Responses to Questions from Regulatory Authorities:

*Measure Twice - Cut Once*

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Julia and Art - experience

**Julia**
- 20 years as a medical writer of clinical, regulatory documents
- Specialised in writing clinical part of CTD dossiers, including responses
- Twice President of EMWA

**Art**
- 40 years’ involvement in many aspects of drug and device development, review, and approval
- Preparation and filing of regulatory documents, worldwide
- Registered Agent with FDA
Aim Today

- Get an overview of regulatory procedures that result in questions being posed to applicants
  - Regional variability (Europe vs. USA)
  - How to prepare for receipt of questions
  - Process once questions have been received
  - Key role of the medical writer

Background

2 key stages for interactions with authorities:

1. Prior to submission of application dossier (FDA)
   - Exchanges of information between Sponsor and FDA
   - Formal and informal
   - Associated with Sponsor-requested meetings or response to Agency inquiries

2. After submission of application dossier
   - Regulatory authorities almost always pose questions requiring written responses
   - At the latest, start planning for responding to questions (ideally earlier)
   - Medical writing activities continue during and after dossier review
Different Regulatory Procedures: MAA and NDA Review Processes

European MAA Centralised Procedure Timelines

- **Day 1**: Clock start - Start of review process
- **Day 80**: Initial assessment reports from rapporteur to CHMP and applicant
  - First insight into reviewers’ reaction to dossier
- **Day 120**: Applicant receives Consolidated List of Questions from CHMP - Clock stop

CHMP = Committee for Medicinal Products for Human Use, the European Medicines Agency’s (EMA) committee responsible for human medicines
European MAA Centralised Procedure Timelines

- **Day 121**: Submit responses - Clock restart
- **Day 150**: Assessment report from rapporteur to CHMP (cc. applicant for information)
- **Day 180**: CHMP decides whether oral explanation (OE) needed to address outstanding questions
  - If OE is needed, specific questions of concern - Clock stop
  - Further questions, but no need for OE

US FDA NDA/BLA Review Timelines

- **Day 1**: date the NDA was submitted = start of review clock
- **By Day 60**: FDA makes decision on fileability
  - Is application sufficiently complete to allow a substantive review
  - Communicates by Day 74 (known as Day 74 letter)
- Per Prescription Drug User Fee Act (PDUFA), FDA expects to review & act on at least 90% of NDAs for standard drugs
  - No later than **10 months** after applications are received (standard review)
  - Review goal is **6 months** for priority drugs (priority review)
- **Advisory Committee** typically 2-3 months prior to end of review
  - Always for BLAs
  - For NDAs: for unclear risk/benefit ratio, concerns with choice of endpoint or trial design, troubling safety signals, or potential need for further studies
US FDA NDA/BLA Questions and Responses

- Reviewer questions possible any time through to the Action Letter
  - Questions come independently from specific reviewers (CMC, Nonclinical, Clin Pharm)
- FDA generally puts no time limit on response
  - On occasion they may specify they want a request within a certain time
  - Don’t have to respond to all questions at the same time (can split them up)

EU MAA Centralised vs. US NDA/BLA

- MAA: Consolidated List of Questions provided on Day 120/Day 180
  - Initial assessment reports on Day 80/Day 150 (i.e. early insight possible)
  - Timing of questions is predictable, easier to plan resources
  - Time to respond is flexible (between 1 to 6 months) and thus more practical
- NDA/BLA: Questions can be sent to applicant any time after start of review
  - Timing of questions is not predictable, more difficult to plan resources
  - Generally answers need to be provided ASAP
Preparing for Questions (Irrespective of Region)

Get ready early!

“Give me 6 hours to chop down a tree and I will spend the first 4 sharpening the axe.”

— Abraham Lincoln

“Measure twice - cut once.”

