International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

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The Problem

- Over the years: differing regulations for pharmaceutical registration in different regions (US, EU, Japan, etc.)
- Key question: Why harmonize?
- Example – illustrate frustrations of sponsors
- More work and more time: Is this value-added? Does this contribute to the quality of your document?
History of ICH

Why harmonize regulatory requirements for pharmaceuticals?

- Rising cost of healthcare and R&D – don’t have the extra money to waste on duplicating things. Cases where same fundamental data (quality, safety, efficacy) is sought, but detailed technical requirements different enough in each region (US, EU, etc.) that many expensive procedures had to be duplicated.

- Provide for a more economical use of resources around the world (human, animal, etc.) while maintaining safety – i.e., reduce duplication: For ethical reasons, don’t want to duplicate the use of human subjects in a trial if no value added, or animals either.

- Need for expeditious availability of safe, new drug treatments for patients: increased burden of work = more time to get new drugs to patient
History of ICH

- 1980’s - Harmonization of regulatory requirements pioneered in Europe (now EU) – Goal of a single pharmaceutical market - Discussions were also underway in US and Japan

- ICH established in 1990 - brings together regulatory authorities in the US, Europe and Japan as well as pharm. industry reps. to discuss pharm. product registration
Process of ICH

- Steering Committee established and general topics of discussion would be: Safety, Quality and Efficacy. Meets twice a year.
- Expert Working Groups would be set up to discuss each topic. They report on their progress to the Steering Committee.
- Eleven topics were designated for discussion at the 1st ICH.
ICH Process

- Observers present as well such as World Health Organization (WHO) and Canada (represented by Health Canada). This important group of non-voting members acts as a link between the ICH and non-ICH countries and regions.
ICH Harmonized Guideline Examples

- First format-based ICH guideline: Content and Format of Clinical Study Reports - Guideline for a single format for clinical study reports to be included in a registration dossier

Common Technical Document

Now also, eCTD:

Many regional differences located in Module 1, however some in other modules as well
Common Technical Document

- This format is also accepted in Australia, China, Canada, New Zealand and India
ICH Guideline Examples

- Safety: Dose selection for Carcinogenicity studies for pharmaceuticals
- Quality: Stability testing of New Drug Substances and Products
Steps in ICH process

- Step 1: Expert Working Group Consensus process begins on topic document
- Step 2: EWG Consensus obtained - Steering committee sign off on document
- Step 3: Regulatory consultation and discussion (in 3 regions) – comment on document and EWG agrees
- Step 4: Steering committee agrees on consensus
- Step 5: Implementation
Consensus Building

- Chronic Toxicity testing: Clash regarding EU standard of 6 months testing for a marketing application vs. 12 month standard in US
- Compromise reached of 6 months testing in rodents and 9 months in non-rodents
Differences remain

- About one-third of the drugs marketed in Japan, US and EU have different approved doses, the Japanese doses usually being usually. Example: Capecitabine (anti-cancer drug) dose in Japan is 1,657 mg/m2/day whereas in the EU and US it is 2,500 mg/m2/day.

- Pharmacogenomic advances may some day enable us to predict drug actions at individual patient level, beyond ethnic groups. But currently such ethnic differences are unforeseeable without clinical trials. Japan therefore requires clinical data obtained in the Japanese population in application dossiers, unless there is ground for exemption.
Differences remain

- Module 3: Quality of CTD-differences in regions: US uses polyethylene bottles for drugs, EU usually blister packs
- Different brand names in many cases across regions
Continuing the theme of Harmonization ....
The European Clinical Trials Directive
The Directive


Came into force May 2004

Purpose: to create a harmonized framework across Europe for clinical drug research
Previous European Union Regulatory Environment

- Multiple regulatory schemes as per individual member state law with differing degrees of sponsor burden
- No vehicle for sharing of clinical trial information between member states
- May need multiple approvals for multi-center trials within same member state
| Parallel Submission: EC with Regulatory Notification | Belgium  
Denmark  
The Netherlands |
|-----------------------------------------------------|------------------|
| Parallel Submission: EC with Regulatory Approval     | Ireland  
Spain  
Sweden  
U.K. |
| Sequential Submission: HA Notification after EC Approval | Finland  
France  
Germany  
Portugal  
Switzerland |
| Sequential Submission: HA Approval after EC Approval  | Greece  
Italy |
| Ethics Committee Only                                | U.K. (phase I only) |
Scope of the Directive

...“relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use) is a European Union directive that aimed at facilitating the internal market in medicinal products within the European Union, while at the same time maintaining an appropriate level of protection for public health. It seeks to simplify and harmonize the administrative provisions governing clinical trials in the European Community, by establishing a clear, transparent procedure.”
Articles of the Directive (select)

- Protection of clinical trial subjects
- Clinical trials on minors
- Clinical trials on incapacitated adults not able to give informed consent
- Ethics Committee
- Detailed guidance
- Conduct of a clinical trial
- Exchange of information
- Verification of compliance of investigational medicinal products with good clinical and manufacturing practice
- Notification of adverse events
Scope

