

Health Authority Questions: how to deal with the diversity

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ABSTRACT

A few months after the submission of a dossier, the first health authority questions take place. As each regulatory authority has its process and timelines, the statistical programming group will have to collaborate with project team to respond to health authority questions while adapting the organization of the work according to the different runs of questions.

The intention of the paper is to highlight the differences between each health authority functioning, the questions that can be expected, the kind of issues that can happen and how to face and solve the problems... in other words how to be successful and have a positive feedback on your submission.

INTRODUCTION

Often, pharmaceutical companies decide to submit a dossier for a new product simultaneously in all worldwide markets, this means sending the dossier to the different health authority agencies: Food And Drug Administration (FDA), European Health Authority (EMA), Japan Health Authority (JHA), Rest Of the World (Australia, Canada, Switzerland...). Each agency has their own process when reviewing the dossier and doesn't focus on the same part, even if for all, the overall quality remains the most important element.

On this paper will try to give an overview of the contents of the dossier, what happens during the questioning process in term of timelines, the actual questions and work organization. Some recommendations are also described to make this difficult period easier and obtain the approval without becoming crazy.

CONTENTS OF THE DOSSIER

CONTEXT

The team worked for a submission of an oncology product in patients with metastatic carcinoma of the kidney. This submission was done on an interim analysis. This involved some fairly major changes:

- On the submission timelines: timelines were shortened, submission plan was setup just after the GO decision
- On the contents: because of the early data, an update of efficacy and safety data based on a new cut-off was also submitted to the FDA and EMA respectively 60 days and 90 days after the first submission. This updated data was used for the Japanese submission.

WHERE ARE THE DIFFERENCES ON THE DOSSIER

Since 2007, FDA requires an electronic submission. This electronic file contains:

- The CSR (Clinical Study Report) for the pivotal study plus all supportive studies
- The SCS (Summary of Clinical Safety) which is a pooling of safety data coming from supportive studies
- The SCE (Summary of Clinical Efficacy)

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- The transport file datasets including:
 - ✓ For pivotal studies:
Raw and derived datasets, Blank annotated CRF (Case Report Form), Dataset Definition document describing the contents of the derived datasets and the derivation

In addition to the above it is recommended but not mandatory to deliver:

- ✓ Some key programs (primary efficacy endpoint derivation for example)
- ✓ The pooled datasets for SCS and SCE
- ✓ All the PK data (reports, datasets and POP PK)

This should be agreed with the FDA during the Pre NDA meeting (NDA=New Drug Application)

In comparison the FDA, the EMEA and JHA don't require any datasets but are more focused on the documents, Tables, Listings and Graphs provided with the CSR. In particular, listings of raw data should be included in the dossier.

The EMEA requires a special document called Risk Management Plan which is an overview of the potential safety risk of the product, this document contains special tables and should be submitted within the file. Although FDA expect most product to be handled by package insert (PI), sponsor may volunteer or FDA may request a RMP.

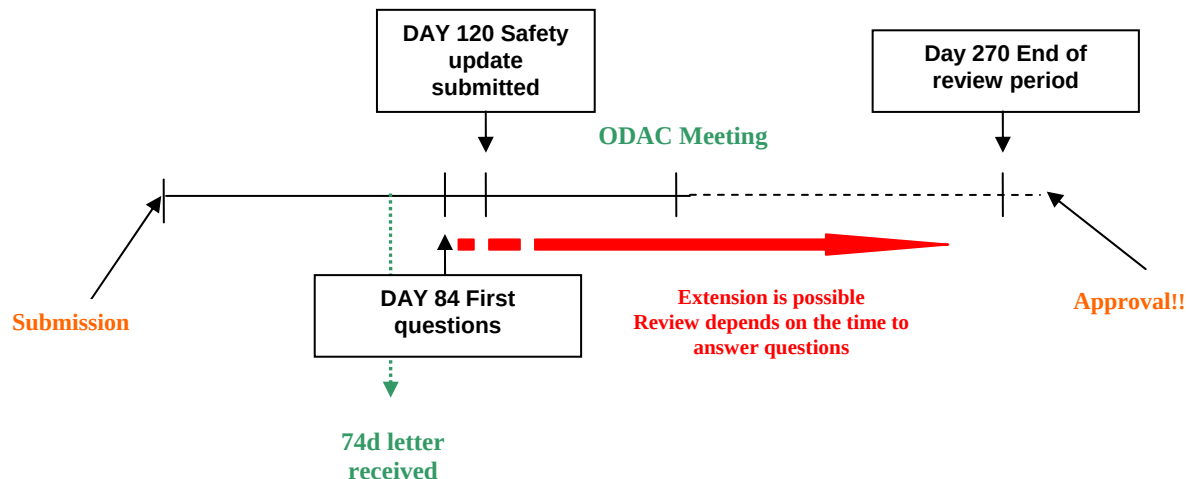
For the Japanese NDA, all data obtained in clinical studies should be listed. Indeed submission of electronic datasets is not required, but all data should be presented in CSR because JHA pays attention to data quality and is focused on data errors. In addition, the JHA conducts paper raw data review (CRF, analysis plan, monitoring report, etc,...), and consistency with CSR. A 100 % check of Japanese patients can be expected.