— Old carpenters’ saying
First: Assemble a Rapid Response Team

- Assemble team representing key functions
  - Clinical
  - Biostatistics
  - Clinical Pharmacology
  - Preclinical (including CMC)
  - Regulatory
  - Medical writing and document management
- Clarify process
  - Frequency of meetings, availability
  - What can be expected, and when

Second: Collect Thoughts

- Identify potential issues before they are asked
  - Weaknesses of drug or class of drug
  - Deficiencies in development program
  - Deficiencies in data analysis
  - Issues of interest to regulators
- Everything must be label-focused
  - Don’t spend energy on other ideas!
- For MAA, benefit of having issues raised in initial assessment reports at Day 80 and Day 150
Goals for Initial Preparations - Be Ready to Run!

• Prepare and review outlines of responses and strategies
  • Do not try to craft detailed responses: these may need to change depending on how the questions are worded
• Conduct anticipated data analyses
• Aim for ambitious timelines to
  • Maintain momentum and ideas in the team
  • Ensure thoughts are gathered before questions arrive
  • For MAA: useful to have strategies developed and new analyses ready by Day 80

Managing the Planning and Writing Process

Both in Preparation Phase & Response Phase
Keep the Team Focused

• Clear definition of steps and responsibilities
  • Post-submission motivation of team
  • Definition of (written) deliverables (brainstorming)
  • Responsibilities for contributing to deliverables
  • Review process
  • Binding timelines!

• Effective to have a medical writer coordinate written contributions from across the team

Organisation is Everything!

• Start a spreadsheet itemizing
  • Potential issue that could generate question
  • Name of person responsible for providing response (core authors)
  • Storyline for response (text or bullets)
  • Status with date (completed, re-analysis pending, clarification by regulator, awaiting expert input, etc)

• Medical writer is well positioned to create and update this spreadsheet
Medical Writer Pulls it All Together

- Co-ordinating MW
  - High-level involvement across all areas
- May assign a different MW to each core team
  - Preclinical, microbiology, clinical pharmacology
  - Phase III efficacy
  - Phase III safety

Several Medical Writers May be Needed
Medical Writing Skills Needed

- Writing skills
- Knowledge of document templates
- Document review skills
  - Ensure guidance is followed
  - Maintain version control
- Organisational skills (coordinating review of numerous files, compilation of comments)
- Presentation skills (advantageous ways to get message across)
- Diplomatic skills (reduce friction between team members under stress)

Helpful Hints for Managing the Process

- Be proactive
  - Let teams know immediately if more data are needed
  - Clarify questions as they arise
- Ensure regular meetings are held
  - Between MWs and team members
  - Between all MWs (even daily)
Responding to the Questions

When Questions Arrive

- Identify questions already addressed by preliminary work
  - Do drafts already exist and are content authors already assigned?
  - Is response strategy the same?
- Assign authors for new questions
  - Discuss and agree on response strategies
- Agree which questions are critical and/or will take more time to ensure teams focus on these first
Process for FDA Questions

- Questions can arrive any time
- Define a process for action once questions arrive
  - Meeting called same or next day
  - Responsible people assigned
  - Time to final response agreed on
- Agree with team on response time goals
  - Routine requests (e.g., looking up and providing existing data): 24 hours
  - Complex requests (e.g., new analyses, expert input needed): 2-5 days, as appropriate

Be Systematic in Organising Activities

- Create a system for identifying individual responses, for example:
  - EMEA: Clinical Concern #54
  - FDA: by date and item
- Prepare a single file for each question and response
  - Simplifies ongoing, parallel reviews
  - Collate only when all are final
- Ensure that associated source documents and references are filed with each response
Tracking Sheet

- Create a spreadsheet to track each response
  - Drafted, Reviewed, Final
  - Outstanding issues/action items
  - Appendices
    - Yes, No; available or under construction?
  - Literature
    - Yes, No; available?

