

Aim

One of the aims of the PHUSE Education Regulatory Environment Workstream is to provide greater clarity about the submission process.

The workstream has produced single page visualisations of the submission process for the US and EU regions and these highlight the timeframe and interactions between regulators and sponsors.

Introduction

Regulatory agencies and governance organisations around the world play a vital role in ensuring the safety, quality and efficacy of medicines.

Every country has its own regulatory authority, which is responsible for enforcing the rules and issuing guidelines to regulate activities such as licensing, registration, manufacturing, marketing and labelling of pharmaceutical products in their region.

Major regulatory bodies that pharma companies interact with include

- US FDA (Food and Drug Administration)
- EMA (European Medicines Agency)
- PMDA (Pharmaceuticals and Medical Devices Agency)

Data analysts/scientists are considered experts in the structure and analysis of clinical data submitted to regulatory authorities. However, there can be limited understanding of the data submission process amongst the various regulatory authorities unless individuals are fortunate enough to have been involved directly in a submission.

Submission Process

Generally, the submission process follows a similar pattern (Fig. 1) although the specifics are different between the agencies.

- ❖ Submission by the sponsor
- ❖ Evaluation by the regulatory body;
 - An initial review to make sure that agency requirements have been met followed by a more detailed evaluation which can involve significant work for sponsors in order to answer questions from the agencies. There is also the potential for face to face meetings during this stage.
- ❖ Finally comes the agency decision.

Figure 1. The general submission process

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graph LR; A((Pre-submission activities)) --> B((Submission)); B --> C[Regulatory Agency]; C -- Evaluation --> D((Decision)); D --> E((Post-submission activities)); S[Sponsor] --> B; S --> C; S --> E;
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Figure 2. Initial Review by the CHMP

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graph LR; A((Submit initial MAA or line extension)) --> B((Initial Evaluation)); B --> C[The CHMP Rapporteur and Co-Rapporteur share draft respective assessment reports with all the CHMP and Pharmacovigilance Risk Assessment Committee (PRAC) members, together with a list of questions for the applicant. The assessment of the risk management plan, which also contains questions for the applicant, is also shared with the CHMP and PRAC members for comment. The company also receives the preliminary reports at this stage for information only.];
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The Agencies

US FDA: New drugs receive extensive scrutiny before US FDA approval through regulatory review of an application, for example a new drug application (NDA). The US FDA is a centralized agency, with the drug evaluation process carried out by its own staff.

EMA: The Committee for Medicinal Products for Human Use (CHMP) is the EMA committee responsible for human medicines. A Rapporteur and Co-Rapporteur are appointed from two EU markets and lead the evaluation of an application; other EU agencies have the opportunity to review and input during the process. The same countries continue to lead the assessment throughout the life of a drug.

Figure 3. Initial Review by the US FDA

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graph LR; A((Application)) --> B[Initial Review]; B --> C((eCTD Validation Criteria)); B --> D((Technical conformance checks)); B --> E((Filing Decision Date)); B --> F((Day 74 letter)); C --> G[FDA plans to implement eCTD validation checks (Sept. 15 2021). Submissions which fail this validation will be subject to rejection.]; D --> H[Technical rejection possible at this stage]; E --> I[Accept/Refuse to file designations are made by Day 60]; F --> J[Notification of potential review issues provided to the company];
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What is covered by the visualisations?

A timeline for the submission process including interactions between the sponsor companies and regulatory agencies from the initial submission to final decision.

They also cover the critical areas for ensuring a submission will pass technical requirements such as those required by the CHMP (Fig 2) and US FDA (Fig 3). Snapshots of these areas from the full visualisations have been included within this poster to indicate the level of detail and approach taken, but for the overall picture please see the actual visualisations on the PHUSE website.

In addition, there are other interactions with the agencies that are detailed which may result in additional work for programmers and statisticians within the sponsor company.

Summary

Often people work on studies and once they have completed their hard work, they don't have any further involvement with the actual submission process. Hopefully the visualisations that have been published allow everyone to get an overall idea of what happens after the data packages have been submitted.

Two visualisations have currently been produced by the workstream covering FDA and EMA submissions.

These outputs can be found under the **Regulatory Environment** tab at <https://phuse.global/Education>

A visualisation for the PMDA process will also be released.

The Regulatory Environment Workstream

If you have submission experience and would like to share that knowledge with the wider PHUSE community via this workstream please contact Sheetal.2.Patel@gsk.com

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