HEALTH AUTHORITIES QUESTIONS

WHAT ARE THE DIFFERENCES IN THE TIMELINES FOR THE QUESTIONS

A couple of months after the submission, the FDA starts to review the dossier and ask questions as they arise. To avoid delay in the review process, the answers and extra analyses have to be sent as soon as possible in particular when questions occur at the end of the review period.

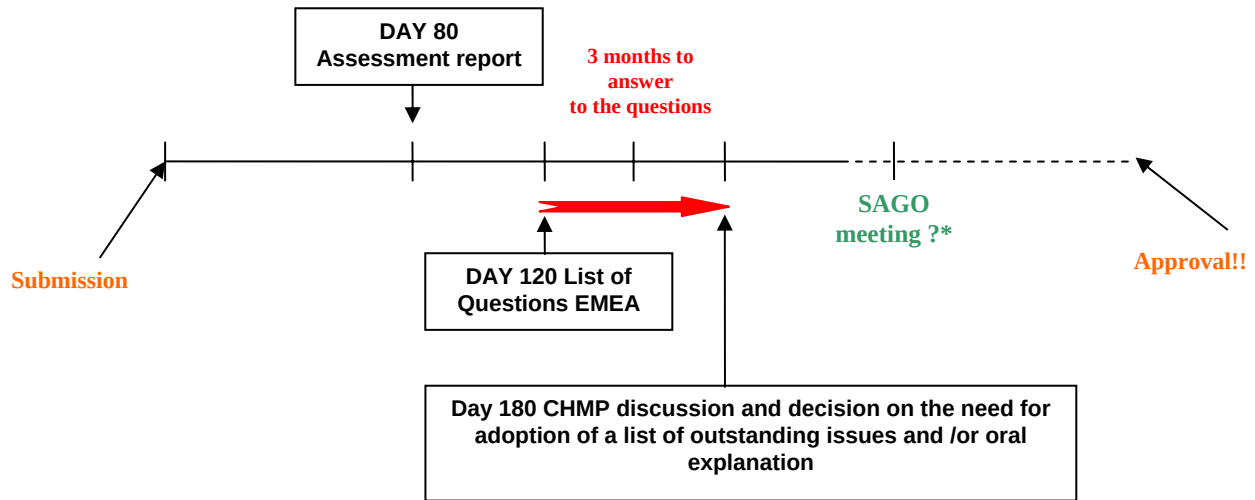
In the specific case of our submission, because the primary results were based on interim analyses, HAs requested the sponsor to run subsequent analyses using updated safety and efficacy data (a 60 days update for efficacy and a 90 (instead of 120) days update for safety).



ODAC Meeting = Oncology Drug Advisory Committee

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Concerning the EMEA review, the process is organized differently and is a succession of reports and meetings as described below:

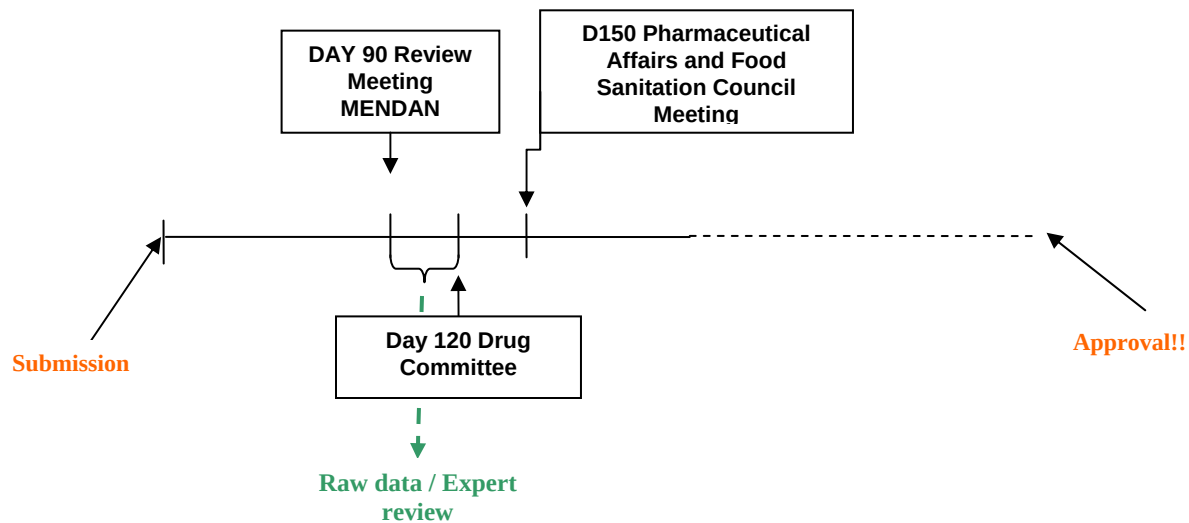


CHMP = Committee for Medicinal Products for Human Use

*The SAGO meeting is established and decided by the EMEA to provide an independent recommendation on scientific /technical matters. The aim of this meeting is to identify scientific issues that may need further discussion. This meeting is not mandatory.

