Paper SA10

It’s Easy Peasy Submitting Data to the China NMPA – Really?

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ABSTRACT

Submission of a drug can be challenging at the best of times and submission to the CDE (Center for Drug Evaluation) at the NMPA (National Medical Products Administration) we've found to be no different.

Contents

1. INTRODUCTION

Within this paper we will share our current internal Roche approach when submitting data to the NMPA (China). We will share the different study models we define to help us determine the filing support that is needed from the local and global teams, the challenges we've encountered, our approach to translations and the timelines we work to. Our hope is that this will help you determine for yourself if it is really easy peasy to submit data to the NMPA.

2. CHINA FILING PREPARATION AND REQUIREMENTS

We'll begin by listing the eSubmission data package components that the data science teams create and their translation needs for any China filing. These components are for a CDISC submission, where CDISC submissions are recommended (not mandatory) when doing a submission in China.

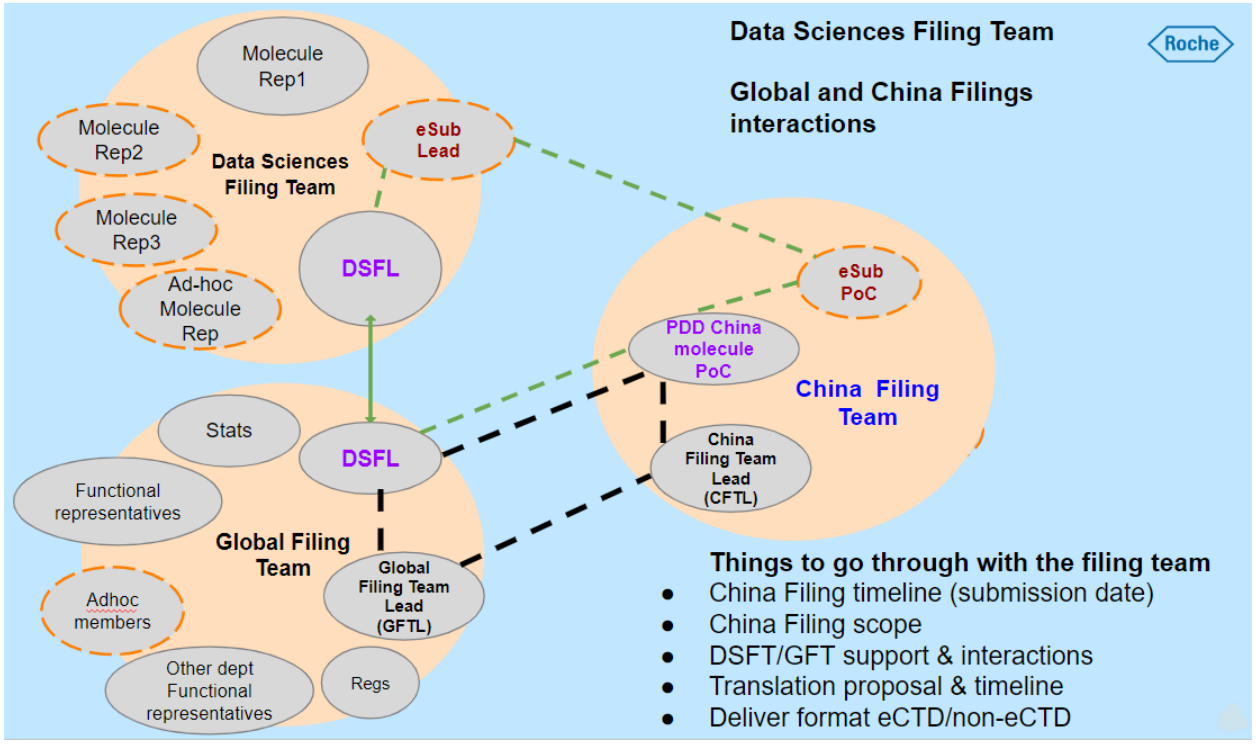
- ✓ eSub annotated CRF
  - Translate all except for Var name
- ✓ SDTM Define
  - Translate all except for Var name
- ✓ SDTM SAS xpt's
  - Translate Var & dataset label & MedDRA + WHODrug/GNE coding
- ✓ SDTM Reviewers Guide pdf (SDRG)
  - Translate all except for Var name
- ✓ ADaM Define
  - Translate all except for Var name
- ✓ ADaM SAS xpt's
  - Translate Var & dataset label & MedDRA + WHODrug/Legacy GNE or Roche coding List
- ✓ SAS programs
  - No explicit requirement for translating SAS or R programming comments
- ✓ ADaM Reviewers Guide pdf (ADRG)
  - Translate all except for Var name

As you can see all the data submission components are aligned with the CDISC deliverables that are typically submitted to the FDA however, with one additional requirement being that of translation. The amount of translation required varies based on the different components.

