



Drug Product Life Cycle

Clinical Trial Safety - CIOMS VI / VII, Vol. 10 and beyond.

Sidney N. Kahn

Senior Principal, Pharmacovigilance Practice.

SCIFORMIX



Highlights of CIOMS – VI

Management of Safety Information from Clinical Trials

<http://www.cioms.ch>

Published June 2005

- Systematic, evolving PROCESS for early identification, assessment, and management of identified and potential safety issues throughout product life cycle
- Proactive, not reactive
- Not regulatorily binding, but part of evolving regulatory environment
- A procedure / process, not a “document”
- Development Risk Management Plan as basis of postapproval pharmacovigilance / risk management plan (ICH E2E)

- Begin process at decision to expose humans
- General issues applicable to all products
 - e.g. hepatotoxicity, cardiac conduction
 - FDA DILI guidance - “Hy's Law” (Jul 2009)
 - ICH E14 QTc guideline (Oct 2005)
- Specific issues / actions customised for each product
 - e.g. immunogenicity, interactions
 - one size does NOT fit all
- Multi-disciplinary team

- Anticipated product profile
- Non-clinical information
 - PK/PD, toxicology, interactions, special studies
- Clinical experience
 - Clinical pharmacology, interactions, dose-response
 - Efficacy & safety (individual + class), subpopulations, specific organ system effects
- Known / anticipated risks
- Potential new risks
- Population epidemiology
 - Natural history, event background rates
 - Possible need for cohort, e.g. if no available data
- Risk evaluation / mitigation planning

- Ultimate goal – medically useful label information
- GIGO vs. good medical information
 - well documented cases
 - standardised terms / case definitions, e.g. hepatotoxicity
- Events of special interest
 - non-serious, but potential indicators of serious sequelae, e.g. muscle pain / slight CK elevation as indicators of potential rhabdomyolysis
- Avoid over-collection
 - data that will never be analysed, e.g. investigator causality for non-serious AEs
- Decrease data collected with increasing experience
 - e.g. non-serious events, routine laboratory analytes in phase IV studies

- Good medical information
 - medically skilled codification
 - diagnoses rather than symptoms / signs
 - can be assigned by sponsor, if obvious
 - consistent codification cf. strict verbatim adherence
 - abnormal LFTs
 - hepatitis
 - hepatic necrosis
 - standardised case definitions, esp. for events of special interest
 - leucopenia
 - agranulocytosis
 - aplastic anaemia
- Apparently conflicting recommendations regarding codification and analysis (verbatim vs. standardised terms)
- Only medically meaningful terms in DCSI (cf. SmPC / FDA label guidances)

- Goal – early detection of important signals
- Patient population characteristics, incl. disease natural history
- Existing treatment standards
 - benchmark for benefit-risk balance
- Timing of analyses
 - routine / predetermined
 - *ad hoc*
- Analyse **ALL** safety-related information
 - serious and non-serious AEs
 - vital signs
 - laboratory analytes
- Customised criteria, e.g. product indication, nature of illness, alternative treatment(s)

- Investigator / sponsor causality assessment of single cases primarily for regulatory reporting
 - binary categorisation
 - standard list of non-drug causes
- DCSI (CIOMS III/V) used to determine expectedness
- Aggregate assessment
 - investigation results (including laboratory analytes)
 - numerology / statistics vs. clinical judgement
- Consistent criteria for assessment of aggregate data for DCSI inclusion
 - incl. statistical analyses when appropriate / relevant
 - clinical judgement is paramount!

- Good codification practices
 - don't "overcode" or "undercode"
 - don't code vague terms
 - "gastrointestinal disorder"
 - use medically meaningful terms
 - company term vs. investigator term
 - ICH E2B. FDA RM guidances, vol. 9A, SmPC guidance

- Adverse events vs. adverse reactions
 - no established / standardised differentiation criteria
 - limited value of numerical / statistical analysis
 - proposed criteria for standardised causality evaluation
 - modified from CIOMS III

- Brief overview of major statistical issues
- Points to consider, NOT prescriptive for analysis
- “a tool in the process but ...by no means the process itself”
- Limitation of small numbers
 - e.g. for α 0.05, power 90%, relative risk of 2.0 with background 0.1% requires >30,000 subjects per group
- ITT not necessarily optimal for safety analyses

- Formal analysis difficult
 - power
 - multiplicity
 - sample size / sub-groups
 - repetitive analysis
- Time dependence
 - crude incidence rate (proportion, person years) inadequate
- Grouping / terminology
 - dynamic tension between lumping / splitting
 - no simple or easy answer

- Person-years as denominator assumes constant hazard rate
- Constant hazards are rare
 - high then falling (e.g. first-dose effects, hypersensitivity)
 - low then rising (e.g. mitochondrial toxicity of ARVs)
- Take account of “healthy survivors”
 - low-risk group?
- Kaplan-Meier plots
 - stratified where possible

