



# Health Authority Questions

How to deal with the diversity

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# Introduction

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- New product submitted simultaneously in all worldwide markets:
  - Dossier is sent to several agency
    - Food and Drug Administration (FDA)
    - European Health Authority (EMA)
    - Japan Health Authority (PMDA)
    - Rest of World
      - ↳ Australia
      - ↳ Canada
      - ↳ Switzerland...
  - For each agencies
    - Different contents of dossier
    - Different process of review
    - Different question process
- ↳ Most important point → overall quality of the dossier

# Summary

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- Elements of Context
- Contents / differences on the dossier
  - Food and Drug Administration (FDA)
  - European Health Authority (EMA)
  - Japan Health Authority (PMDA)
- Health authority questions
  - Timelines / review process
  - Expected questions
  - How to organize the work
- Conclusion

# Elements of context

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- Oncology submission for patients with metastatic carcinoma of the kidney
- Submission on an interim analysis → major changes on:
  - The timelines: shortened (two and a half months to produce a clinical study report (CSR) and a summary of clinical safety (SCS))
  - The submission plan was setup just after the GO decision from the Independent Data Monitoring Committee (IDMC)
  - The contents of the dossier: because of the early data, efficacy and safety update based on a new cut-off was sent later to FDA and EMEA and used for Japanese submission

# Contents / differences on the dossier

Food and Drug Administration (FDA)

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- Electronic submission containing:
  - 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 including supportive studies
  - The SCE (Summary of Clinical Efficacy)
  - The transport file datasets
    - For pivotal studies:
      - ↳ Raw and derived datasets
      - ↳ Blank annotated CRF (Case Report Form)
      - ↳ Dataset Definition and Handling Document describing the contents of the derived datasets and their derivations

# Contents / differences on the dossier

Food and Drug Administration (FDA)

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- Additionally, in agreement with the FDA during the Pre NDA\* meeting :
  - 👉 Some key programs (primary efficacy endpoint derivation for example)
  - 👉 The pooled datasets used for SCS and SCE
  - 👉 All the PK data (reports, datasets and POP PK)

\*NDA=New Drug Application

# Contents / differences on the dossier

European Health Authority (EMA)

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- No datasets required
- EMA is more focused on documents, Tables, Listings and Graphs provided along with the CSR

But the dossier should contain:

- Listings of raw data
- Specific document called Risk Management Plan:
  - Overview of the potential safety risk of the product
  - Specific set of safety tables

# Contents / differences on the dossier

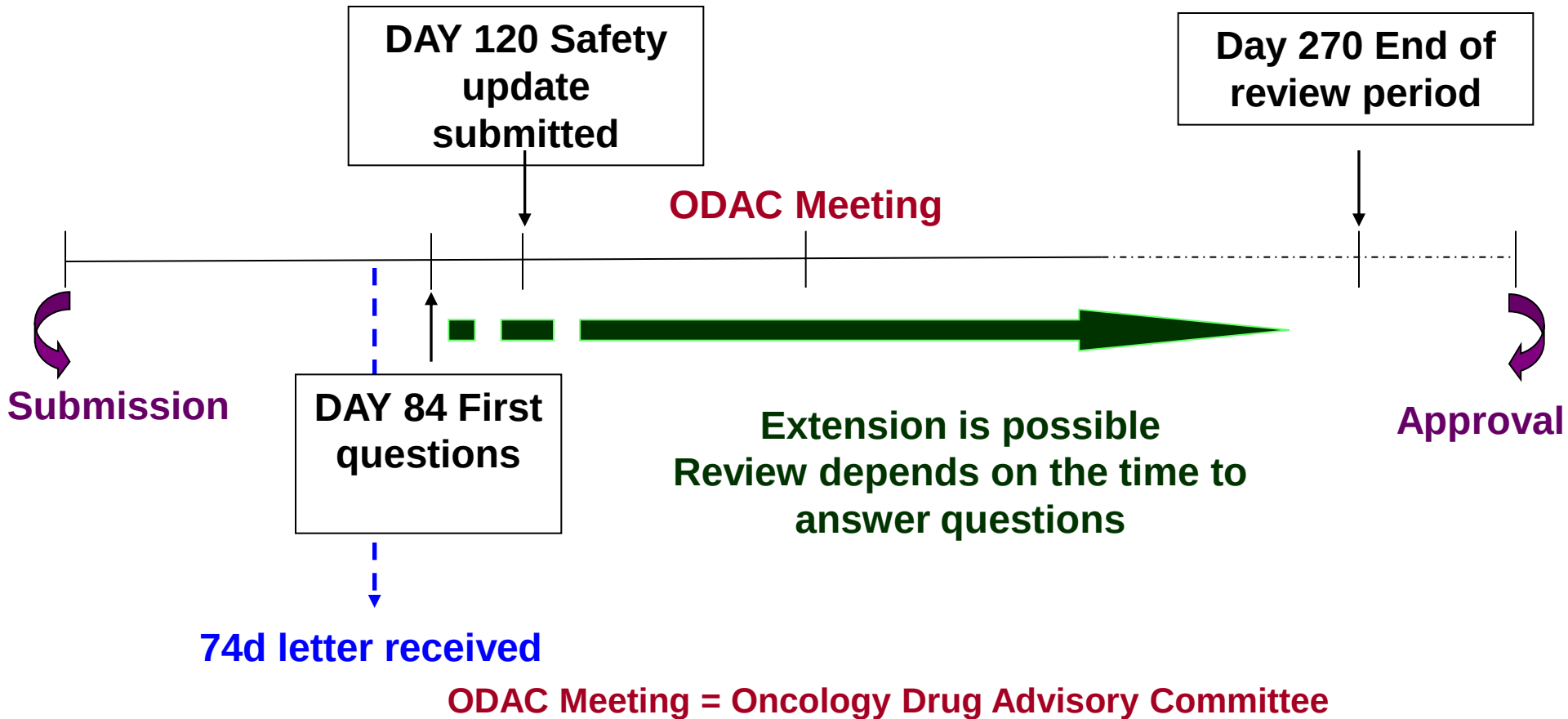
Japan Health Authority (PMDA)

