Medical Writing Between Dossier Submission and Drug Approval

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Session based on experience working as Lead MW for Drug X over 3-year period

Global dossier for Drug X was submitted in US and Europe

Over 2 years working on post-submission activities for Drug X
  – Mostly related to FDA requirements
Contrary to ICH pre-submission, no harmonization in post-submission activities (US and Europe)

Demand for medical writing can be unpredictable

Little regulatory guidance on documents that need to be written
Session outline

- Between dossier submission and drug approval
  - Description of NDA (FDA) and MAA (EMA, CHMP) review processes
  - Medical writing activities
- FDA Advisory Committee hearings
- CHMP Oral Explanations
- Medical writing roles and responsibilities
- Questions
NDA and MAA Review Processes
NDA review (1)

- Applicant submits dossier to FDA

- **Day 1:** Start of review process
  - Reviewer questions possible at any time through to Action Letter

- **By Day 60:** FDA decision on fileability, review period, need for Advisory Committee hearing
  - 6-month review for priority applications
  - 10-month review for standard applications

- 4-month safety update
  - Safety update submitted 4 months after NDA
Requests from reviewer for further information
  – Rapid response needed from applicant

Advisory Committee hearing, if convened by FDA
  – Extensive preparations required by applicant

Labeling negotiations
  – Meetings between FDA and applicant towards end of review process

By Month 6 or 10: FDA communicates decision (Action Letter)
  – Approved: drug can be marketed in USA
  – Approvable: problems need to be addressed before approval
  – Non-approvable: drug may need additional research or reformulation
NDA review (3)

- **Issue of Action Letter = end of review**
- In case of approvable or non-approvable
  - *Drug X approvable in 3 of 4 indications*
  - Sponsor negotiates strategy with FDA
  - NDA may be amended and resubmitted
  - If resubmitted, new review cycle is started
- **Day 1**: Start of review process
  - Reviewer questions possible any time through to Action Letter
- **By Month 2 or 6**: FDA communicates decision (Action Letter)
  - *Drug X approvable in 3 of 3 indications*
MAA review (1)

- Applicant submits dossier to EMA
- Validation of dossier within 10 working days
- **Day 1: Clock start** - Start of review process
- **Day 80:** Initial assessment reports (ARs) from rapporteur to CHMP and applicant
  - First insight into reviewers’ reaction to dossier
- **Day 100:** Comments on ARs from CHMP to rapporteur
- **Day 115:** CHMP receives draft questions from rapporteur
- **Day 120:** Applicant receives List of Questions (LoQ) from CHMP - Clock stop to prepare responses (3 months)
MAA review (2)

- Applicant submits responses to LoQ to CHMP
- **Day 121:** Restart of review process - Clock restart
- **Day 150:** Response AR from rapporteur to CHMP (cc. applicant for information)
- **Day 170:** CHMP comments to rapporteur
- **Day 180:** CHMP issues List of Outstanding Issues (LoOI) and decides if oral explanation (OE) needed - **Clock stop to prepare responses (1 month)**
  - *Further questions on Drug X, but no need for OE*
MAA review (3)

- Applicant submits responses to LoOI to CHMP
- **Day 181-210:** Clock restart
- AR on Applicant’s responses to D180 LoOI
- If OE is needed, usually held 1 month after submission of written responses
- Applicant submits final draft labelling to CHMP
- **Day 210:** CHMP opinion and AR sent to applicant
  - *Drug X recommended for approval in all 4 indications*
- **Day 277:** Final Commission Decision

Source: EMEA/75401/2006 Rev. 2
EMA website (Q&A on Pre-submission Guidance)
Documents / Writing Required
- Responses to reviewer questions (FDA + EMA)
- 4-month safety update (FDA) / RMP update (EMA)
- NDA amendments (FDA)
- Materials for AC hearings and Oral Explanations
  - Responses to questions (EMA)
  - Briefing document (FDA)
  - Rehearsal materials (EMA + FDA)
  - Presentation slides and scripts (EMA + FDA)
- [Labelling (FDA + EMA)]
- [Grounds for appeal (EMA)]
FDA: Questions can be sent to applicant any time after start of review
  – Timing of questions is not predictable, difficult to plan resources

EMA: Applicant receives List of Questions on Day 120
  – Often based on initial assessment reports from Day 80 (i.e., early insight possible)
  – Timing of questions is predictable, easier to plan resources
Responses to reviewer questions (2)

- Ideally, directly after submission of dossier (before questions arrive)
  - Identify appropriate “rapid response” team
  - Define a process for preparing responses
  - Identify potential issues based on known weaknesses in submission dossier
  - Prepare and review draft responses and/or conduct anticipated data analyses
Responses to reviewer questions (3)