The Directive covers ALL clinical trials on medicines, including all phase I, II, III & IV, multi-center, bioavailability and bioequivalence trials, that involve human subjects.
Definition of CTA- An authorization of a clinical trial by the competent authority of a member state will be a Clinical Trial Authorization (CTA) and will only be valid for a clinical trial conducted in that member state.
Request for a CTA

- The sponsor or legal representative of the sponsor in the community must submit a valid request for authorisation to the competent authority.
CONTENT

AND FORMAT
Documentation to be supplied in CTA

- Covering Letter
- Application form and EUDRACT printed form giving the trial number
- Part 1: Clinical Trial dossier
  - Investigator’s brochure
  - Complete protocol with amendments to date
  - Protocol Summary
  - Informed consent form
  - Subject Information leaflet
  - Provision for indemnity or compensation in the event of injury or death
  - Any insurance or indemnity to cover the liability of the investigator and sponsor (according to national requirements)
  - Financial arrangements: compensations to investigators and subjects
  - Insurance details
  - Copy of Ethics Committee opinion where available (con.)
Documentation to be supplied to request a CTA (con.)

- Manufacturing licence
- Declaration of the qualified person that the manufacturing site works in compliance with EU GMP
- List of Competent Authorities to which the application has been submitted and details of decision
- If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor
- Copy of authorisation for contained use or release of genetically modified organisms (when applicable)

Part 2: The investigational medicinal product dossier (IMPD) – summaries of quality, nonclinical and clinical information
National Health Authority Approval

- Formal submission
- Max. 60 day review period - One shot at amending the content after a request to do so by the competent authority
- Need approval in each country where trial is conducted; 1 HA approval only needed for multi-centre trials within country
Ethics Committee Approval

- Max. 60 day review period
- EC may “stop the clock” once for supplementary information
- A single EC opinion for multi-center studies within a single member state
Article of Clinical Trials Directive: Increased GCP (Good Clinical Practice) implemented

- Ensures trials conducted with high ethical and scientific standards
Trial Subject
Risks & Benefits

- **Strong** emphasis on the protection of the rights of the special populations unable to give consent, especially children and the mentally handicapped.

- Special populations are only to be used when there is direct benefit to be gained by that special population by their inclusion that can’t be gained in other ways.
Trial Subject Risks and Benefits

- Must be opportunity for subject (or legal representative) to review trial risks, objective, logistics and conditions with investigator or team member
- They must be informed of their right to withdraw from the trial at any time
Trial Subject Risks and Benefits – Children -

- Trials must be designed to minimize pain, discomfort, fear and any other foreseeable risk to the particular patient group being studied.
- Trials must be reviewed by ethics committees with specific expertise (e.g. pediatrics) in the study population or make use of consultants with that expertise.
Trial Subject Risks and Benefits – Incapacitated Adults - (i.e. dementia, psychiatric pts.)

- Written consent of a patient’s legal representative with the cooperation of the regular treating doctor is required before entering into a trial.

- Above all, the interests of the individual patients always prevail over those of science and society.
Article of Clinical Trials Directive: Exchange of information

To help avoid redundant efforts by clinicians & scientists, a European database of clinical trials should be established that is accessible to all member states that takes into account necessary trial subject and sponsor confidentiality.
Once a year during a trial, the sponsor shall provide the Member States where the trial is being conducted and their ECs with a listing of all suspected SAEs which have occurred over this period and a report of the subjects' safety.
IMPACT
Directive- Pros

- Parallel filing with EC application now possible in all countries including Finland, Greece, Switzerland, Italy, Portugal, France, and Germany
  - Previously these were done in series
Directive (Pros)

- Instituted more Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) – better protection of clinical trial subjects
- Better exchange of information
Directive - Cons

- Formal applications are now required in: Austria, Belgium, Germany, France, Luxembourg, Netherlands and Portugal
- Previously these only needed simple notifications
Directive - cons

- Cons: Harmonization has been hampered and process is costly and more time-consuming – Do you really need 27 different evaluations for different countries for one product?
- Cons: Particularly stresses resources for academic institutions
Suggested Improvements

- Single CTA in English for multi-national trials
- One central European authority for all member states
- Single ethical opinion throughout EU that would apply to all European countries
- If not, then more guidance needed to better harmonize approaches
- Agreed definitions on: substantial amendment, etc.
Interview EU Regulatory

- Complexities of CTAs – very burdensome - spreadsheet of different requirements by country- i.e., some want original documents, differing language requirements, etc.
- In one country, .. In France: they request that you send in the CTAs on a Monday or Friday
- Other countries: Germany- very conservative in interpretation – many questions
- Many deficiencies
- Definition of substantial amendments vary
Conclusion

- Correct intent with aspiring to harmonize, but not there yet – not even close. Much more work needs to be done.