



**Breakthroughs that
change patients' lives**

**Managing Simultaneous Drug
Submission with Breakthrough
Designations – Lessons Learned
from Programming Perspectives**

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Background and Submission Scope

Tafamidis (Vyndaqel/Vyndamax) Transthyretin Cardiomyopathy (ATTR-CM) Submissions

- Pfizer acquired Tafamidis from FoldRX in 2010.
- Tafamidis has been approved in Europe for transthyretin familial amyloid polyneuropathy (TTR-FAP) in 2011, but rejected by FDA.
- Tafamidis submission case study presented here is for treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
- Two formulations - Vyndaqel (tafamidis meglumine), Vyndamax (tafamidis)
- More than 25 studies included in submission package including phase I, II, III studies, natural history and observational study.
- Mixed data standard – legacy non-CDISC, CDISC-like, CDISC
- Multiple integrated data analysis pools (ISS and ISE)

Submission Key Dates

- Feb 17, 2017 – FDA Orphan drug designation
- March 27, 2018 – Japan Sakigake designation
- May 17, 2017 – FDA Fast Track designation
- May 18, 2018 – FDA Breakthrough Therapy designation
- May 24, 2018 – Japan Orphan Drug designation
- Nov 2018 – simultaneous submission to PMDA and FDA
- March 26, 2019 – Japan PMDA approval
- May 3, 2019 – FDA approval



LESSON #1: SAKIGAKE, BREAKTHROUGH AND THEIR IMPLICATIONS

SAKIGAKE vs Breakthrough therapy (US) vs PRiority MEDicines (EU)

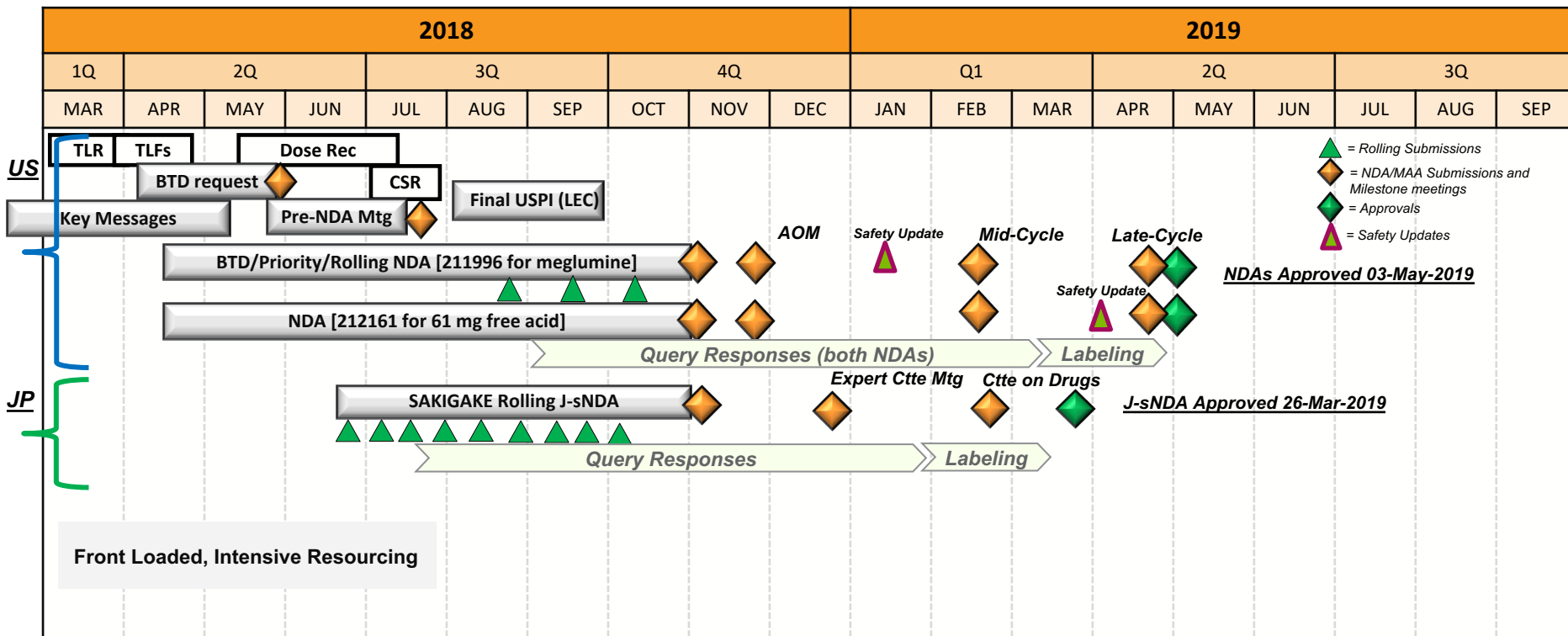
	SAKIGAKE	Breakthrough therapy	PRiority MEDicines (PRIME)
Establishment	April 2015 (trial)	July 2012	March 2016
Designation Criteria	• New mode of action • Life threatening or no radical treatment • Prominent efficacy • First NDA in the world	• Serious condition • Substantial improvement on clinically significant endpoint(s)	• Unmet medical need • Potential to address to unmet medical need
Project Manager	• Review partner (Concierge)	• Senior manager • Cross-disciplinary project lead	• Dedicated contact point • Appointment of rapporteur
Consultation	• Priority consultation	• Intensive guidance on an efficient drug development program	• kick-off meeting about the overall development plan and regulatory strategy • Scientific advice at key development milestones
Rolling review	• Eligible (SAKIGAKE comprehensive assessment Consultation)	• Eligible	—
Priority review	• Review within 6 months (shorter than 9 months in ordinal priority review)	• Not automatically designated	• Eligible (Accelerated assessment)
Other	• Relation with drug pricing		