- Questions vary in nature
  - Simple, technical (little or no MW input)
  - Complex, scientific (extensive interaction between MW and project team to draft and review responses)

- Can cover any aspect of the submission
  - Nonclinical, clinical pharmacology, clinical efficacy and safety, quality (CMC issues)
No official regulatory guidance for format and content of responses
- Stay strongly focused on the question being asked
- Ensure reviewer friendliness: keep response \textit{as long as necessary, and as short as possible}

No new data may be submitted
- Data already submitted can be reanalyzed
NDA: 4-month safety update

- Little regulatory guidance for structure and content
  - 21 CFR 314.50: “...required to include the same kinds of information... in the same format as the integrated summary”

- Submit CSRs for studies completed since NDA
  - 5 Phase I and 1 Phase III studies

- Include summaries of new information for key areas
  - CMC, Nonclinical, Clinical pharmacology (Phase I), Safety/Efficacy (Phase III)
  - Updated labeling
Safety updates - MAA

**MAA: Risk Management Plan update**

- Revisions based on Pharmacovigilance Risk Assessment Committee (PRAC) comments and questions
NDA Amendments

- At request of FDA or applicant
- Opportunity to submit new data and updated interpretations
- Resembles an NDA
- Include summaries of new information for key areas
- *Two NDA Amendments for Drug X*
NDA Amendment 1

- Clinical study reports
  - 4 Phase I studies
  - 2 Phase III studies
  - 1 Japanese Phase II study
- 1 White Paper on cardiac safety
- Update of ISE/ISS after data censoring
- 3-month preparation time
In response to “approvable” decisions after AC hearing and Action Letter

Clinical study reports
- 8 Phase I studies
- 3 Phase III studies
- 1 Japanese Phase III study
- 1 large safety study (24,000 subjects)

Post-marketing data

Update of ISE and ISS

1-year preparation time
AC Hearings and Oral Explanations
Decisive face-to-face meetings that can make or break an approval

Generally a one-off chance to be persuasive, have to get it right the first time round

Need careful preparation, starting well in advance

Familiarity with the procedures helps

Important to transmit the correct message in the limited time available - *good medical writing skills are vital!*
AC hearing / OE team

- Project team
  - Project leader, subject area responsibilities: therapeutic area leader, clinical director, pharmacovigilance, clinical pharmacology, microbiology, nonclinical, CMC
  - Support services (regulatory, medical writing, publishing, project management, media relations)

- Logistical services
  - Audio-visual professionals (slidemaking, [technical services for presentations]), [meeting planning, training, background research]

- Expert consultants for individual subject areas
  (e.g., cardiac, hepatic, microbiology, etc)

- Upper management
AC Hearings
Public review of benefit-risk by a committee of independent experts

Committee votes on approval recommendation
- Hearing 1: 1 of 4 indications recommended for approval
- Hearing 2: 3 of 3 indications recommended for approval

FDA decides on approvability
- Hearing 1: 3 of 4 indications considered “approvable”
- Hearing 2: 3 of 3 indications still considered “approvable” but...
Agenda for AC hearing

- Formalities (15 min)
- Applicant presentation + Q&A (100 + 30 min)
- FDA presentation + Q&A (100 + 15 min)
- Other expert presentations (45 min)
- Open public hearing (60 min)
- Discussion of questions and vote on approvability by committee (120 min)
  - Process now changed from sequential to simultaneous voting
FDA and Applicant presentations

- FDA and Applicant often have different approaches to presenting and interpreting facts

- FDA
  - Protects and promotes public health
  - Political constraints

- Applicant
  - Promotes product under review
  - Commercial constraints

- FDA and Applicant
  - Determine benefit versus risk based on available information
Hepatotoxicity was seen in rats, dogs, and monkeys and this hepatotoxicity was manifested as increases in AST and ALT. Hepatic necrosis was seen in a 4 week rat study and hepatocellular hypertrophy and multi-nucleated hepatocytes were seen in some but not all of the preclinical animal studies.

Effects typical of macrolide antibiotics were observed. In rat, dog, and monkey toxicity studies, elevations of liver enzymes associated with histological correlates of liver cytolysis were noted at high doses in some but not all studies. These effects were slight, dose related, and fully reversible.
Nonclinical studies

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Phase I adverse events

- Doses up to 3200 mg were investigated. Generally, the number of subjects with AEs increased with dose. The most frequent AEs possibly related to Drug X were gastrointestinal effects (nausea and diarrhea). There were no serious adverse events. No subjects were discontinued due to AEs.

