products marketed in the EU
- Once invoked, the European Medicines Agency via its committees is requested to conduct a scientific assessment of this medicinal product or a class of medicinal products marketed in the EU

One option: Urgent Union Procedure

- The new procedure is called “Urgent Union Procedure”
- Designed to assess significant emerging safety issues linked with a medicinal product available in the EU independent of its authorization route:
  - Centralized
  - Decentralized
  - National

How does it work?

Legal basis:

- **Urgent Union Procedures – Article 107i, 107j and 107k of EU Directive 2001/83 as amended**
- **Definition in the legislation: "… urgent action is considered necessary as a result of the evaluation of data resulting from pharmacovigilance activities"**

“Urgency” as the key driver

- **Issues leading to procedures – examples**
  - New Epidemiological study
  - Post Authorization Safety Study
  - Post Authorization Efficacy Study
  - Publications
  - Single cases
  - Studies to generate data for a new indication
  - Observation studies

PASS and PAES

- Post Authorization Safety Study
- Post Authorization Efficacy Study
- Can both be part of the Risk management plan
- Are legal requirements coming with a registration and have to be performed and reported
- Designed to qualify potential efficacy or safety issues following approval (or later after approval)
  - CV outcomes study
  - Long term survival data following an approval based on surrogate markers, e.g. PFS

The Role of PRAC

- **The Pharmacovigilance Risk Assessment Committee shall be responsible for**
  - **Providing recommendations to the Committee for Medicinal Products for Human Use and the coordination group on any question relating to**
  - **Pharmacovigilance activities for medicinal products for human use and on**
  - **Risk management systems**
  - **Responsible for monitoring the effectiveness of those risk management systems**

PRAC – Internal work procedure

Steps:

1. **Referral will be invoked**
2. **Rapporteur and Co-Rapporteur will be nominated**
3. **Both will prepare an assessment report**
   - **60 days for full assessment of case and recommendations**
     - Changes in labeling (SPC, PIL)
     - Revocation of marketing authorization
     - Doing new PASS or PAES studies
     - No action at all

Types of changes in labeling (SPC, PIL)

- Deletion of an indication
- Introduction of new contra-indications
- Inclusion of additional side effects, warnings
- Change in dosing
- Change in duration of treatment
- Change in wording on pharmacology

What's next?

- Recommendation of PRAC Rapporteurs is discussed at committee
- Vote will be taken by members on actions recommended. Majority is 50% of all members plus one vote
- Recommendation will then be forwarded to CHMP for centrally approved products and to CMDh for nationally (national, DCP, MR) approved products

PRAC recommendation

- CHMP or CMD have 30 days to reach a position
  - Should be in accordance with PRAC recommendation
  - If not: needs justification
- CHMP or CMD position will be ratified by EU commission as defined prior

Issues:

- Tight time line of only 60 plus 30 days for the work to be performed by two truly EU wide international committees
- Involvement of the marketing authorization holder
  - Hearing and written response
- Final commission decision may lead to:
  - Withdrawal, change in labeling, costly additional studies or epidemiological investigations

Implications on CHMP

- The CHMP remains the upper drug regulatory body for all centrally approved products but loses final opinion making in safety questions to the CMD
- Post approval it will no longer recruit the Pharmacovigilance expertise from their own members but has a new Expert committee to live with

Implications on CMDh

- It received power which was held by CHMP before
- It had to get structured to cope with the new responsibilities
- For all nationally approved products it has become the “final” regulatory body

Consequences for industry: Summary

- **PRAC has the power to**
  - **Ask for label changes**
  - **Ask for withdrawals of products**
  - **Ask for the performance of studies**
    - PAES: Post approval efficacy studies
    - PASS: Post approval safety studies
    - Epidemiological studies
- **Risk management plans became standard for all new approvals, including even generics**

Examples

- **PRAC recommends restricting use of domperidone**
  - The PRAC has concluded an in-depth review of domperidone-containing medicines, carried out over concerns about the medicines' effects on the heart. The Committee has recommended changes to their use throughout the European Union (EU), including using these medicines only to relieve symptoms of nausea and vomiting, restricting the dose and adjusting doses carefully by weight where it is licensed in children.
- **Following re-examination, PRAC recommends diacerein remain available with restrictions**
  - The PRAC has also recommended that diacerein-containing medicines remain available but with restrictions to manage the risks of severe diarrhoea and effects on the liver. These recommendations are the outcome of a re-examination of the PRAC’s November 2013 opinion to suspend marketing authorisations for diacerein.

Zolpidem

- **PRAC recommends updates to the product information of zolpidem**
- **The PRAC has recommended changes to the product information of zolpidem-containing medicines. These changes are aimed at further minimising the known risks of next-morning impaired driving ability and mental alertness (including somnambulism) with these medicines**

Zolpidem

- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of zolpidem-containing medicines, used for the short-term treatment of insomnia (inability to sleep).
  - The benefit-risk balance of these medicines remains positive, but the PRAC recommended changes to the product information, which are aimed at further minimising the known risks of next-morning impaired driving ability and mental alertness (including somnambulism).
  - The review of zolpidem was initiated after reports of impaired driving or road accidents the morning after patients took the medicine… However, it was considered that a detailed review and analysis involving additional information on the benefits and risks of zolpidem, should be made to the marketing authorisations of these products across the EU.

Zolpidem Recommendations

- The PRAC has recommended ***changes*** to the product information of zolpidem, including further ***highlighting the risks*** of impaired driving and mental alertness and ***strengthening warnings and precautions*** aimed at minimising these risks. The PRAC considered that the ***recommended daily dose*** should remain at 10 mg of zolpidem, and this dose must not be exceeded … In ***elderly patients*** and in patients with reduced liver function, the recommended dose remains 5 mg of zolpidem per day. Furthermore it is recommended ***not to drive or perform activities that require mental alertness*** until 8 hours after taking zolpidem. Zolpidem should not be taken together with other medicines that have an effect on the central nervous system (brain and spinal cord). Similarly, alcohol or other substances that affect mental function ***should not be used*** when taking zolpidem.

Company activities

- Comment on proposal
- Ask for Oral Explanation at PRAC and, later, at CMDh
- Appeal against recommendation of PRAC/CMDh
- Referrals procedure

Oral Explanations

- ***Article 15 (***Pharmacovigilance Risk Assessment Committee, RULES OF PROCEDURE)
- The PRAC shall invite a marketing authorisation holder to provide oral explanations in connection with an evaluation procedure where requested by the marketing authorisation holder, unless urgent measures need to be adopted for reasons of public health. The PRAC may also invite, on its own initiative, a marketing authorisation holder to provide oral explanations. The oral explanation should normally be based on data submitted in advance and assessed by the Rapporteur. Exceptionally, other data to be presented at the oral explanation should be submitted in advance
- Oral explanations shall be indicated clearly in the draft agenda and timeschedule of the meeting.
- The PRAC shall not make any conclusions during these presentations in the presence of the company representatives or third parties.
- The marketing authorisation holder is informed of the trend at PRAC level at the end of the scientific discussion ahead of any formal vote to conclude the evaluation process.

Critical Issues

- PRAC is a safety committee, not an efficacy committee
- Time from initiation of procedure to Assessment Report: 60 days – half of the time CHMP has for initial (Day 120) report
- Hearings shall focus on safety aspects only
  - How to do a benefit/risk analysis in a balanced fashion?

Latest news

- The committee provides output (examples we have discussed)
- Companies have the chance for hearings and comments
- Often difficult to get the information across properly
- Focus merely on safety, the efficacy part is often „forgotten“

Thank you

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