Cited from : Regulatory update from MHLW/PMDA. <https://www.pmda.go.jp/files/000221880.pdf>

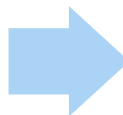
Condition of SAKIGAKE: simultaneous application

- The definition of “simultaneous application”:
 - Not documented in writing (not clearly stated in the notification)
 - MHLW official publicly stated that J-NDA submitted **about one month after** the 1st application in the world is considered as a “simultaneous application” when implementation started in 2015.
 - Since 2015, three SAKIGAKE designated products approved. All submitted first in Japan.
- PMDA review partner’s comments (Sept 2018):
 - Vyndaqel ATTR-CM has been designated as a SAKIGAKE product. Therefore, the J-NDA submission date has to be **earlier or on the same day** as the US-NDA submission date.

ATTR-CM Submissions (FDA and PMDA)



Learnings/Observations



Implications/Actions

- Some of benefits of SAKIGAKE:
 - SAKIGAKE review is generally ≤ 6 mos (4 mos for tafamidis ATTR-CM). Regular review is 12 mos; ODD 9 mos.
 - Strong engagement with MHLW/PMDA, prioritized consultation, close support by concierge (Cross-disciplinary support).
 - Frontloaded and intensive resourcing from both Global and Japan teams
 - Originally, MHLW indicated that a 30 day difference between US and Japan submissions was acceptable. However, PMDA indicated that J-NDA submission date has to be earlier or on the same day as the US-NDA submission date.
 - Not fully aware upfront of potential consequence to withdrawing from SAKIGAKE.
 - Regulatory agencies sent queries immediately after receipt of each rolling sequence.
 - Pivotal study data submitted prior to submitting our NDA
- Plan for a demanding workload that requires simultaneous resourcing (Japan, US, EMA).
 - Agencies expect short turnaround time to their queries
 - Important to understand that withdrawing from SAKIGAKE could have potential consequences to product and to Sponsor's portfolio.
 - Manage finalizing ISS/ISE, eSUB together with query response.
 - Ensure sufficient and dedicated programmers
 - Balance in-shore/off-shore resources
 - Effective/proper documentation and request tracking