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- No datasets are required but all data presented in CSR should be listed because
  - PMDA pays attention to data quality
  - PMDA is focused on data errors
- PMDA conducts paper raw data review
  - ↳ CRF
  - ↳ Analysis plan
  - ↳ Monitoring report, etc,...
- PMDA check consistency with CSR
  - A 100 % check of Japanese patients can be expected

# Health Authority Questions

Timelines / review process → FDA



# Health Authority Questions

Expected questions → From FDA

- Attention must be given when providing dataset / programs to FDA with the eCTD submission
  - 👉 Provide user-friendly datasets and well documented programming specifications in your dossier (provide only the variables used in the analyses...)
- FDA inspectors do their own analyses → several questions are about discrepancies found between the CSR results and FDA analyses
  - 👉 Ask for clarifications from the FDA via email or teleconference if you can't explain discrepancies

# Health Authority Questions

How to organize the work → FDA

- Delay in the review process should be avoided
  - Team has to be very reactive in answering the questions:
    - Clinicians, statisticians and programmers meet to check the common understanding of the requests
    - They agree on the strategy for answering these requests
    - Programmers should get clear specifications from statisticians / balanced with aggressive submission timelines
  - Programming processes needs to be quicker but well organized
    - Naming convention for the programs
    - Stored all programs and deliverables in one folder
    - All the questions and the corresponding outputs could be tracked in an excel sheet
  - ⇒ Processes needs to be sped up without losing quality