Questions are sent in the DAY 120 report. Once this questions list is received, the clock starts and you have 3 months to give an answer.

The Japanese review is comparable to the EU review: a face to face meeting is held 3 months after the Japan new drug application. After the meeting, all queries are provided and the answers are expected 2 months after.



Time limit for review and answers (as a standard) PMDA: 1 year /Applicant: 1 year

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WHAT KIND OF QUESTIONS CAN BE EXPECTED AND HOW ORGANIZE THE WORK

FROM FDA

From a programming perspective, very thorough attention must be given when providing dataset / programs to FDA with the eCTD submission. Indeed, FDA inspectors like to do their own analyses and several questions are about discrepancies found between the CSR results and FDA analyses. Generally, you receive only a table summarizing the numbers obtained by the FDA and you have to find what were the programming conventions used and explain the differences. The best way to avoid these questions is to provide user-friendly datasets and well documented programming specifications in your dossier (for example, in your datasets provide only variables used in your analyses, don't give the same variable names if the content of the variables is not the same). In any case if you can't find why you have discrepancies, you should ask for clarifications from the FDA via email or teleconference.

As the delay in the review process should be avoided, the team has to be very reactive in answering the questions. This has an impact on the work organization as well as the team organization.

Clinicians, statisticians and programmers meet to check the common understanding of the requests and agree on the strategy for answering these requests. Ideally, programmers should get clear specifications from statisticians to avoid going back and forth, although this will have to be balanced with aggressive submission timelines. Indeed, all the programming processes should be faster but well organized. This can be prepared ahead by using naming convention for the programs, by dedicating one folder to storing the programs and deliverables and by tracking all the questions and the corresponding outputs in an excel sheet, for example.

In other words the processes should be speed up without losing quality.

Moreover, the workload can dramatically increase: stress, overtime and work during the weekend is very likely. To avoid overwork of the team, try to plan the work during the weekend, plan sufficient resource allocated to your submission, identify a programming submission coordinator who can organize the work and have an overview of the dossier.

FROM EMEA

80 days after the submission, the assessment report is sent by the EMEA. This assessment report is a first input on your dossier made by two or more reviewers. Even if it is only for information, as soon as you received this report, you can have an idea of what kind of questions (more efficacy, safety or PK questions) you will have in the 120 day report. This means planning of work and estimation of workload are clearly possible.

Once you received a list of questions from EMEA, the clock starts and you have 3 months to give an answer otherwise your review can be extended. This can overlap with the FDA question responses, you then have to deal with all the questions and again this can have an impact on the resource.

On the other hand as you have three months, the work is easier organized. The submission team can write statistical specifications, programming specifications and shells in advance before the programming work.

Moreover the team has gained experience with previous FDA requests and can identify possible risks beforehand and use this knowledge effectively. Finally some outputs produced for FDA can be used for EMEA.

FROM JAPAN

During the Japanese review, the health authority can ask for an update of the SCS with studies containing Japanese patients to increase the number of subjects and check the safety for Asian subjects. JHA are really keen on safety results: lab box plots, additional adverse events tables can be required. Some extra listings may be asked for because Japan needs the listing of all data presented in the clinical trial. Some subgroups tables and analyses to detect ethnic differences in efficacy, safety, and PK are also expected.

To answer to Japan questions, the input from the Japanese team on the request is necessary. Indeed Japanese colleagues define specifications and programming conventions because they have a better overview of the Japanese submission requirements. Moreover the language barrier has an impact on your timelines because all the tables and the text delivered to the JHA should be translated. This can be done by the medical writer but the deliverables should be ready earlier. Finally as the data quality is one of the most important component for JHA, the Japanese team needs time to make their own validation. As a result some extra validation time should be planned and considered in the work plan.

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Finally, not far from the approval, the label negotiation with each regulatory authority takes place and programmers have to plan the risk of having to do some extra figures and tables specifically for the label.

DON'T FORGET: REST OF THE WORLD

During or after FDA, EMEA and JHA review, some questions from Canada, China, Australia, and Switzerland.... are always possible, for example the Chinese health authorities are really interested by subgroup analysis on Asian patient. This extra work can't be planned in advance and requires not decreasing immediately the resource allocated to the submission after the FDA and EMEA approvals

CONCLUSION

A worldwide new drug application is a significant challenge for any team because the work effort should focus first, on the quality of the dossier and a short time after, on the questions process. The key points to be successful are a high level of quality of the submitted documents and a full commitment of the team.

A good advantage is to institute and train a team dedicated to rapid, complete, and clear responses to any questions. This team should be able to communicate with the different health authorities as well as the different line functions. The should have a complete oversight and be 100% available throughout the registration procedure.

Submission of a new drug means a lot of effort and a big dedication to the job, but it is also a great achievement for the team if an approval is the end of the story.

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