3. GLOBAL AND CHINA FILING INTERACTION

In order to set the scene, it's firstly important to understand how our data science team interacts. Typically we have a Global Filing Team (GFT) that oversees the submission to the FDA and other agencies. For China filing, we typically have a localized China Filing Team (CFT). Each of these teams consists of representatives from various functions such Regulatory, Drug Safety, Clinical Science and Data Sciences to name a few. The Data Science Filing Lead (DSFL) plays a key role globally (to FDA) within the Global Filing team (GFT), locally within the China (or other) Filing team (CFT) and also within the Data Science Filing Team. Wrt to China filings, the DSFL leads discussions on China Filing timelines, China Filing scope, translation proposals and timelines and delivery format. They seek key input from the relevant China Filing Team members. Diagram 1 below shows these interactions and examples of topics covered.

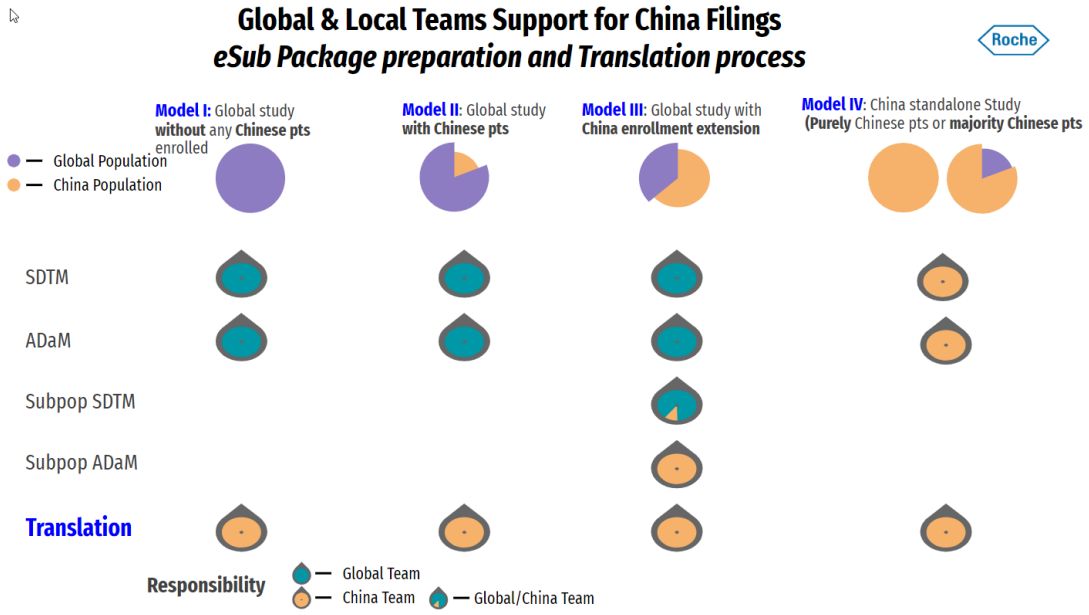
Diagram 1 Global and China Filings interactions



4. GLOBAL AND LOCAL TEAMS SUPPORT FOR CHINA FILINGS

The following visual (diagram 2) depicts the 4 study model categories that we use to help determine the support needed from global data science teams for the China filings, who's responsible for preparing the key data components and the translation to Chinese. The top row (circles & segments) of the visual below shows the 4 models ranging from fully Global studies with no China patients to fully (or majority) standalone China studies. Based on the study model category, the visual below shows who would typically be responsible to generate the different data requirements. Responsibility of the key data components is shown in green (fully global), orange (fully China) or green and orange (Global and China).