# Health Authority Questions

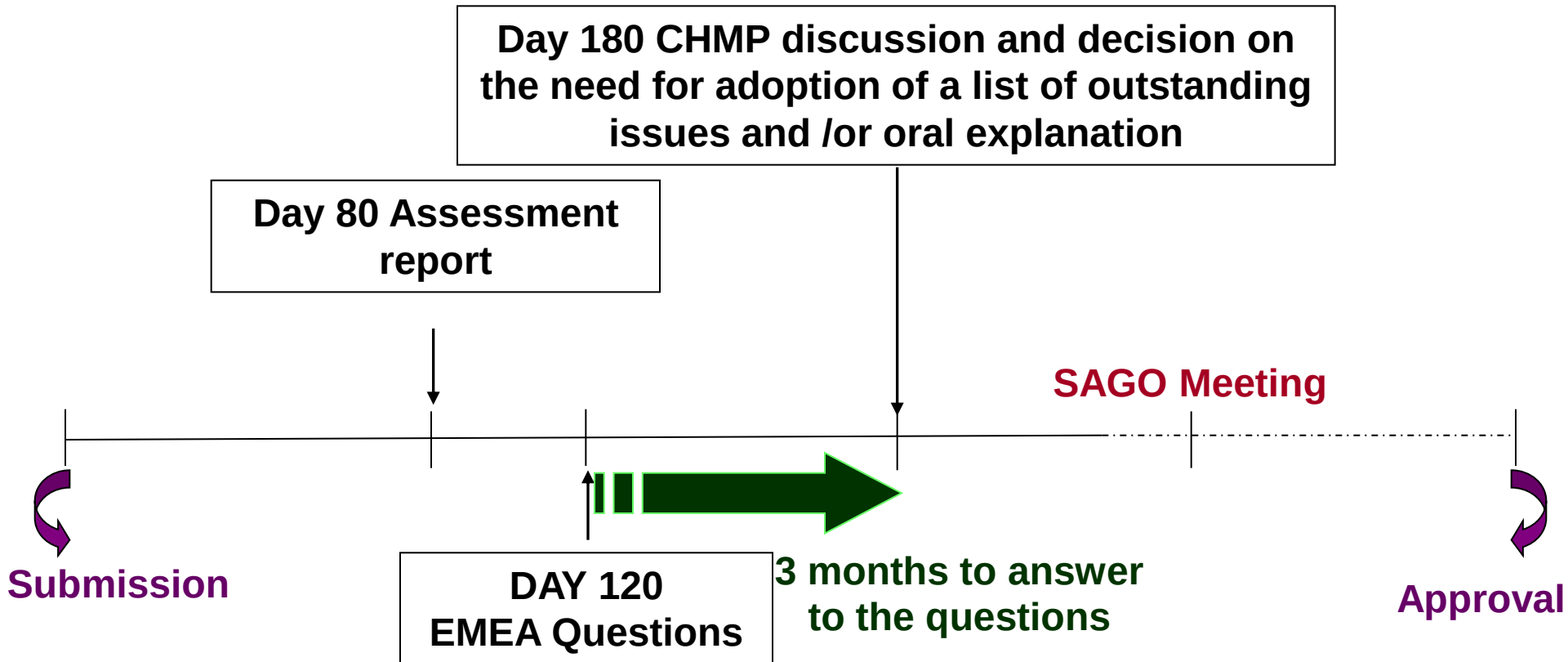
How to organize the work → FDA

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- Workload will dramatically increase:
  - Stress
  - Overtime
  - Work during weekends
- ✚ Try to organize the work during the weekend
- ✚ Plan sufficient resources allocated to your submission
- ✚ Identify a programming submission coordinator who can organize the work and have an overview of the dossier

# Health Authority Questions

Timelines / review process → EMEA



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.

**CHMP = Committee for Medicinal Products for Human Use**

# Health Authority Questions

Expected questions → From EMEA

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- The 80 days assessment report is:
  - A first glance on your dossier made by two or more reviewers.
  - Give you an idea of what kind of questions (more efficacy, safety or PK) you will have in the 120 day report.
- Final list of questions is contained in the 120 day report

