Regulatory pharmacovigilance

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- In this talk
  - Regulatory requirements for companies for pharmacovigilance
    - Differences between regions
    - Differences within regions

EU Clinical Trials

- Part of Volume 10 of the Rules Governing Medicinal Products in the EU
  - Implements EU Directive 2001/20
- All clinical trials with EU sites
  - All phases
  - All investigational medicinal products (IMP)

EUROPEAN COMMISSION

ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels,
ENTR/CT 3

Revision 2

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use

April 2006

Sponsor Responsibilities

- Ongoing safety evaluation
- Promptly notify investigators, Ethics Committee and authorities of findings that
  - adversely affect health of subjects
  - impact on trial conduct
  - alter decision to authorise the trial
- Structures, systems, SOPs
- Keep detailed records of all AEs
- Evaluate seriousness, causality, expectedness
- Recognise and process “alerts”
- Process aggregate case data
- Standards / laws on confidentiality / data protection

Expedited Reporting

- SUSARs: suspected unexpected serious ADR
  - EU trial / trial in any country / spontaneous / publication
- Fatal or life-threatening SUSARs
  - ≤7 days from receipt; follow-up ≤ 8 more days
- Other SUSARs and safety issues
  - ≤ 15 days; relevant follow-up a.s.a.p.
  - other issues affecting benefit-risk or trial conduct
  - major finding from animal study
  - halt of a trial in another country

Comparator, Placebo, study procedures

- Report all SUSARs on comparator products in the trial
- Only report placebo SUSARs, not AEs
  - e.g. reaction to excipient
- Report serious AE associated with trial procedures
  - e.g. during run-in period

Ethics Committee and investigators

- Report to ECs:
  - Individual SUSARs in that country
  - All SUSARs every 6 months
- New safety issues within 15 days
- Inform investigators on findings that could affect safety of subjects
  - line listing of SUSARs with concise summary of evolving safety profile

Annual Safety Report

- Annually throughout the trial, and on request: to concerned authorities and Ethics Committees
  - a safety report taking into account all new available safety information for the period
  - based on all sponsored trials
  - with a concise global analysis of the safety profile of the IMP

Imminent EU change

- In 2011, EU Development Safety Update Report (DSUR) instead of Annual Safety Report
  - ICH E2F guideline
  - More complex document, broader scope
  - Critical evaluation of risks and potential benefits

CLINICAL TRIALS IN THE USA

US CLINICAL TRIALS PRE-LICENSING IND SAFETY REPORTS

- Notify FDA and all participating investigators of potential serious risks
  - A.S.A.P: SUSARs no later than 15 calendar days; no later than 7 days for unexpected fatal or life-threatening suspected ADR
- Promptly investigate all safety information
  - Submit relevant followup information to an IND safety report as soon as available
- Identify all similar previous IND safety reports
  - Analyse significance of the suspected ADR in light of previous reports and other relevant information

IND ANNUAL REPORT

- 21CFR312.33
  - Summary of progress of studies
  - Submit within 60 days of IND anniversary
  - N of subjects planned, entered, completed, withdrawn
  - All AEs (related or not) and pre-clinical findings suggesting significant human risk
  - Summary of most frequent and serious AEs
  - List of deaths and dropouts due to AE
  - Summary of all IND safety reports submitted in the year
  - List of pre-clinical studies completed or in progress

US IMMINENT CHANGE: CLINICAL TRIAL REPORTING

- Amendments to 21 CFR Parts 312, 320
  - FDA Draft guidance, September 2010
- Final Rule effective Sep 2011
  - Review all relevant safety information promptly
- Draft FDA Guidance
  - Report SUSARs:
    - Suspected ADR: reasonable possibility drug caused AE;
    - Report only if evidence for causal relationship

NEW DRAFT FDA GUIDANCE: CLINICAL TRIALS

- Report findings from epidemiology studies, pooled analyses, other clinical studies, animal / in vitro studies
  - If suggest significant risk in humans exposed
- Report clinically important increase in rate of serious ADR over that in the protocol or IB

NEW US REQUIREMENT: CLINICAL TRIALS

- Bioavailability and bioequivalence studies
  - Report all SAEs
  - Notify FDA and all participating investigators
  - A.S.A.P: no later than 15 days; fatal or life-threatening SAE within 7 days
  - Submit relevant follow-up information as soon as available

*EU post-marketing

Volume 9A: EU post-marketing PV rules

- EU Qualified Person for Pharmacovigilance
- Regulatory authority Inspections
- Quality management systems, validated systems
- Risk Management Plans
- Monitoring for safety signals
- Notify changes of benefit-risk to the authorities
- Weekly screening of the published literature
- Expedited reporting
- PSURs
- Post-authorisation safety study (PASS) guidance
- Direct to healthcare professional communication

*VOLUME 9A

- *Marketing Authorisation Holder should have
  - *an appropriate system of Pharmacovigilance in place
  - *permanently and continuously at its disposal, resident in the EEA, a qualified person for Pharmacovigilance
- *One QPPV responsible for all EU products
- *Qualified, experienced in all aspects of PV
- *Medically qualified or with access to a medic
- *Name and 24-hour contact details notified
- *Some countries also require a named person with obligations for local PV

Role and Responsibilities of the QPPV

- Maintain / manage PV system
  - oversight of PV system structure, performance
  - single contact point for Authorities 24/7
  - Responsible for ICSRs, PSURs, other reports
  - Continuous PV evaluation post-authorisation
  - overview of safety and emerging concerns
  - Ensures request from Authorities for info on benefit risk is answered fully and promptly
  - Contact point for PV inspections