- Follows ICH E2A
- ICSR causality for expedited reporting to regulators
 - “reasonable possibility” based on clinical judgment, NOT “cannot be ruled out”
 - “individual case reports are generally not an effective means of communicating important new safety information”
- Reporting to investigators / ECs
 - no individual ICSRs
 - periodic communication
 - communicate evolving benefit/risk profile
 - newly identified risk requiring informed consent update
 - no blinded reports
 - no reporting for phase IV studies except for CSI updates
 - partially adopted by EU / FDA

- Expectedness for unblinding decision relates to the investigational drug
- Incorporate Development Core Safety Information (DCSI) in IB (CIOMS III/V)
- Report all unblinded SUSARs for active comparators to regulators without expectedness assessment (cf. EU CTD)
- Consider informing comparator manufacturer
 - avoid choosing Reference Safety Information for comparator

- Use same threshold for inclusion of a suspected adverse drug reaction in DCSI, Informed Consent form (ICF), and CSI
- Urgency of ICF update proportional to importance of new information, cf. threshold for CSI inclusion
- DCSI for ongoing trials of an approved product \approx CSI for approved indication(s) (CIOMS III/V)
- Event level determination of reportability; i.e. must be actual serious, unexpected, related event, not combination of serious expected / non-serious unexpected events

- SOP for non-ICSR expedited reports (e.g. non-clinical finding, unexpectedly high AE incidence)
- Procedural determination of clock start
 - e.g. date assessment team / committee determines reportability
- Mechanism for *ad hoc* review for any special concern
- Immediate notification of regulators, investigators, and ethics committees of any significant safety issue identified from individual cases or aggregate data, with associated updates to IB and ICF

- MHRA guidance, 2007 requires 7-day expedited reporting of serious breaches of GCP or trial protocol
 - a “serious breach” is a breach which is likely to effect (sic) to a significant degree
 - (a) the safety or physical or mental integrity of the subjects of the trial; or
 - (b) the scientific value of the trial
 - SAEs / SUSARS resulting from GCP or protocol breach (not all SAEs / SUSARs)
 - normal SUSAR reporting still required
 - not limited to occurrences in the UK

- Regular review of safety information
 - e.g. quarterly pre-approval (synchronize with annual reports, IB updates)
 - vary with size of program / stage of development / extent of knowledge of safety profile, etc.
- Annual Development Safety Update Reports (DSURs)
 - for development **program**, not individual protocols
 - consistent format, content, timing (international development birthdate)
- During early development, periodic reports to investigators and ECs at least quarterly, including
 - SUSARs reported in last period
 - current DCSI if changed, with explanation
 - summary of safety profile
- For approved products
 - synchronise with PSUR schedule
 - replace DSUR with PSUR for well established safety profile (e.g. only phase IV studies ongoing)
- CIOMS VII / E2F

- CIOMS VII - The Development Safety Update Report – DSUR: Harmonizing the Format and Content for Periodic Safety Reporting during Clinical Trials, 2006
- ICH Draft Consensus Guideline E2F: Development Safety Update Report, Step 2, June 2008

- Objective

- ongoing assessment of risk to trial subjects
- informing stakeholders of evolving safety profile of investigational agent
- common standard for annual CT safety reporting, replacing existing reports throughout ICH
- comprehensive, thoughtful, annual review and evaluation of pertinent safety information collected during reporting period to
 - summarise current understanding and management of identified and potential risks
 - describe new safety issues with potential impact on CT subject protection
 - examine whether safety information consistent with current knowledge
 - update status of clinical investigation/development programme

- Mainly applicable to interventional studies
- Includes all information relevant to subject safety, e.g. non-clinical studies
- Include comparator information only if relevant to subject safety
- Concise - assurance of adequate monitoring and safety profile evaluation
- One DSUR for a single agent, wherever possible
 - in co-development arrangements, agree on responsible partner
- Data lock based on first global authorisation of study conduct – Development IBD
 - can use last day of month rather than actual date for DIBD
 - switch to IBD on approval to synchronise with PSUR
- Combination products
 - fixed combo – single DSUR
 - non-fixed combo (regimen) – limited guidance, “most appropriate option”
- RSI – IB in effect at start of period
 - DCSI not mentioned
 - IB remains RSI even if approved SPC

- Stand-alone, suitable for submission to ECs etc.
 - introduction – report version and reporting period
 - investigational drug – mode of action, class, indications, dose, route of administration
 - estimated cumulative CT exposure
 - marketing authorisation(s)? (yes/no) – If yes, number of countries
 - summary of overall safety assessment
 - summary of important risks (based on Section 15 of the DSUR)
 - actions taken for safety reasons including significant changes to IB
 - conclusion
- All sections should be present, state when no information available