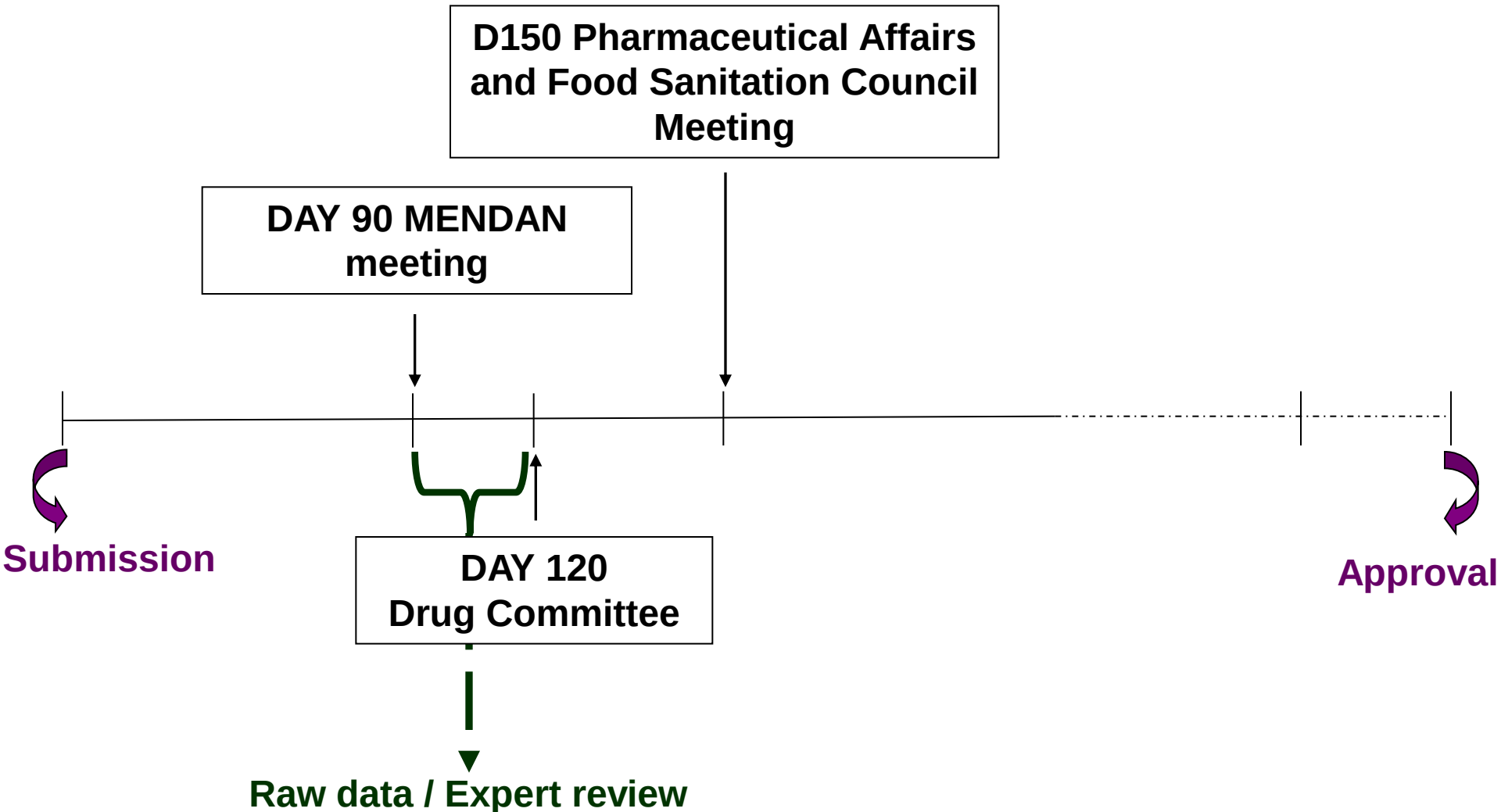
# Health Authority Questions

How to organize the work → EMEA

- As you have 3 months to answer the questions:
  - Work is easier to organize
  - Submission team can write statistical specifications, programming specifications and shells in advance before the programming starts.
- Moreover the team has gained experience with previous FDA requests:
  - Identify possible risks beforehand
  - Use this knowledge effectively
  - Some outputs produced for FDA can be used for EMEA
- ✚ EMEA questions 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

# Health Authority Questions

Timelines / review process → PMDA



# Health Authority Questions

Expected questions → From PMDA

- PMDA can ask for an update of the SCS with studies containing Japanese patients to:
  - Increase the number of subjects
  - Check the safety for Asian subjects.
- PMDA are really keen on safety results: lab box plots, additional adverse events tables can be required
- PMDA might request additional listings to complete their review
- Some subgroups tables and analyses to detect ethnic differences in efficacy, safety, and PK are also expected

# Health Authority Questions

How to organize the work → PMDA

- In your timelines input from the Japanese team on the request and translation of documents should be considered
    - Japanese colleagues define specifications and programming conventions because they have a better overview of the Japanese submission requirements
    - Japanese team needs time to make their own validation
    - Japanese medical writer has to translate all the tables and the text delivered to the PMDA
- 👉 Deliverables should be ready earlier

# Don't forget

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- Label negotiation with each regulatory authority
  - ✚ Extra figures and tables specifically for the label can be required
- Questions from Rest of the World:
  - Canada, Australia, and Switzerland
  - Chinese health authorities → subgroup analysis on Asian patients
  - ✚ These requests can't be planned in advance
  - ✚ Do not decrease immediately the resource allocated to the submission after the FDA and EMEA approvals

# Conclusion

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- A worldwide new drug application is a significant challenge for any team:
  - Work effort should focus first on the quality of the dossier and, very quickly after, on the questions process
- Key points to be successful:
  - High level quality of the submitted documents
  - Institute and train a team dedicated to rapid, complete, and clear responses to any questions
    - Communication with the different health authorities and the different line functions
    - Complete oversight and be 100% available throughout the registration procedure