

Clinical Trial Applications for New Chemical Entities: Sharing Strategies on Global Submissions to Help Minimize Unnecessary Resources

Moderator: Gail Owens, sanofi-aventis U.S. Inc.

Panelists: Jim Segretario, Abbott Laboratories
Mary Vandekauter, Pharmion
David Ziering, Bristol-Myers Squibb

Disclaimer

◆ The views presented here are the personal views of the presenters and do not necessarily reflect the views of their companies.

Introduction

- ◆ *Interactive* discussion on the possibility of preparing a CMC section for a clinical trial application that can be used in more than one region/country

Topics of Discussion

- ◆ Can we have a Global clinical Trial Application at Phase I?
- ◆ How do we facilitate documentation preparation to enable global submissions?
- ◆ What advice does Regulatory CMC provide to achieve a CMC section that can be used in more than one country/region?
- ◆ What “hot topics” are we encountering in dealing with regulatory agencies?
- ◆ How do we track questions/responses/changes in guidances to improve our global dossiers?
- ◆ What about later Phases II/III?

Topic One

◆ Can we have a Global clinical Trial Application at Phase I?

Topic One - Guidances

◆ Canada:

- Quality Overall Summary Chemical Entities (Clinical Trial Applications – Phase I)

◆ US

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

◆ EU:

■ EMEA:

- ◆ Guideline On The Requirements To The Chemical And Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products In Clinical Trials
- ◆ Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.

Topic One - Guidances

◆ EU (National Guidances)

- **France:** Content Of The Dossier Relative To The Chemical Or Biological And Pharmaceutical Quality Data And To Non-clinical Data Concerning The Investigational Medicinal Products Used In Phase I Clinical Trials
- **Germany:**
- **Ireland:** Guidance On The Investigational Medicinal Product Dossier
- **Netherlands:** Investigational Medicinal Product Dossier
- **United Kingdom:** Illustrative Guidance For Applications To The Competent Authority To Commence A Clinical Trial In Early Phase Of Development

Topic One – *Interactive* Discussion

- ◆ Good background document in RAPS regarding global submissions - Peters and Yamashita (RAPS Focus Mag)
- ◆ How much risk and information to share and take between regions? Provide the same level of information in more regions?
- ◆ Concern of approval times for amendments, etc. Management of CMC information, approvals, etc.
- ◆ Requires company strategy to accomplish.

Topic Two

- ◆ How do we facilitate documentation preparation to enable global submissions?

Topic Two – *Interactive* Discussion

- ◆ Global clinical trial quality templates for US and EU. Including author advice on what to add between regions and phases. Same numbering system between regions (e.g. 2.1 numbering system).
- ◆ Have set of templates for each phase or to cover all 3 phases.
- ◆ Amendments may add difficulty in terms of IMPD, clear strategy for IND but company decision for IMPD.
- ◆ Page limits do not seem to be requirements although EU wants summarized information. Will cause companies to think of how to present and prepare summaries rather than just including reports.
- ◆ Japan does not seem to be out of line compared to other regions. Japan is very concerned about safety so often asks for bridging clinical trials to lower the dosing requirements. For early stage, requirement is not so strict but becomes more strict with later phases. Do need to be very careful about excipients and demonstrate that another approved drug uses same excipients and same levels. Excipient information publically available.
- ◆ China has requirements close to NDA for first clinical trial submission.

Topic Three

- ◆ What advice does Regulatory CMC provide to achieve a CMC section that can be used in more than one country/region?

Topic Three – *Interactive* Discussion

- ◆ Always been some differences between regions. Japan for example, requires validation and evaluation for marketing approval but US just validation.
- ◆ Very similar from clinical trials standpoint. For example, from CMC standpoint, no issue to move from US to EU.
- ◆ For example, method validation at Phase I includes list of attributes studied so that can move easily between regions. Actual data not included since not needed even for EU.
- ◆ Some companies do minimum validation up front and then do additional validation at point that API and product is "locked-down". Need to differentiate critical and non-critical methods to produce sufficient data package to support submissions.
- ◆ GMP certificates needed for EU submissions. These can be critical if site hasn't been inspected recently.
- ◆ For EU, need to consider timelines for preparation and review of changes (e.g. 60 days for Agency review).
- ◆ Some differences between US and EU particularly for sterile products (e.g. bioburden specifications etc) even at Phase I.
- ◆ Definition of representative batch for different countries - does this mean same batch size, same testing, etc. Need to consider when company wants to move quickly into the clinical trial. Should be manufactured by the same process and with same profile. Need to evaluate as a company how much risk you accept regarding use of "representative batches".
- ◆ France asks for batch analysis information to be actual clinical batch data.
- ◆ Stability data at minimum typically 1 month of stability to cover Phase I but for EU it is hard to propose a shelf life on 1 month data. No specific Agency requirements for amount of stability data.
- ◆ Method validation – typically note included in the IND but for marketing application may be different regional expectations (e.g. Japan). For Phase II in India, a brief method validation summary is not sufficient, need to provide at least 1 to 3 pages of information.

Topic Four

- ◆ What “hot topics” are we encountering in dealing with regulatory agencies?

Topic Four – *Interactive* Discussion

- ◆ Genotoxic impurities are currently a very hot topic. Europe already applying a draft guidance used for marketing applications for early clinical trials.
- ◆ Many companies are setting up committees to look at genotoxic issues and genotoxic potentials.
- ◆ EU and US expect to see 1.5 microgram (50ppm level) limit for genotoxic impurities.

Topic Five

- ◆ How do we track questions/ responses/ amendments/changes in guidances to keep our dossiers global?

Topic Five – *Interactive* Discussion

- ◆ Many companies trying to develop “lessons learned” to apply throughout the product line.

Topic Six

◆ What about later Phases II/III?

Topic Six – *Interactive* Discussion

- ◆ Usually bringing in international regions (e.g. India, Latin America, etc) in Phase 2 or 3. Proprietary information is very much a challenge here.
- ◆ Often companies need to make business decisions to manage international registrations/intellectual information.

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 Thanks!