Safety Reporting and the New Regulations, a Perspective from Pharma and the EU

Boston 20th – 22nd May 2013

Dr Simon Day

Lots going on

- Me… an Industry reaction
- Also… a European reaction

- Disclaimer…
  - Until recently, worked for Roche (in Europe)
  - Prior to that, a European regulator
  - Now, a freelance consultant

- Experiences in this talk come from *all over*

Case Study 1

- From MHRA / CHMP
- Company A with established (approved) product, but with a new safety concern
- Approximately 110 trials conducted by the sponsor
  - Worldwide
  - Over many years

Case Study 1

- “Clinical study reports” (as per pharma industry)
  - Typically 200 – 400 pages

  - Many older ones, only 20 – 50 pages

Case Study 1

- From MHRA / CHMP
- Company A with established (approved) product, but with a new safety concern
- Approximately 110 trials conducted by the sponsor
  - Worldwide
  - Over many years
- 20 – 400 pages long; total ≈ 30,000 pages

Case Study 1

- From MHRA / CHMP
- Company B, C, D, E with similar established (approved) products, in the same therapeutic class
- Asked to provide copies of all study reports
  - Worldwide
  - Over many years
- Responses varied from
  - Can we have a week?
  - Can't do; too many; too much resource

Case Study 2

- From consulting
- Company with established (approved) product, and an alleged serious side effect (teratogen)

- Approximately 1100 academic papers/reports with results of studies
  - Worldwide
  - Over many years

Case Study 2

- “Academic papers/reports”
  - Typically 2 – 6 pages

  - Some only 1 or 2 pages, or just short letters

Case Study 2

- From consulting
- Company with established (approved) product, and an alleged serious side effect (teratogen)

- Approximately 1100 academic papers/reports with results of studies
  - Worldwide
  - Over many years

- 2 – 6 pages long; total ≈ 3,500 pages

The general issue (or problem)

- Instead of “PSURs” (Periodic Safety Update Reports)
- Now we have “PBRERs” (Periodic Benefit–Risk Evaluation Reports)
- ICH guideline E2C (R2)
  - Came into effect in EU, 1st Januray 2013

Sponsors have to think!

ICH E2C (Revision 2), 17th December 2012

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

E2C(R2)

The purpose of this Guideline's revision…

- "The purpose of this Guideline's revision is to ensure that the periodic safety update reports for marketed drugs have the role of being periodic benefit-risk evaluation reports by covering: Safety evaluation, evaluation of all relevant available information accessible to marketing authorisation holders (MAHs) and benefit-risk evaluation."

- "…an *evolution* of the traditional PSUR from an interval safety report to cumulative benefit-risk report and with a change in focus from individual case reports to more aggregate data evaluation."

- Source: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

From old…

- “PSURs” (Periodic Safety Update Reports)

- Just a pile of paper
- Not even (necessarily) a very well organised pile of paper
- Little more than a list of reported adverse events

- Every 6 months, you just add more events at the end of the list

To new…

- “PBRERs” (Periodic Benefit–Risk Evaluation Reports)

- Just a pile of paper
- But, showing both the reported risks (aka “adverse events”), and the reported benefits (aka “efficacy”)

- And, a sensible, critical discussion of the two
- To arrive at a “current” view on benefit–risk

“Adaptive Licensing”

- Some of the licensing options in Europe:
  - Post-marketing commitments
  - Approval under “exceptional circumstances”
  - “Conditional approval”

- Historically (some) companies very averse to adaptive (or phased) licensing
- Want a product on the market (or not)

“Adaptive Licensing”

- Licensing decisions are not easy
- They ultimately have to binary
  - Even if binary, with conditions
- But that binary state should not be irrevocable

- “Want a product on the market (or not)” is unrealistic

B/R and The Safety of Medicines

- Companies still don't understand benefit–risk

- Obvious examples exist where licensed products are considered for line extensions, further indications, etc.
- "The safety of XXX has already been established"

- No it hasn't!
- "The safety of XXX has already been established in YYY, the relevance to this new indication is that…"

“Adaptive Licensing” and the New Pharmacovigilance

- This seems (to me) the appropriate regular review process

- In future, we will regularly review the evidence for
  - Safety (already being done)
  - Efficacy (this now added), and
  - The balance of these two

Case Study 3

- In the new world of PBRERs
- Company with established (approved) product
- Approximately 4000 trials (mostly academic-led) known by the sponsor to be in the published literature
  - Worldwide
  - Over many years

Case study 3

- We’re in this scenario again
- 4000 × 2 to 6 pages each
- Approximately 10,000 – 15,000 pages of documents?

“Can’t do; too many; too much resource”

Case study 3

- We're in this scenario again
- 4000 × 2 to 6 pages each
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Sponsors have to think!
And Sponsors have to work hard!

Some sympathy(?)

- All large companies have hundreds of marketed products
- And this was an over-night change (although we could see it coming for a long time!)

- The effort to produce the *first* PBRER for *each* and *every* marketed product (each with potentially 1000s of publications…) is huge
  - But we did know it was coming

Some sympathy(?)

- Whilst the initial effort…

  (that should have been started a long time ago…)

  …is huge

- "…an *evolution* of the traditional PSUR from an interval safety report to **cumulative** benefit-risk report and with a change in focus from individual case reports to more aggregate data evaluation."
- It is a one-time effort

Safety Reporting –

“Two years after the implementation of new safety reporting regulations, what has worked?”

Robert Lindblad, MD
Chief Medical Officer
The EMMES Corporation

A recent case…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
EMA/405725/2012
Press Office

Press release

European Medicines Agency acts on deficiencies in Roche medicines-safety reporting

15,000 unreported deaths…

The deficiencies are identified in a May 2012 report from the UK medicines regulatory agency (MHRA) following an inspection at Roche. This was part of a coordinated European programme of routine inspection of safety reporting systems.

At the time of the inspection the company identified some 80,000 reports for medicines marketed by Roche in the USA that had been collected through a Roche-sponsored patient support programme, but which had not been evaluated to determine whether or not they should be reported as suspected adverse reactions to the EU authorities. These included 15,161 reports of death of patients and it is not known whether the deaths were due to natural progression of the disease or had a causal link to the medicine. More recent information from the company indicates a smaller number of reports, but this information needs to be verified by the authorities.

What has worked?

- We have new mantras
  - “Safety is our number one concern”
  - “Safety is the new efficacy”

Safety the number one concern?

- Being risk-averse in the pharma industry is easy
  - Just stop developing new medicines
- Developing new medicines is hard and it's risky
- Rightly or wrongly, the public are not sympathetic

What has worked?

- We have new mantras
  - “safety is our number one concern”
  - “safety is the new efficacy”

- Something has worked…
- Like it – or not(!) – companies have been *forced* to do something

In summary

- In my view, pharmaceutical companies have brought many good medicines to many patients who need them
- In my view, pharmaceutical companies still do *not* embrace risks and safety as strongly
  1. as they should, and
  2. as they say they do

- Companies haven't done so historically, and many continue to be deficient
  - Not completely deficient, but still "could do better"