Key elements: ICSRs

- Record reports of all suspected ADRs
- Expedite health professional spontaneous / literature reports < 15 days of first receipt
  - Serious EU ADRs to the national authority
  - Serious unexpected non-EU: to EU countries + EMA
- Follow up serious ADRs and request health professional to confirm consumer reports
- Also collect reports – for the PSUR - of
  - Pregnancy: direct exposure or via male
  - Lack of efficacy
  - Abuse, misuse, overdose
  - Medication error

Multiple national differences

- E.g. Consumer reports not expedited - Except for Hungary and Denmark
- E.g. Other country EU serious cases not reportable – except for UK
- E.g. French experience in PSURs
- E.g. French causality algorithm
- E.g. German case assessment

Literature screening

- 1x/week, worldwide literature searches for all products (active substance), looking for ADR reports
- Also, ADRs presented at conferences in abstracts, posters, lectures
  - Also “local” publications must be reviewed
- Expedited report for serious ADRs
- Report also in the PSUR if published safety information

PSURs

- Every 6 months until product marketed for 2 years in EU, then annually for 2 years, then every 3 years
- ADRs reported worldwide in the period, usage data, registration status, new regulatory actions, findings from studies
- Any need to change the prescribing information (CCSI)?
- Any change to benefit risk for the product?

Other elements of EU regulations for marketed medicines

- Monitoring of compliance by regulatory authorities
  - Inspection process for pharmacovigilance
- Risk management plans
- Guidance on how to carry out post-authorisation safety studies (PASS)
- Direct to Healthcare Professional Communication

Monitoring benefits and risks

- Ongoing monitoring of safety is a regulatory requirement in the EU
  - Methods are not specified
- Changes to benefit-risk balance must be reported to the regulatory authorities

Electronic reporting

- Electronic submission of expedited reports of serious ADRs is mandatory in the EU
  - To Eudravigilance Post-authorisation module
  - To Eudravigilance Clinical Trial Module
- There is a very complex registration process followed by rigorous testing and certification
- Submission can be *via* a gateway or using WebTrader / EV-Web
- Uses ICH E2B standards for data elements, xml files

Imminent EU changes

- 2012: Major changes to postmarketing PV
- Regulation 1235/2010 amends 726/2004
- Directive 2010/84 amends 2001/83
  - List of medicinal products requiring additional monitoring
  - EMA will screen literature for specified products and enter cases on Eudravigilance
  - Regular audits, prepare CAPs, retain in PV Master File

Imminent EU changes

- Simplified expedited reporting
  - Reporting to Eudravigilance only
  - All serious ADRs worldwide within 15 days
  - All non-serious EU ADRs within 90 days
- Change in PSUR scope and structure
  - analysis of risk-benefit balance rather than detailed list of ICSRs
  - no PSURs for generics or products with well established use

US post-marketing

US Regs: Marketed products

- 21CFR314.80 Drugs marketed under NDA
- 21CFR314.98 " " " " " ANDA
- 21CFR600.80 Biological products
- 21CFR310.305 Drugs marketed with no approved NDA (for prescription drugs)
  - Promptly review all AE information …
  - From any foreign or domestic source including:
    - commercial marketing experience
    - postmarketing clinical investigations, epi / surveillance studies
    - scientific literature and unpublished scientific papers

Marketed products

- Written procedures for pharmacovigilance
- Retain all records for 10 years
- 15 day alert reports: assume causal association
  - Domestic or foreign serious + unexpected AE
  - Serious and unexpected AEs in published case reports or studies
- If under IND, also submit IND safety reports for suspected study ADRs - domestic and foreign
- Promptly follow up within 15 days of receipt
- For post-marketing studies, only submit 15 day alert report if a “reasonable possibility” of causation

US Periodic reports

- For 3 years after approval, quarterly periodic report
- After 3 years, annual reports
- May request waiver to submit ICH PSURs
- For the period include
  - Non-serious or expected AEs
  - Analysis of submitted 15 day alert reports
  - 3500A for each AE not expedited
  - Line listing of patient ID Nos. and ADR terms
  - Actions taken in response to AEs
  - Narrative summary and analysis

SWITZERLAND: DIFFERENCES FROM EU

PRE-AUTHORIZATION (CLINICAL TRIALS)

- Domestic SUSARs only as individual case safety reports
- Annual reports for every trial conducted in Switzerland (incl. multinational trials)

POST MARKETING SURVEILLANCE – SPONTANEOUS REPORTING

- Mandatory for
  - MAH
  - Health professionals
- Possible for
  - Consumers
- Swissmedic accepts spontaneous reports from consumers without medical confirmation

INDIVIDUAL SAFETY CASE REPORTS

- Domestic reports only
- All serious OR unexpected ADRs to be reported:
  - Serious ADRs within 15 days max
  - Non-serious unexpected ADRs within 60 days max

MARKETING AUTHORISATION HOLDERS (MAH)

- Also have to report:
  - Safety issues originating outside Switzerland as concise summary (ad hoc reporting) incl risk minimization action taken or planned
  - Quality problems (only if batches concerned are also being distributed in Switzerland)
  - Production/distribution „bottle necks“

PERIODIC UPDATE SAFETY REPORTS

- PSURs to be submitted yearly for 5 years, then stop
- Coordination with international life cycle possible
- New 5-year submission period starts with changes to MA (new indication or dosage, new formulation etc)

PV PLANNING – RISK MANAGEMENT PLANS

- Not part of the Swiss Law on Therapeutic Agents but ICH Guideline (E2E): ICH Guidelines are considered the gold standard to be followed
- Mandatory with every marketing authorization (MA) submission for products with new active substances, for vaccines and for herbals not well documented
- Part of MA
- Results of PVP/RMP to be submitted according to milestones planned

QUALIFIED PERSON FOR PHARMACOVIGILANCE

- Adequately qualified
- Not 24/7 : the MAH must be available 24/7

ELECTRONIC REPORTING