LESSON #2 COMPLEX PRIMARY
ENDPOINT AND STATISTICAL
METHODS MIGHT BENEFIT FROM
EARLY DISCUSSION WITH AGENCY

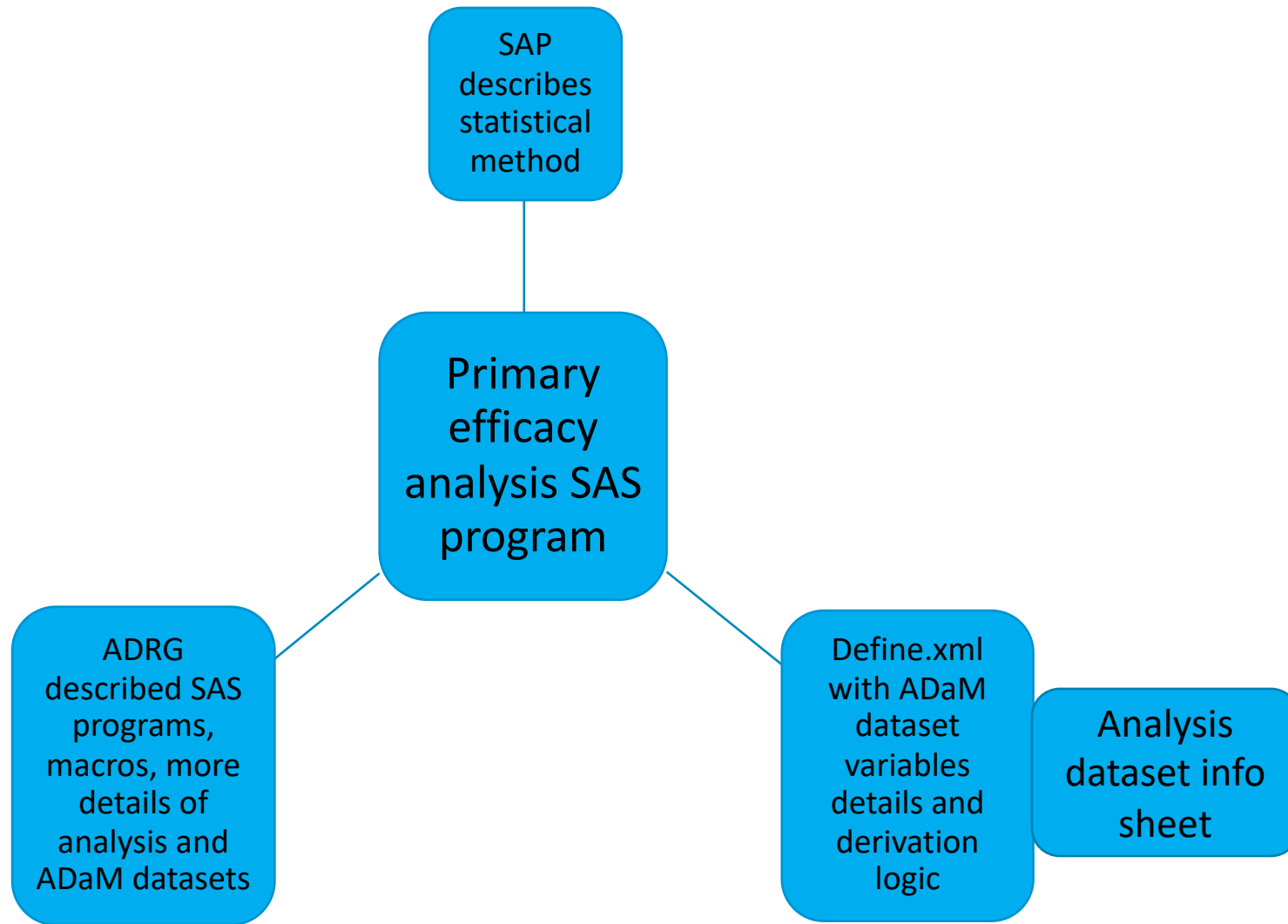
Primary Analysis for Pivotal Study ATTR-ACT Trial

- All-cause mortality and frequency of cardiovascular hospitalization were analyzed using Finkelstein-Schoenfeld method
- Combines all-cause mortality and frequency of CV-related hospitalizations in a hierarchical fashion using all-cause mortality first.
- Compares every participant with every other participant within strata, assigning a +1 to the "better" participant and a -1 to the "worse" participant and 0 if they are "tied".
- Participants who discontinued for transplantation (heart transplantation or combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, were handled in the same manner as death.
- 'Win' represents a participant doing better based on hierarchical comparison. The reported unit is the total "wins" for each treatment group from performing such a hierarchical comparison across all 4 strata in the study.
- Less known but complex analysis method increases the sensitivity and power of data analysis.

Challenge for data submission #1 - Program submission

- FDA guidance –
 - “4.1.2.10 Software Programs Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. The specific software utilized should be specified in the ADRG. Refer to FDA Statistical Software Clarifying Statement for more information. The main purpose of requesting the submission of these programs is to **understand the process** by which the **variables for the respective analyses** were created and to **confirm the analysis algorithms and results**. Sponsors should submit software programs in ASCII text format. Executable file extensions should not be used.”