Diagram 2 – model types and support

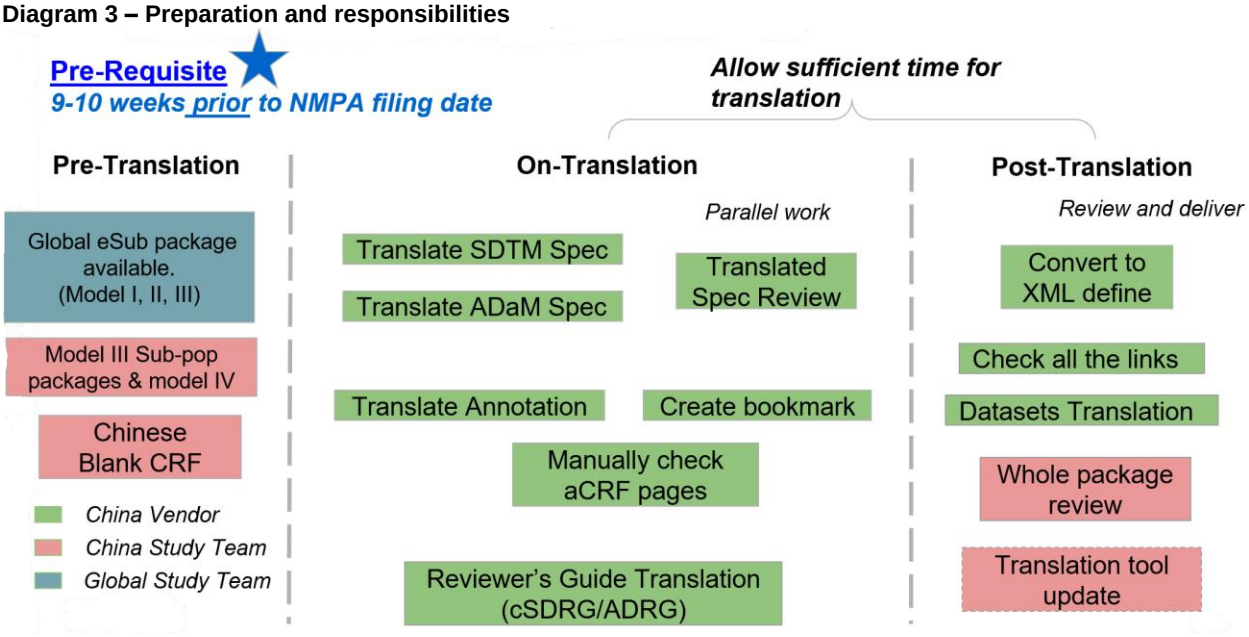


For study model categories I, II & III, the study reporting activity and the creation of the submission components would typically be done by the global data science team. If these studies are to be used for a China filing, then the China data science teams would typically use the global eSubmission data packages and conduct a translation of them prior to submitting to the NMPA. For China standalone studies, the data packages would be created by the China data science team in English first and then translated into Chinese prior to submission to the NMPA. This helps enable the delivery of the data packages in both English and Chinese if needed.

5. ESUBMISSION PACKAGE TRANSLATION

The following visual (diagram 3) covers the detailed preparation and responsibilities for translation of CDISC studies. It's vitally important to start these preparation and translation pieces in good time and at Roche, we recommend this happens at least 9-10 weeks prior to the China filing date.

Diagram 3 – Preparation and responsibilities



During the Pre-translation phase, we need to ensure that all the relevant files are available, and amended where necessary, before the translation activity begins to avoid re-work. One key area is the annotated CRF. Although an annotated CRF may already be available based on a previous FDA filing, this will still need to be amended to use the Chinese version of the blank CRF and then re-applying the SDTM annotations.

