Paper SA12

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

LiFeng Good, Pfizer Inc, Collegeville, PA, USA

ABSTRACT

In March 2018, the Ministry of Labor Health and Welfare (MHLW) in Japan granted SAKIGAKE designation to Tafamidis for treatment of patients with transthyretin cardiomyopathy, a rare, fatal, and underdiagnosed condition associated with progressive heart failure. Two months later, in May 2018, Pfizer received breakthrough designation (BTD) from the Food and Drug Administration (FDA) for Tafamidis for this indication. Simultaneous submission to multiple agencies is challenging to begin with and requires upfront planning, harmonization, interaction and negotiation with internal/external customers and careful resource planning. Breakthrough and SAKIGAKE designations increased the complexity in supporting competing priorities: pivotal study close, top line results prep, shortened submission timeline, key data presentations and publications, rolling submissions/queries (US, Japan), multiple health authorities pre-submission meetings and correspondence (United States(US), Japan, European Union (EU)). We hope that by sharing our experience, lessons learned and suggestions for best practice, other organizations can benefit from to better support future submission.

INTRODUCTION

Tafamidis was granted orphan Drug Designation for transthyretin mediated amyloidosis (ATTR-CM) in both the EU and US in 2012 and in Japan in 2018. In June 2017 and May 2018, respectively, the FDA granted tafamidis Fast Track and Breakthrough Therapy designations for ATTR-CM. Additionally, in March 2018, the Ministry of Labor Health and Welfare in Japan granted SAKIGAKE designation to tafamidis for this indication. Following the SAKIGAKE designation, a regulatory marketing application for tafamidis for ATTR-CM was submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in November 2018 simultaneously to the FDA. The FDA also granted Priority Review designation for the NDA for tafamidis meglumine – one of the two formulations submitted for tafamidis [1]. On March 26, 2019, PMDA approved VYDAQEL® (tafamidis meglumine) for the treatment of the heart disease (cardiomyopathy) caused by ATTR-CM in adults, followed by FDA approval on May 3, 2019. The review times were < 5 months and 6 months respectively for PMDA and FDA. Tafamidis submission included a large number of studies with mixed data standards. The intention of this paper is to share key lessons learned with focus on statistical programming and analysis support and electronic data submission.

LESSON #1: SAKIGAKE, BREAKTHROUGH AND THEIR IMPLICATIONS

Accelerated pathways for new drug development in US, Japan and EU present opportunities and benefits for patients and pharmaceutical companies to bring new medicines to market sooner. But the varied nature and diversity of different accelerated pathways also present new challenges that sponsors need to fully understand and plan strategically. The table below summarizes the nature of the three main accelerated pathways [2] (this paper will only touch upon SAKIGAKE and Breakthrough). Implemented in 2015, the SAKIGAKE (Forerunner) Designation system [3] is applicable to innovative medicines, medical devices, or regenerative medical products in practical use in Japan sooner than or simultaneously with other countries, aiming at early practical application with various supports such as “Rolling Review,” “Priority Consultation,” and “Priority Review.” It offers ongoing regulatory support and data review throughout development and requires stronger post-marketing safety measures in exchange for faster approvals. Some of the benefits of SAKIGAKE includes shortened review time – from regular 12 months to 6 months or shorter and strong engagement with MHLW/PMDA, prioritized consultation, and close support by concierge (Cross-disciplinary support).

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		

The Food and Drug Administration has developed four distinct and successful approaches to making drugs that treat serious diseases available as rapidly as possible:

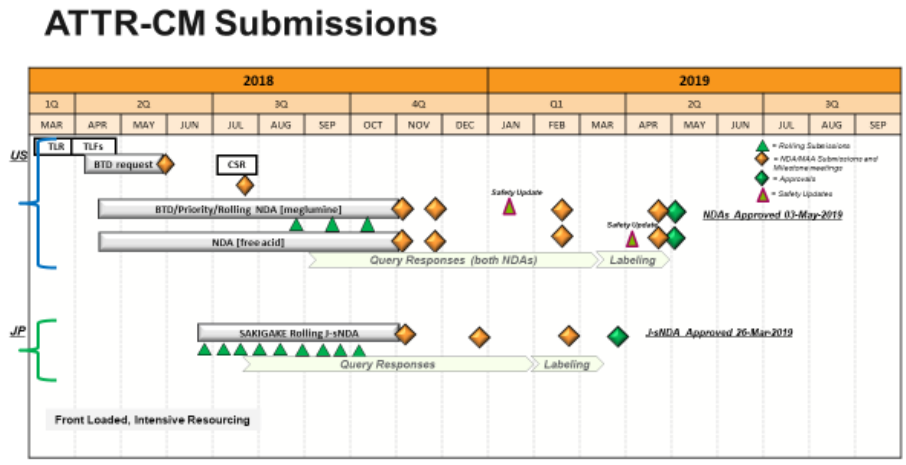
- Priority Review
- Breakthrough Therapy
- Accelerated Approval
- Fast Track

Because each of these approaches implies speed, there can be confusion about the specific meaning of each and the distinctions among them. FDA issued the guidance document 'Expedited Programs for Serious Conditions – Drugs and Biologics' [4] to provide a single resource of information on FDA's policies and procedures for these four programs as well as threshold criteria generally applicable to concluding that a drug is a candidate for any of these expedited development and review programs. There are many similarities between SAKIGAKE and BTD, one difference is that Priority review is not automatically designated for BTD.

