EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Translating regulatory science into better processes

Eight Stakeholders forum on the implementation of the Pharmacovigilance legislation: Building on two years of operation

Presented by: Xavier Kurz
Head of Monitoring & Incident Management, Pharmacovigilance Department

An agency of the European Union

Introduction

- EMA has central role and primary responsibility to promote and protect public health though the evaluation and supervision of medicines
- EMA is engaged in research activities, notably regulatory sciences aiming to improve the evaluation of quality, efficacy and safety of medicinal products by:
  - Supporting research in areas of emerging and innovative sciences
  - Developing and testing methods in the evaluation and supervision of the benefits and risks of medicines
  - Improving and evaluating the regulatory framework
  - Developing and testing an infrastructure to build capacity for benefit-risk monitoring.

Objectives

1. To develop a conceptual framework for the review of the regulatory impact of results of regulatory science projects
   - Have the projects achieved their objectives
   - Are the results good enough to be implemented
   - Which impact on regulatory processes and activities
   - Which lessons can we draw in terms of investment of resources
   - How can we improve

Using the PROTECT project as an example:

2. To test this conceptual framework to the outcomes of PROTECT.
3. To make recommendations to EMA and its committees for an appropriate action on PROTECT results.

Scope: Regulatory science

EMA definition: Range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. It encompasses basic and applied medicinal science and social sciences, and contributes to the development of regulatory standards and tools.

European Medicines Agency process for engaging in external regulatory sciences and process improvement research activities for public and animal health EMA/14946/2013.
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139888.pdf

FDA definition: Science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

Advancing Regulatory Science. -Moving Regulatory Science into the 21st Century.
http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm?utm_campaign=Goo

Questions to be addressed

- When are results matured enough to form a basis to implement changes in regulatory or clinical practice?
- Depending on the types of outcomes, to what extent should results/recommendations from regulatory science projects be validated, scrutinised and peer reviewed in the scientific community before their implementation?
- Should there be a trade-off between timing of implementation and scientific replication/validation?
- Which outcomes should be prioritised for implementation?

PROTECT as an example

- Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT): partnership of 34 public and private partners supported by IMI JU with funding from European Commission and in-kind contribution from EFPIA.
- Goal of PROTECT: strengthen the monitoring of B/R medicines in Europe by testing methods to collect data on drug utilisation and safety directly from patients, enhance signal detection, evaluate methods to decrease variability of results of pharmacoepidemiological studies and support the integration and presentation of data on benefits and risks (http://www.imi-protect.eu)
- Impacts of PROTECT on innovation, benefit-risk evaluation of medicines and ultimately public health need to be evaluated.
- EMA Panel established to develop a methodology for the assessment of the impact of PROTECT and evaluate its generalisability to other projects.

Components

1. Domains

Intended target of research activity

Process: changes in process reflected in changes in guidelines, procedures, work instructions, training courses

Behaviour: behaviour of individuals or targeted entities affected by the deliverable

Outcome: actions implemented and final results

Adapted from Coglianese C. Measuring Regulatory Performance-Evaluating the impact of regulation and regulatory policy, OECD, August 2012.

Components (2)

2. Indicators

Impact of change: level of benefits brought by the change, considering affected stakeholders and estimate of public health impact

Maturity*:* stage of development in relation to intended application; eg.

- **inadequate**: output has not reached such a stage of development that it can be communicated to scientific community;
- **incomplete**: significant further development is still needed (e.g. independent confirmation, re-testing in another setting)
- **nearly complete**: need for peer review process or minor adjustments
- **complete**: no further development is needed

Components (3)

2. Indicators (2)

Feasibility:

- impact of the implementation of the deliverable in terms of resources (human, financial, infrastructure, IT or other resource needed)
- acceptability by concerned stakeholders
- alignment with applicable legislation.

Timing of implementation

Delay within which the deliverable can be implemented, eg. <1 year, 1-2 years, >2 years.

Components (4)

3. Scoring

- Semi-qualitative, eg. +, ++, +++
- Weighting possible
- Perspective may differ according to stakeholder: patient, HCP, industry, regulator,...

Example

PROTECT Adverse Drug Reaction Database

- Structured downloadable Excel database of all ADRs listed in section 4.8 of the SPC of CAPs authorised in the EU, based exclusively on MedDRA. Also includes information on gender, causality, frequency, class warning and source of information for ADRs for which additional information is provided in the SPC. (see http://www.imi-protect.eu/adverseDrugReactions.shtml)

- Created through a stepwise approach using automated mapping of ADR terms listed in section 4.8 of SPCs to MedDRA terminology, fuzzy text matching and expert review. Updated periodically.

- Intended result:
  - Improvement of the efficiency of signal detection by filtering or flagging electronic reaction monitoring reports (eRMRs) for signals related to unlisted reactions only (= OUTCOME)
  - Research purpose: evaluation of adjustment of statistical signals for known ADRs, and of the effect of background restriction on the performance of statistical signal detection (=PROCESS)

Example

PROTECT ADR database: Impact assessment

Indicators	
Intended target - Process - Behaviour - Outcome	 + + - + + +
Impact of change	+ + +
Maturity	+ +
Feasibility - impact on resources - acceptability - alignment with legislation	 + + + + + + +
Timing	+ +

Summary

- EMA is involved in research projects which may lead to improvements in pre- and post-authorisation regulatory processes

- Criteria may be needed to prioritise implementation of results regulatory science activities:
  - Identification of activities with highest impact
  - Efficient use of resources

- Work in progress

- Systematic analysis of PROTECT outputs is planned

- Stakeholders' consultation