- With many questions and short time frames, **this can be a daily task** to ensure nothing falls through the cracks

### Tracking Sheet

<table>
<thead>
<tr>
<th>Section</th>
<th>CC No.</th>
<th>Question content</th>
<th>Author</th>
<th>File status</th>
<th>Notes</th>
<th>QC status</th>
<th>QC person</th>
<th>Append/Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>25a</td>
<td>Why was this design used</td>
<td>JFK + Clinician</td>
<td>1st draft in review</td>
<td>Standard design; guidelines recommend</td>
<td>Ongoing</td>
<td>QC1</td>
<td>Append: No Refs: Yes</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2.1</td>
<td>25b</td>
<td>Perform analyses excluding all children</td>
<td>DF + Statistician</td>
<td>Awaiting new analyses</td>
<td>Need to present in a way clearer for physician</td>
<td>Not yet</td>
<td>QC2</td>
<td>Append: No Refs: No</td>
</tr>
<tr>
<td>2.3</td>
<td>26</td>
<td>What was incidence of toe infections</td>
<td>JFK + PV person</td>
<td>Final</td>
<td>Done + revised</td>
<td>QC1</td>
<td></td>
<td>Append: Yes Refs: No</td>
</tr>
<tr>
<td>2.3 Safety</td>
<td></td>
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<td></td>
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</tbody>
</table>
Appendices and References

- Identify responses needing appendices or references (including new analyses)
- Separate files needed for each appendix
- List of references needs to be created
  - Can have a list after each question or a single list at end of file
  - Good to maintain list within each question while writing, then collated into single list in consolidated response document
- Ensure copies of all references are available for submission

What is Expected in Responses

- No official regulatory guidance for format and content of responses
  - Stay strongly focused on the question being asked
  - Ensure reviewer friendliness: response should be brief as possible to answer the question
- No new data may be submitted, unless requested or agreed to by Agency
  - Data already submitted can be re-analysed
- Keep format and layout consistent with dossier
Case Study: EU Centralised Submission

- Rapid response team identified
  - Clinicians, statisticians, medical writers, regulatory, etc.
- Expected analyses were initiated
- Did not begin crafting responses until Day 80 questions arrived
- But confirmed all would be available from Day 80 until submission of responses on Day 121

Case Study: EU Centralised Submission

- Day 80: received first set of questions from Rapporteur and Co-rapporteur
  - Team determined which are most likely to stay and need considerable effort (e.g. re-analyses, etc.)
  - Began work on getting all information needed for these
Case Study: EU Centralised Submission

- Day 120: list of consolidated questions
  - 84 clinical questions, several with multiple questions
  - A few questions had been removed but new ones had been added to Day 80 set

Case Study: EU Centralised Submission

- Coordination by lead writer
  - Created tracking sheet for all questions
  - Divided responses among available writers
  - Each day, monitored progress and tracking sheet updated
  - Responses were reassigned on a rolling basis to writers with capacity (i.e. who completed their questions or were waiting for data or team input)
Case Study: EU Centralised Submission

• 7 writers
• 89 questions (including subquestions)
• 292 pages in compiled response file
• 17 additional appendices

• All responses final within 55 days

Helpful Hints for Writing

• Don’t expect the Agency to do your work for you
  • It isn’t sufficient to say the information is in Listing 86
  • Give pre-digested information they can use in their assessment reports

• When asked for something already provided
  • Remember: reviewers are only humans confronted with a complex dossier and little time
  • Politely provide the information again (do not just refer to where it is)

• Demonstrate you have thoroughly reviewed applicable guidance and correspondence
  • Make reference to these as part of the response
The Bigger Picture: Associated Documents and Activities in the Response Process

• Meeting Requests
  • Know what type of meeting is appropriate

• Maintain contact with FDA Project Manager or Consumer Safety Officer

• Briefing Packages (aka Briefing Books)

• Do your homework...be prepared
Meetings with Sponsor

Notification of Easily Correctable Deficiencies
• FDA informs applicants of need for more data, information, or technical changes
• Usually doesn’t apply to major scientific issues

Other Meetings

• Other meetings between CDER/CBER/CDRH and applicants may be held to discuss scientific, medical, and other issues that arise during the review process
• CDER/CBER/CDRH makes every effort to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times
Meetings with FDA

During the course of reviewing an application, FDA usually communicates often with Sponsors about scientific, medical, and procedural issues that arise during the review process.