- There was a clustering of events at the 2000 mg dose (19%). At higher doses, there was somewhat of a fall-off (4% at 3200 mg). In one study in elderly subjects up to 2000 mg, there were 3 patients who achieved increases in ALT and AST with levels ranging from approximately 100 to 300 U/L... The third patient was a 62-year-old male who... 14 days after 2000 mg dose of Drug X experienced increases in ALT and AST; as part of the serologic evaluation for etiologies of hepatitis this patient had a positive result for Epstein Barr Virus-IgM. The viral serologies do not provide definitive evidence of diagnosis of a viral etiology and this could therefore represent a possible drug effect. In such a situation, the drug effect would have a 7- to 17-day latency period given the chronology of events here.
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Almost all reports of hepatic AEs in Phase III studies refer to asymptomatic liver enzyme abnormalities, which were generally mild and reversible. The frequency of these hepatic AEs was well balanced between Drug X and active comparators. In all studies, serious hepatic AEs occurred in 3 (0.1%) subjects treated with Drug X and 1 (0.1%) subject treated with comparator.

In Phase III studies, the hepatic AE rates were similar for Drug X (800 mg once daily) and comparators. With regards to serious hepatic AEs, from the comparative studies, there were 2 Drug X-treated patients and 1 comparator-treated patient who experienced a serious hepatic AE. In the non-comparative studies there was 1 additional Drug X-treated patient who experienced a serious hepatic AE.
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With regards to combined abnormalities, the late Dr. Hy Zimmerman in his book, "Hepatotoxicity", stated that drug-induced hepatocellular injury with overt jaundice is associated with a mortality of at least 10%. Hy's law... is a surrogate for this..., we often look at AST or ALT > 3x ULN combined with total bilirubin >1.5x ULN. No patients met this criterion strictly. However, there are some patients in the Drug X treatment arm that I’d like to comment on. The first is a patient who has an ALT elevation of 19x ULN and a total bilirubin of 1.55x ULN based on local laboratory data. This patient also had a slightly elevated ALT of 81 U/L (ULN = 49 U/L) at baseline. There were 2 other Drug X patients who didn’t quite achieve the level of elevation of 3x and 1.5x ULN but were close. One of these 2 patients also had a mild increase in alkaline phosphatase. 

The rate of ALT increase was similar between Drug X (0.5%) and the comparators (0.4%) in subjects with normal transaminase levels at baseline. In those with elevated transaminases at baseline, who were mainly enrolled in CAP studies, the frequency of ALT >3 x ULN was 8.5% for Drug X and 11.1% for the comparators.

In CAP subjects with normal transaminase levels at baseline, there was a small difference in the frequency of ALT increase >2x ULN (2.5% Drug X vs. 1.0% comparator) similar to what is observed with a macrolide; no signal was observed for ALT >3x ULN (0.8% Drug X vs. 0.5% comparator).

There were no cases of transaminase increase of >3x ULN and bilirubin >1.5x ULN.
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A 53 year old male treated for CAP was enrolled with elevated transaminases and elevated eosinophils. He had 2 episodes of transaminase increase, with return to baseline after the first episode and a second episode occurring nine months later. To our knowledge there has been no published report of drug-induced liver injury or 2 distant episodes that were triggered by 1 drug intake. Therefore, we believe it is unlikely that Drug X is the etiology of the hepatitis episode observed in this patient.

This case is really unique in my experience. I'm not aware of any really well documented cases of autoimmune hepatitis that have followed a drug-induced injury, but this I suppose could be the first one. Overall, the first liver biopsy certainly looks like drug-induced liver disease. The second one, I have to admit, I'm not really sure what exactly is going on there.
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Oral Explanations
Indications in the "Summary of Conclusions" received on **Day 80** that an oral explanation may be impending

- ...the product is approvable if satisfactory answers are given
- ...the product would be approvable provided answers are given and indications, other elements, and conditions are amended
- ...the product can at present not be recommended for registration
Oral Explanations (2)

- Presentation by Applicant to panel of CHMP members
- Maximum of 11 delegates from Applicant
- Only relatively small amount of presentation material required
  - Applicant presentation (short and precise) must fit the allotted time
  - Only address “outstanding issues”
  - No new information permitted
  - Backup slides for anticipated, related questions
Guideline specifies overall duration of 60 min
- Sequential responses to each outstanding issue, followed by a conclusive statement (30 min)
- Main SmPC amendments and main specific obligations/follow-up measures (10 min)
- Question & Answer session (20 min)