Tafamidis CM was the first Pfizer submission granted SAKIGAKE designation; therefore, the process was brand new to our submission team. Back in 2015, MHLW indicated that a 30-day difference between US and Japan submissions was acceptable. However, it became clear later to our team that the aim is to file an initial application for the product in Japan, ahead of any other country at the time of designation, there should be no problem with other preferential systems applied in other countries. [5] Two months after SAKIGAKE designation, Tafamidis submission also received Breakthrough Designation from FDA, which made it eligible for, among other things, rolling and expedited review. The accelerated timelines from FDA and PMDA required frontloading of work and intensive resourcing from both the global and Japan teams. Our late understanding that our PMDA submission had to be filed ahead of our FDA submission presented additional pressures for the team and required them to adjust their initial planning and prioritization to deliver multiple submissions using the same shared resources. It is worth mentioning that withdrawing from SAKIGAKE has potential consequences for the product and sponsor's portfolio, especially to drug pricing. The sponsor should fully understand this prior to applying for SAKIGAKE. A sponsor should also ensure its application can be submitted in Japan first.

One key challenge with rolling submissions associated with these accelerated pathways is that regulatory agencies often send queries immediately after receipt of each rolling submission sequence. FDA assigns senior staff to

monitor breakthrough therapy trials and PMDA provides close support by concierge. The Agencies, in turn, expect the same level of commitment from the sponsor, including short turnaround times to their queries. The chart below highlights the overlapping submission timelines rolling submission dates and responses to FDA and PMA queries while or simultaneously preparing our EU and RoW submission. There are two NDAs submitted to FDA based on two forms of tafamidis: meglumine salt and free acid. The tafamidis meglumine form was granted Priority Review and the tafamidis free acid form was under Standard Review. This added an additional layer of complexity for submission preparation.



Rolling submission is done in waves. A sponsor submits completed sections for review, as opposed to waiting for the entire application to be completed. As an example, a sponsor submits their non-clinical portion in the first wave, followed by a chemistry, manufacturing and controls (CMC) wave and then a final wave containing clinical. For tafamidis, we submitted our pivotal study data prior to submitting our NDA. Submitting the pivotal study data first presented additional challenges for our statistical programming team. Not only did the team have to support accelerated timelines, queries from regulatory agencies came at the busy time we were finalizing ISS/ISE outputs and electronic data submission packages. Thus, the submission programming lead must be flexible and be able to adapt and re-prioritize when needed. It is critical to have sufficient and dedicated programmers. For this particular submission, the programming supports were CROs with offshore resources. In order to provide more efficient support to urgent requests, we had to negotiate and make arrangement with the CRO to ensure programmers were available in multiple time zones. Offshore resources can also be leveraged to continue programming support during US evening time as long as there is good communication and collaboration between the onshore and offshore programmers. With multiple information requests coming from multiple agencies, sometimes there could be similar or related requests. Effective and proper documentation and request tracking are critical to ensure consistent responses, reference to previous programs and inspection readiness.

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

The pivotal study for tafamidis development program, ATTR-ACT trial [6] demonstrated a robust effect of tafamidis on the primary endpoint ($p = 0.0006$), with a win ratio (number of pairs of tafamidis-treated patient wins divided by number of pairs of placebo patient wins) of 1.695 (95% confidence interval: 1.255 to 2.289). In the primary analysis, all-cause mortality and frequency of cardiovascular hospitalization were analyzed using Finkelstein-Schoenfeld method [7]. The method combines all-cause mortality and frequency of CV-related hospitalizations in a hierarchical fashion using all-cause mortality first. The method 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. This method of analyzing endpoint increases the sensitivity and power of data analysis. It is also a less known but complex analysis method which have several areas for consideration for data submission.

Program submission

The FDA Study Data Technical Conformance Guide [8] contains the following section about software programs:

"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."