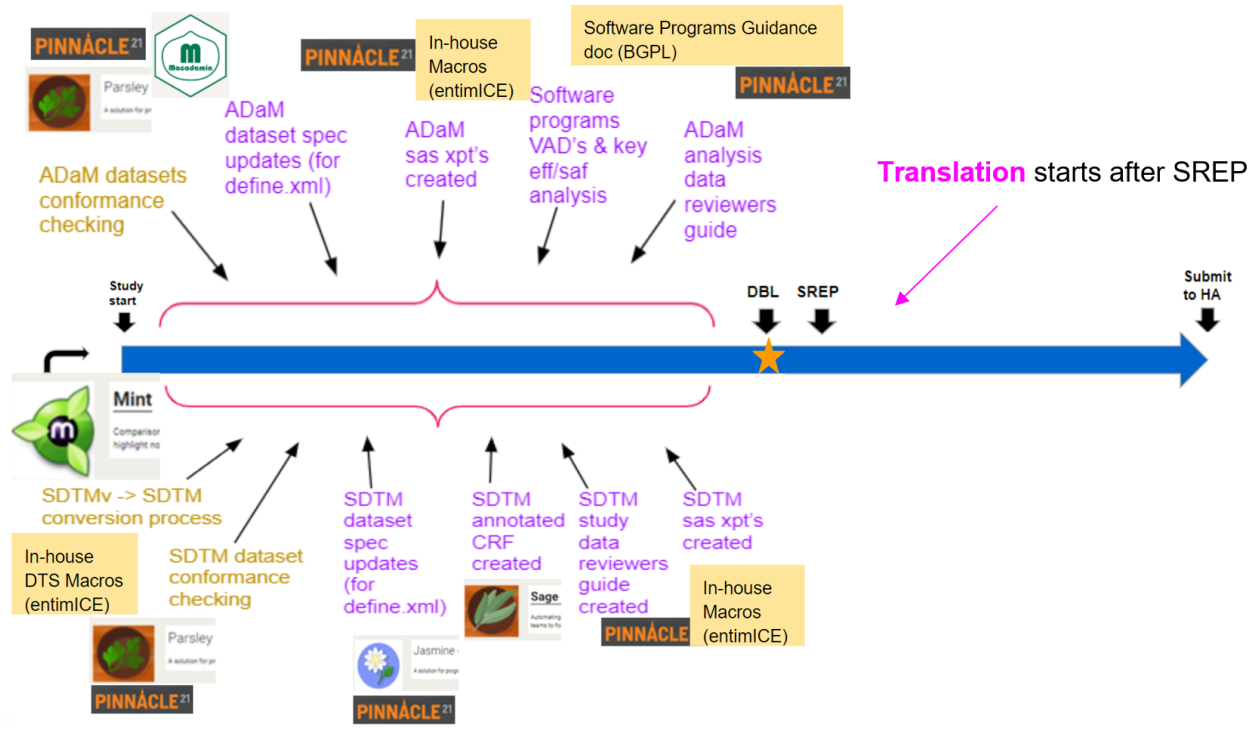
During the On-Translation phase, we begin the actual translation activity based on the final English version of the files. The amount of translation done on each file varies based on the content. For example, there is a greater amount of translation required for the Reviewers Guide compared to the aCRF. The amount of overall time and effort required to complete this whole activity also varies based on the size of the trials, so in general we allow 4-6 weeks to complete this.

During the Post-Translation phase, the dataset translation happens through a combination of internal macros (using labels from the specifications) and the use of an internal dataset containing Chinese-English metadata to aid with dictionary translations. Then the translated files are converted back into the required format, i.e. XML or PDF, and a review is conducted to ensure everything has been completed and that the translated files reflect the content of the English versions of the files for consistency. This ensures that quality data packages are delivered to the NMPA.

6. EARLY PLANNING AND SMOOTH DELIVERY

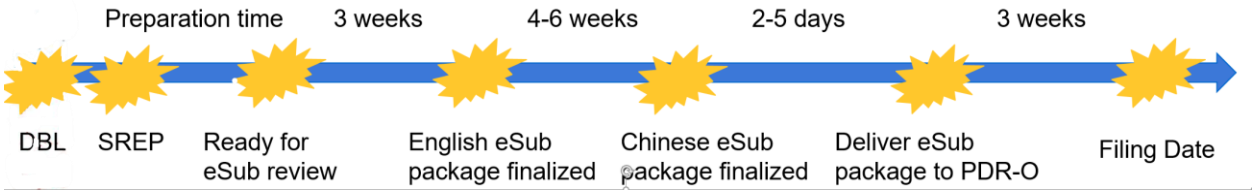
As always, early planning is essential to ensure a smooth delivery. At Roche, we try to do a lot of the work upfront (prior to any DBL) to ensure key components can be ready as soon as possible after lock to ensure translation can begin in good time. You can see below in diagram 4, that we have both internally developed tools/macros and readily available off-the-shelf products available to us, to help us prepare up front and prevent delay on any translation activities required. The components listed (and tools used to develop them) underneath the blue line are everything that's required on the SDTM side, whereas those above the blue line are everything that's required for ADaM.

Diagram 4 – Early planning tools



To aid with planning and timelines at Roche, for every filing that is planned to happen, an internal Filing ticket is opened which contains relevant details for that filing. Embedded into the filing ticket, a Data Collection Sheet (DCS – see diagram 5 below for example timelines collected) is needed which details filing scope, filing components required and estimated timelines for each study or part of the submission. This DCS gets drafted by the DSFL (with help from the eSubmission lead) after discussion with the filing team for the health authority concerned. When the filing is for China, appropriate time needs to be planned for China specific tasks. The yellow 'flashes' below in diagram 5 depict key milestones in relation to the final filing date (furthest right flash).