Source: CPMP/2390/01
EMA/605261/2012 covers OEs referred to PRAC (30 mins duration)
Contrasts between AC hearings and Oral Explanations (1)

- **AC**: Generally positive connotation
- **OE**: Generally negative connotation
- **AC**: Review of entire development program
- **OE**: Focus on “outstanding issues”
- **AC**: Panel of consultants to FDA
- **OE**: Panel of CHMP members
- **AC**: Panel delivers a recommendation to FDA, not binding but usually followed
- **OE**: Positive or negative outcome decided upon directly by panel (CHMP members)
- **AC**: Documents and transcripts are disclosed via the internet ([www.fda.gov](http://www.fda.gov))
- **OE**: Documents and transcripts are not made public
Contrasts between AC hearings and oral explanations (2)

- **Documentation required from Applicant**
  - *AC*: Applicant briefing document to be submitted to FDA 1 month before hearing, and presentation slides 1 day before.
  - *OE*: Answers to outstanding issues to be submitted to CHMP 10 days before meeting. Presentation slides 1 day before (plus 60 paper copies on the day itself).

- **Documentation issued to Applicant**
  - *AC*: FDA briefing document to be sent to applicant ca. 2 weeks before hearing, and presentation slides 1 day before.
  - *OE*: No specific documentation provided by CHMP.
Contrasts between oral explanations and AC hearings (3)

- **Location**
  - **AC**: Hotel in Washington DC area (variable location, Applicant can organise extensive facilities)
  - **OE**: CHMP plenary meeting room at EMA, London (fixed location, applicant has no facilities)

- **Time allocated**
  - **AC**: 1 day
  - **OE**: 1 hour
Materials required for AC hearing

Guidance:
http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/LawsRegulationsGuidance/default.htm
Documents / Writing required

- Applicant’s briefing document
- Main presentation slides
- Main presentation scripts
- Backup slides
Applicant’s briefing document

- Submitted 1 month before AC hearing
- Concise, high level overview of NDA storyline
- Include an executive summary
- Must not include any new data
- Develop in parallel with main AC slide presentation
- Once submitted, will be in public domain - proceed with caution!
Main presentation slides

- Essential for communicating applicant’s key messages
- Content should reflect applicant’s BD
- Establish slide design and layout early in process
- Include navigation slides to guide presentation structure and who is presenting
- Generally a challenge to match number of slides to limited time available
- Keep all versions of slides - people will change their minds!
Main presentation scripts

- Facilitate development of the presentation
- Help presenters keep to allotted time
- Allow a substitute presenter to step in at short notice
- Can be used for extended team review
Backup slides

- Used to answer AC questions
- Need to cover all aspects of development program
- May need large number of slides (>4000) but...
- Only limited number will be shown (7)
- Requires systematic organisation and identification to enable rapid retrieval by back-up team members
Preparations for Oral Explanation
Day 180: CHMP identifies outstanding issues to be addressed in writing and/or during an OE
- 1 month clock stop for written responses

10 days before OE: Applicant submits written response package to outstanding issues to be addressed in OE
- Include updated SmPC

7 days before OE: Applicant submits draft OE presentation

1 day before OE: Applicant submits e-copy of final slides

Day of OE: Applicant provides 60 paper copies of slides

Many principles for preparing documents and slides for FDA AC also apply to OE preparations
Medical Writer roles and responsibilities
Medical Writer roles and responsibilities

- “Glue that holds it all together”

Preclinical/Microbiology

AV team

Medical Writer

Biostatistics

Regulatory

Clinical pharmacology

Clinical/Pharmacovigilance
Medical writers involved in the post-submission process

- Co-ordinating MW
  - high level involvement across all areas

- Assign MW to each core team
  - Preclinical, microbiology, clinical pharmacology *(1 writer)*
  - Phase III efficacy *(2 writers)*
  - Phase III safety *(2 writers)*
Medical writing skills

- Writing skills (BD, written responses)
- Document review skills
  - Ensure guidance is followed
  - Maintain version control
- Organizational skills (timely distribution of materials for AC rehearsals)
- Presentation skills (advise on slide generation)
- Diplomatic skills (reduce friction between team members)
Meeting activities

- Essential to have regular meetings between MWs and team members
- Rapid response to reviewer questions (as required)
- NDA amendment planning (weekly)
- FDA Advisory Committee hearing
  - AC rehearsals (once/twice weekly)
  - Mock AC (monthly)
  - AC hearing itself (once only)
- CHMP Oral Explanation
  - Compressed programme of meetings in 30-day preparation period
- Regular communication is also essential between MWs
Questions?