- Include
 - refusal of authorisation of a CT for ethical or safety reasons
 - suspension or early termination of a CT due to lack of efficacy or safety issues
 - resumption of a CT after suspension
 - failure to obtain marketing approval for a tested indication
 - risk management activities
 - protocol modifications for safety or efficacy concerns
 - restrictions in study population or indications
 - changes to informed consent for safety issues
 - formulation changes for safety
 - addition of special reporting requirements
 - plans for new safety trials
 - regulatory constraints on development (e.g., requirement for long-term animal studies, ECG study before Phase III). Cumulative listing of regulatory advice
- For drugs with marketing approval, also include
 - failure to obtain MA renewal
 - withdrawal or suspension of MA for safety reasons
 - risk management activities, e.g.
 - restrictions on distribution or introduction of risk minimisation measures;
 - changes in labelling that could affect development, e.g., restrictions to indication or population or new warning
 - new postmarketing study requirement(s)

- Interval data
 - SAR line listings
 - ARs of special interest
 - blinded and unblinded
 - unique subject/event representation
 - list under “most serious adverse reaction ... as judged by the sponsor”
- Cumulative data
 - tabulations of all SAEs
 - only terms defined as serious – not non-serious AEs or incidental findings
 - include comparators
 - AEs of special interest (if applicable)
- Exclude study endpoints (e.g. death in mortality trials, cancer progression) and AEs exempted from reporting in protocol
- Other data e.g. deaths, adverse dropouts, significant study results, relevant findings from other sources
- Lack of efficacy in serious or life-threatening illnesses relative to alternative therapies

- Concise, integrated assessment of all new relevant information vs. previous knowledge
- Do not summarise or repeat information in previous sections
 - provide interpretation and implications for CT subjects
- Risk evaluation, where relevant
 - newly identified issues or meaningful changes in known reactions
 - clinically significant adverse effects, including
 - toxicity for liver, bone marrow, kidney, CNS
 - cardiovascular effects, e.g. QT interval prolongation
 - immunogenicity / hypersensitivity
 - fatal ARs
 - special populations
 - overdose / misuse
 - protocol procedures (therapeutic or diagnostic)
 - drug interactions
 - etc.
- Succinct statement on balance between theoretical benefits and identified risks, particularly on changes since previous DSUR and impact on development program
- Conclusion / Summary
 - changes in knowledge since last DSUR, additional actions, important risks (e.g. possible warning, precaution, contraindication), possible basis for E2E safety specification

- Public consultation draft Jan 2010
- Key new topics / issues
 - ▲ extension of advanced therapies (cellular, genetic, tissue engineering) to new science (personalised / regenerative medicine, nanotech, “synthetic biology”)
 - support Innovative Medicines Initiative
 - ▲ public health threat preparedness (e.g. pandemics, bioterrorism, product quality, climate change)
 - ▲ provide benefit balance in risk assessment / communication
 - quantitative approaches
 - stakeholder involvement (prescribers, patients)
 - staggered approvals / conditional marketing
 - change RM plan into B/RM plan

- Improve risk minimisation tools
 - focus on HCPs throughout EU
- Proactive European risk management strategy
 - new data sources for medicine safety monitoring (e.g. ENCePP)
 - closer post-authorisation monitoring
 - international standardisation & collaboration (e.g. FDA Sentinel initiative)
 - support Innovative Medicines Initiative
 - public health threat preparedness (e.g. pandemics, bioterrorism, product quality, climate change)
 - provide benefit balance in risk assessment / communication
 - quantitative approaches
 - stakeholder involvement (prescribers, patients)
 - staggered approvals / conditional marketing
 - change RM plan into B/RM plan

- Enhanced postauthorisation monitoring of medicinal products by
 - multicentre safety / lack of efficacy studies
 - EU pharmacoepidemiology and pharmacovigilance network of excellence
 - research centres
 - medical-care centres
 - healthcare databases / electronic registries
 - existing networks covering certain rare diseases, therapeutic fields and adverse events
- Key part of European Risk Management Strategy (ERMS)
 - proactive monitoring of medicines throughout their lifecycle
 - Phase I - over 80 research institutions identified in EU
 - future
 - establish common research standards
 - develop code of conduct for transparency and independence of network research
 - comprehensive catalogue of resources (research centres, available data)
 - ultimate use by pharma and regulators to further characterise the benefit-risk balance of marketed medicines

- Predicting safety: bottlenecks to accurate evaluation of safety during pre-clinical development process, impacting later clinical development
- Predicting efficacy: bottlenecks in predictability of drug interaction in humans and how it may alter function
- Knowledge management: more effective utilisation of information and data for predicting safety and efficacy
- Education and training: close training gaps in drug development



- Impact of regulatory decisions on public health
 - B/R assessment & communication
 - actual vs. intended use
 - effectiveness of risk minimisation
 - therapy outcome vs. regulatory model



Discussion

- <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/default.htm>
- http://imi.europa.eu/index_en.html
- <http://www.encepp.eu/>
- <http://www.mhra.gov.uk/NewsCentre/CON2030355>



Thank You