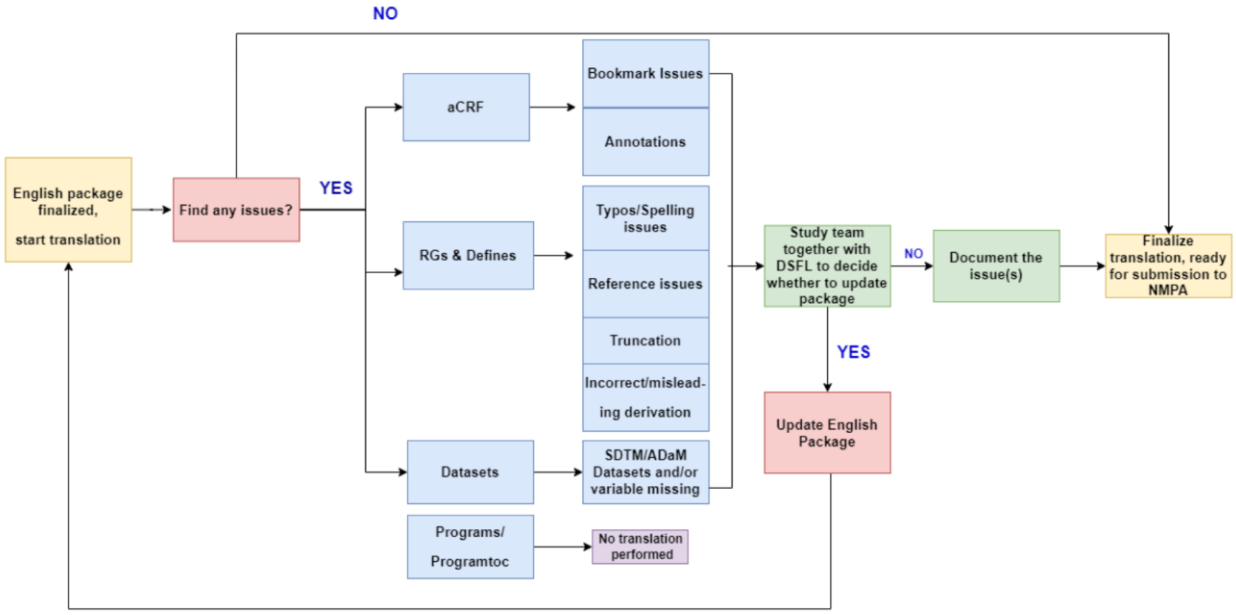
Diagram 5 – Data Collection Sheet timelines



7. ESUBMISSION PACKAGE ISSUES ARISING FROM TRANSLATION

Inevitably issues will be found in the English package during the translation process that are not quite correct and were missed upon initial creation and checking. In order to determine if these issues should be updated in the English package (prior to the translation) the study team should assess the impact on the filing (for process flow see diagram 6 below).

Diagram 6 – Issue process flow



Issues can be grouped and then assessed for impact on the filing, effort to implement change and benefit of making the change (see table 1 below). The 'Risk of Impact on Filing' column below, is really an assessment of any issue hampering the HA review. The 'Effort to implement change' column is simply the effort to correct the issue at hand. The 'Value' column is the benefit of actually fixing the issue. All three should be considered when deciding whether an issue should be fixed or left as-is (and documented).

As an example, If an issue is found with an aCRF bookmark, we should think about the impact this will have on the filing & reviewer. Will this significantly hamper their review? Probably not. Does it take long to make the update ? Probably not, but it creates re-work. Will making the change add significant value ? Probably not. So in this instance, we would consider the issue to have a very low impact on the filing and reviewer, even though making the change wouldn't take much time, it would provide a low amount of benefit & value in doing so.

Table 1 – Categorized issues by risk, effort and value

Category	Example	Risk of Impact on Filing	Effort to Implement Change	Value (benefit of making change)
aCRF	Bookmark	Low	Low	Low
	Annotations	Medium	Low	Medium
RGs	Typos/Spelling issues	Low	Low	Low
	Truncation	Medium	Medium	Low/Medium
	Reference issues	Low	Low	Low
Defines	Typos/Spelling issues	Low	Medium	Low
	Truncation	Low/Medium	Medium	Low/Medium
	Reference issues	Medium	Low	Low
	Wrong methods /comments	Medium/High	Medium	Medium
Datasets	Missing translation-needed variables	Medium/High	Medium	Low/Medium

Perfection is often sought but never found and ultimately this exercise becomes one of accepting (calculated) risks versus spending more time to fix issues (and potentially causing delays).
To emphasize again here, we are referring to issues found in the English package and whether they get updated in the English package or not (and documented). The Chinese package will have all issues updated.