How we submitted



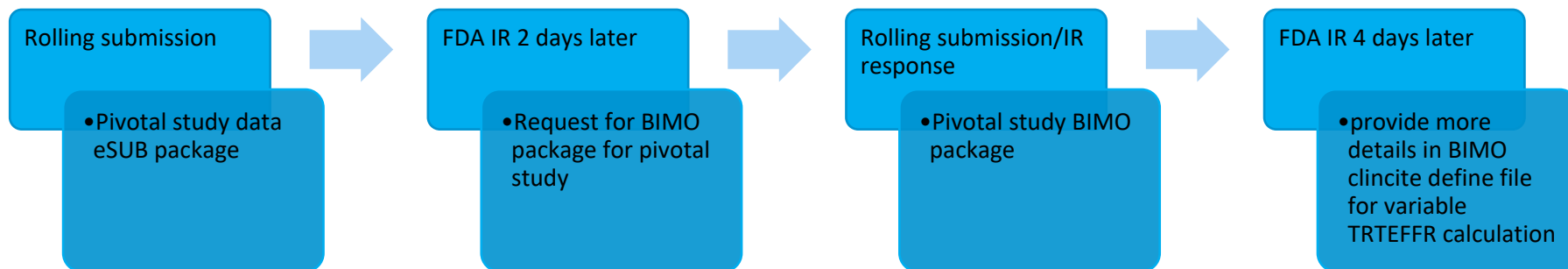
The Agency asked:

..further clarification of SAP vs the SAS programs and dataset to show all subject critical dates and individual scores from all pair-wise comparisons within strata

- In response to FDA IR, we prepared a detailed document with step-wise description on how the analysis was performed, variables and programming conditions were clearly spelled out.
- Provided two datasets with information requested by FDA and structured in the way beneficial for agency review
- Our recommendation:
 - Have a detailed standalone document to facilitate agency review for any complex and novel statistical method.
 - The document used at the time of programming might be sufficient for study team programmers and statistician, but it might not be as clear and easy to follow for an independent reviewer or someone not familiar with the method
 - Always best practice to seek agreement with agency as early as possible on all aspects of electronic data submission package.

Challenge for data submission #2 - BIMO

Summary-level Clinical Site (clinsite.xpt) Dataset



The FDA guidance:

Treatment Efficacy Result (TRTEFFR) — The summary statistic for each primary efficacy endpoint, by treatment arm at a site.

Points to consider:

- Values reported in TRTEFFR generally reflect simple summary statistics for the primary efficacy endpoint(s).
- The composite primary endpoint involving pair-wise comparison within strata requires extensive discussion how to present treatment efficacy result by site.

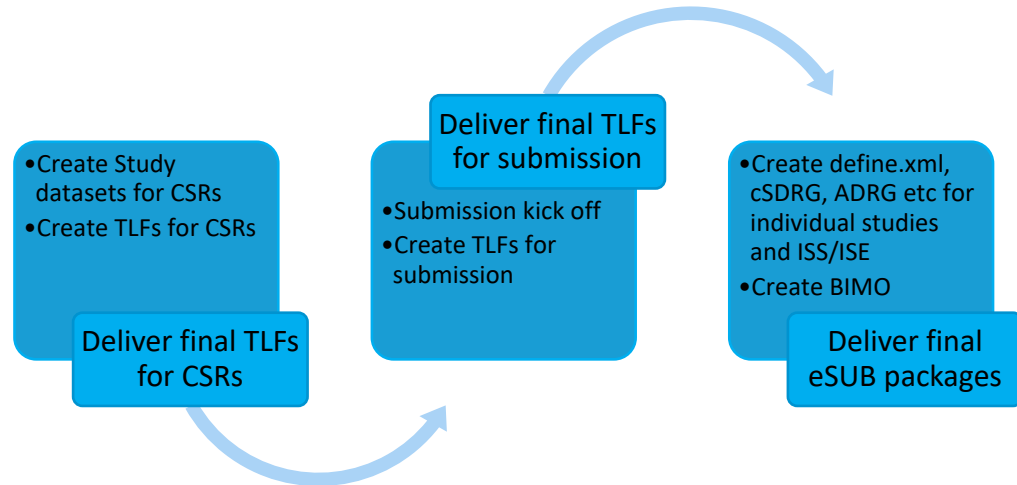
Our recommendation for BIMO submission

- Initiate BIMO submission planning early especially for pivotal studies. Pre-submission meeting with FDA can include BIMO discussion.
- Ensure statisticians included in the discussion of how to present site-level efficacy related variables – especially when primary efficacy endpoint is not simple.
- Ensure BIMO documentations are comprehensive with sufficient details in define file. BIMO reviewer's guide might be needed to further facilitate agency review. If there are 2 data sources, e.g hospitalization data obtained from completed study case report forms and adjudicated data which were obtained from the data submitted to, and reviewed by, the adjudication committee, precise source of derived clinsite variables need to be specified and any special data case documented in reviewer's guide.
- Cross check BIMO variables in clinsite.xpt match those from clinical study data and report.