- CDER Data Standards Manual
  http://www.fda.gov/cder/dsm/drg/Drg00917.htm

- Categorized as A, B, C - based on nature of meetings

Meetings with FDA

- **Type A** Meetings help an otherwise stalled product development program proceed.

  - Examples of a Type A meeting include:
    - Dispute resolution
    - Discuss clinical holds
    - Special Protocol Assessment [SPA]

  - Lead-time: 30 days
Meetings with FDA

- **Type B** Meetings are associated with development milestones.
  - Examples of a Type B meeting include:
    - Pre-investigational new drug application (pre-IND) meetings
    - Certain end-of-phase 1 meetings
    - End-of-phase 2 and pre-phase 3 meetings
    - Pre-new drug application/biologics license application meetings
  - Lead-time: 60 days

Meetings with FDA

- **Type C** Meetings are any meeting other than a Type A or Type B meeting between CBER or CDER and a sponsor or applicant regarding the development and review of a product.
  - Lead-time: 75 days
Pre-IND Meetings

**21 CFR 312.82(a): Early consultation**

(a) Pre-investigational new drug (IND) meetings. Prior to submission of initial IND, Sponsor may request a meeting with FDA-reviewing officials.

- Review and agree on design of animal studies needed to initiate human testing
- Discuss scope and design of Phase 1 testing
- Plans for studying drug product in pediatric populations
- Best approach for presentation and formatting of data in IND

End-of-Phase 1 Meetings

When data from Phase 1 clinical testing are available, Sponsor may again request a meeting with FDA reviewing officials.

- Review and reach agreement on the design of Phase 2 controlled clinical trials
  - Testing adequate to provide sufficient data on safety and effectiveness to support approvability for marketing,
  - Discuss need for, as well as the design and timing of, studies of the drug in pediatric patients.

**21 CFR 312.82(b): Early Consultation**
End-of-Phase 2 Meetings

• Determine whether it is safe to begin Phase 3 testing.
  • Plan protocols for Phase 3 human studies and discuss and identify any additional information to support the submission of an NDA.
  • Agree on overall plan for Phase 3 and objective/design of particular studies.
• One month prior to "end-of-the Phase 2" meeting, Sponsor should submit background information and protocols for Phase 3 studies.
  • Data supporting claim of new drug product
  • Chemistry data
  • Animal data and proposed additional animal data
  • Results of Phase 1 and 2 studies
  • Statistical methods being used, specific protocols for Phase 3 studies
  • Copy of the proposed labeling for a drug, if available.

Pre-NDA/BLA Meetings

• 6 to 12 months prior to submission
• Comprehensive summary of relevant data generated during development
• Discuss all critical issues (that may affect ability to review/approve the application)
• Special Protocol Assessment
Advisory Committee Meetings

- Post-submission and review by FDA of Marketing Application.
- Briefing Book “on steroids"
- Includes PowerPoint slide decks

Briefing Document

- Agenda outlining questions
- Sponsor attendees
- Describes the product, pre-clinical testing, and clinical trial design to date
- Purpose is to educate CDER/CBER/CDRH reviewers about the product, testing strategy, and other issues
1. Address issues
   • Ensure coverage of ALL previously-communicated issues

2. Don’t muddy the waters
   • Stick to relevant topics and data
   • Avoid speculation

3. Triage
   • Create Briefing Book in a way that brings the most critical (and often most difficult) issues to the table first. You only have a limited amount of time (usually 60 minutes)

4. State your position and ask for affirmation
   • This should be in the form: “Sponsor believes that we have sufficient data to support the dosing regimen proposed in the protocol for our first-in-human study. Does the Agency agree?”

5. Take Notes
   • When you receive the meeting minutes from FDA, you will want to be able to challenge any areas of disagreement.
Thank you!

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Questions to discuss

• Who is using similar methods for planning stages of responses?
  • Are rapid response teams standard?

• Is anyone using other methods for coordinating responses?