8. ESUBMISSION PACKAGE FORMAT AND DELIVERY

Delivery of the China eSubmission data package requires close collaboration with the China Regulatory team. There are 2 types of approach to do this, via paper submission or via eCTD submission. Within Roche we're seeing a swing from fully paper based submissions to more and more eCTD based submissions. Should a paper approach be chosen, then the data science team prepare the data package and upload to a common (with regulatory) shared server and then the regulatory team burn the disc and submit it through to the health authority.
Should eCTD be chosen, then the data science team prepare the package and in collaboration with regulatory, ensure the package passes the eCTD checks before uploading to the shared server and the regulatory team package appropriately for an eCTD submission and submit to the health authority.

9. eCTD CHINA FILING CONSIDERATIONS

There are several considerations (bulleted below) to account for when filing to the China HA using the eCTD approach.

- Csv files NOT accepted,
- Submission of both Chinese and English packages currently not possible (via eCTD),
- Miscellaneous folders are not permitted currently,
- Datasets should be no larger than 4GB for a China submission,
- Pdf settings specific for China filings

For now, only certain file types are accepted (i.e. pdf, txt, xml, xsl). For example, csv's are not accepted and need to be converted to an alternative format. There are no available folders to submit both Chinese and English packages simultaneously, so our approach is to submit the China package using eCTD and the English package via CD. There is no 'misc' (miscellaneous) folder allowed in the eCTD folder structure (unlike for the FDA), so our approach is move any files that would normally get placed into the 'misc' folder (for the FDA) into the relevant eCTD folder. Datasets should be no larger than 4GB for a China submission (For the FDA this limit is 5GB). PDF settings (eg aDRG, cSDRG, programtoc, aCRF etc) in translated packages are different to those for the FDA and therefore we ensure the China PDF settings get implemented and get validated using validator software (as provided by CDE).

10. ESUB FOR THE FUTURE IN CHINA

As identified above, there are certain differences when submitting via eCTD to the FDA and the NMPA. Ultimately, it would be great to have a one size fits all solution i.e. alignment across all health authorities wrt eCTD, data format and content requirements. Full acceptance of submission data packages produced by different programming languages such as R by the NMPA as we see the pharma community strongly pushing to go this way. Ongoing internal work on Chinese metadata and E2E translation engine will accelerate delivery greatly. Ultimately, at Roche we will continue to fine tune and streamline our internal processes and tools to become more efficient and to ensure a smoother path to filing in China.

11. CONCLUSION

To conclude, CDISC data standards is mandated by the FDA and PMDA and for the CDE, the draft guidance follows the CDISC standards (Not mandated yet). Within Roche, we have four different China filing study models with different China filing preparation work required for each. It is very important to start early with interactions between China and global teams in order to discuss China filing topics as early as possible. Working on key components proactively in order to be esubmission ready by DBL to allow sufficient time for Chinese translation post-DBL.. Make smart decisions with respect to updates to English packages found during the Chinese translation process in order to minimize impact on timelines. Working closely with Regulatory when delivering the eSub packages is critical and be mindful of the subtle differences of eCTD filing requirements between the FDA and CDE. Going forward, we seek to collaborate with the industry and CDE (and others) on R (and potentially other) submissions in the near future.

Having read through the paper it gives you an idea of what's involved in China submissions (at Roche) and we'll leave it to your own judgement call, as to whether or not it's really easy peasy or not.

12. ACRONYMS

ADRG	ADaM Data Reviewers Guide
CDE	Center for Drug Evaluation
CFT	China Filing Team
CFTL	China Filing Team Lead
CRF	Case Report Form
cSDRG	Clinical SDTM Data Reviewers Guide
DBL	Database Lock
DCS	Data Collection Sheet
DSFL	Data Science Filing Lead
eCTD	Electronic Common Technical Document
eSub	eSubmission
FDA	U.S. Food and Drug Administration
GFT	Global Filing Team
GFTL	Global Filing Team Lead
HA	Health Authority
NMPA	National Medical Products Administration
PoC	Point of Contact
RG's	Reviewers Guides

13. ACKNOWLEDGMENTS

We'd like to acknowledge everyone from the Data Science eSubmission team at Roche, who contributed to the underlying discussion, which ultimately resulted in an internal guidance and process flows.

14. CONTACT INFORMATION

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