LESSON #3 ADJUSTMENT NEEDED FOR
IMPLEMENTING NEW SUBMISSION
PROCESS AND EFFECTIVE MANAGEMENT
OF HARMONIZED APPROACH

Effective management of harmonized approach

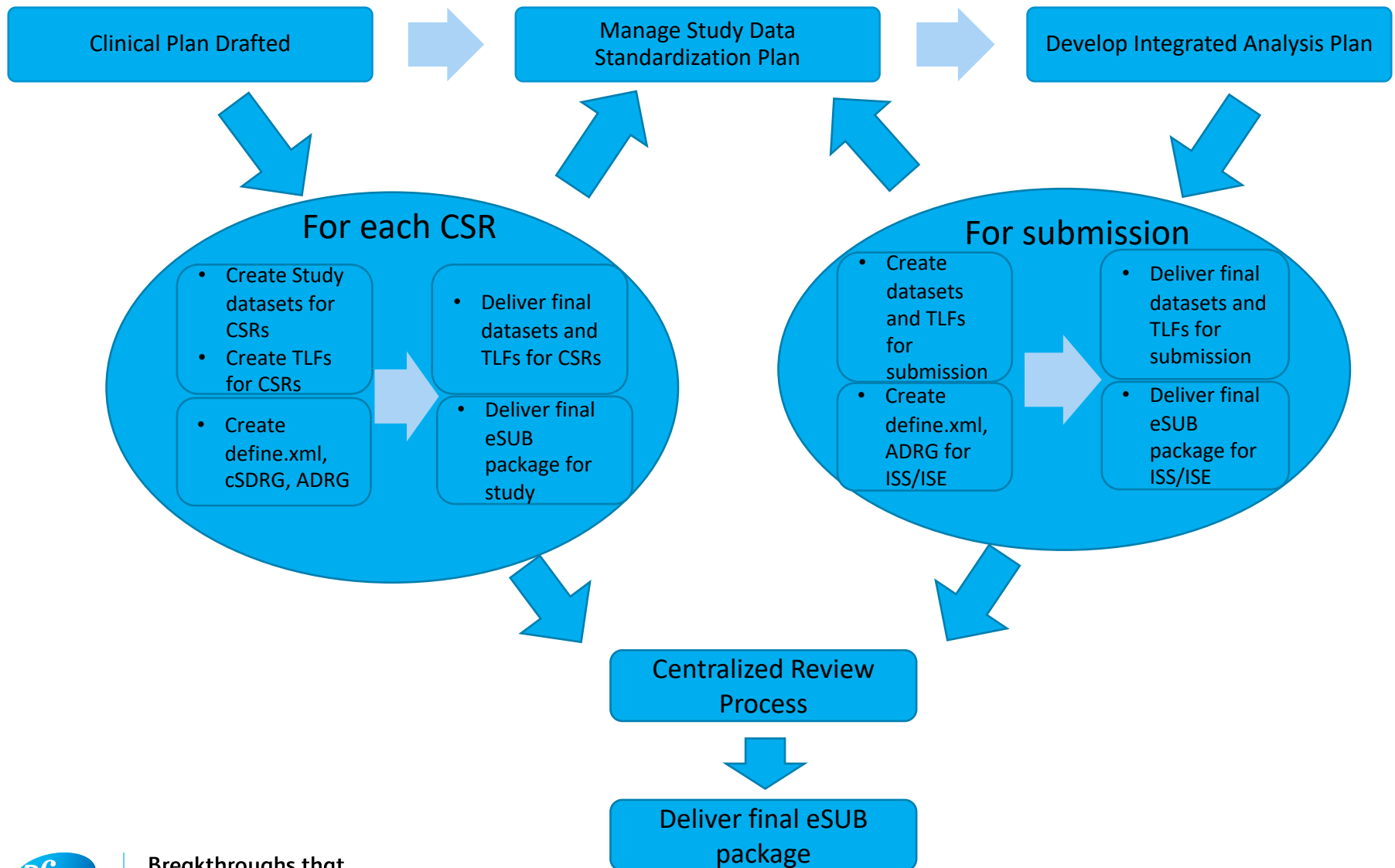
Traditional Process:



Issues with traditional process:

- Compliance issues identified late resulted in unfavorable updates to programming and documentations, which had negative impact on resources and process.
- Difficult to maintain consistency and quality of submission documents across studies.

Harmonized Approach



CONCLUSION

- The sponsors must fully understand the process and requirements and learn how to balance the opportunities and challenges in order to navigate the pathway and lead to a successful drug approval.
- Understand timing for rolling submission sequences and fully appreciate the different data requirements.
- Careful resources planning to support accelerated timeline and rapid responses to agency queries.
- Use harmonized approach to build in submission programming with clinical study programming will improve efficiency and quality for drug submission.

Questions?