Per guidance, besides the description of statistical method in SAP, ADRG included a table to link each TLF with SAS program name as well as any macro used within each program. The purpose of each macro is also described. Due to the complex and novel nature of the statistical method, we also included additional analysis dataset info sheet linked to define.xml which provided detailed derivation logic, the scoring for different scenarios with examples for a few subjects. One week after the NDA submission, we received a FDA Information Request (IR) to seek further clarification of SAP vs the SAS programs. FDA also requested a 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. We also provided two datasets with information requested by FDA and structured in the way we thought would be beneficial for agency review. The lessons learned here is that for any complex and novel statistical method, it is recommended to have a detailed standalone document to facilitate agency review. 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. It is always best practice to seek agreement with agency as early as possible on all aspects of electronic data submission package.

BIMO Summary-level Clinical Site (clinsite.xpt) Dataset

The FDA published the Bioresearch Monitoring Technical Conformance Guide [9] in February 2018. The document provides specifications for clinical data submission by pharmaceutical companies used in planning of FDA Bioresearch Monitoring (BIMO) inspections. Three types of information are required: clinical study level information, subject level data line listings by clinical site, and a summary level clinical site dataset. It is common for many companies to work on BIMO submission at the late stage of submission preparation as it is not considered as a rate limiting step. Tafamidis pivotal study data was submitted as part of the rolling submission prior to final NDA. Two days after FDA received pivotal study data, we received an information request to submit BIMO clinsite data to help agency determine the need for and scheduling of site inspections. Four days after BIMO was submitted, we received FDA IR to provide more details in BIMO clinisite define file for variable TRTEFFR calculation. The FDA guidance for the variable is as follows:

Treatment Efficacy Result (TRTEFFR) — The summary statistic for each primary efficacy endpoint, by treatment arm at a site. Values reported in TRTEFFR generally reflect simple summary statistics for the primary efficacy endpoint(s).

At the time of BIMO preparation, the guidance document was relatively new. It took time for programmers and statisticians to understand the requirement. The composite primary endpoint involving pair-wise comparison within strata also generated extensive discussion how to present treatment efficacy result by site. The key lessons learned are summarized below:

- BIMO submission planning can be initiated early especially for pivotal studies. Pre-submission meeting with FDA can include BIMO discussion.
- Ensure statisticians are 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.
- It is critical to check that 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

Tafamidis data submission to FDA included over two dozen individual studies and multiple integrated analysis data pools. Data standards used for the studies varied –third-party company data standard, Pfizer legacy data standard, vendor-supported CDISC standard, and Pfizer CDISC standard. The pivotal studies for CM indication did follow CDISC standard. We have engaged with FDA early and FDA agreed to accept some of the studies in legacy format. It is not uncommon for companies to separate programming tasks for CSR - focusing on SDTM, ADaM datasets and TLF production and associated programming documentation first then work on the submission components (eSUB data, define file and DRGs) after submission kick off. CDISC and submission requirement knowledge can vary among individuals supporting a study, especially when using an outsourcing model or multiple CRO partners. During

the submission preparation, we have encountered multiple data compliance issues with major CRO partners – from basic exchange format issues such as variables length, to missing EPOCH, to P21 report errors that could have been corrected early in ADaM design and code development stage. The compliance issues identified late have resulted in unfavorable updates to programming and documentations, which had negative impact on resources and process at minimum. We have since introduced the new process to start preparation of cSDRG and ADRG once the code development begins to ensure we check data compliance early on. cSDRG, ADRG and define.xml along with other programming documentations will be finalized when CSR TLFs are final. This can help improve programming efficiency and quality. One other benefit of this process is any special data and analysis consideration can be documented while the memory is fresh and knowledge holders are available.

It is also important to have consistency in submission documents across studies including the level of details provided and how to address common P21 compliance issues. This can be achieved by having a centralized group/dedicated resource to review and perform final QC of the submission documents.

One other agency query we received is the reviewer's preference to have a define.pdf with functional navigational links. This was received shortly after we submitted pivotal study data as part of the rolling submission. Define files were submitted in xml format. In order to better support agency's priority review, not only did we fulfill the agency's request, the submission team decided to include define.pdf with navigational links for all other data packages included in the final NDA submission. This was not previously planned and required a significant amount of effort at the last minute. We do recommend that for other submissions, especially accelerated ones, to reach early agreement with agency on any additional agency preference.

Pharmaceutical industry is heavily regulated, and our process is governed by various company Standard Operation Procedures and Working Instructions. Implementing new processes was challenging because the submission team was already in flight. Adjustments may be needed to adapt new processes - for example, adjustments may be needed depending on Submission Strategies (e.g. rolling submission, multiple simultaneous submissions). When new processes are introduced after the Submission Team has already initiated activities, the current processes need to be retrofitted to the newly implemented submission plan. The team should be flexible and carefully evaluate the risk and benefit of adapting new processes before implementation.

CONCLUSION

Accelerated pathways (AP) for drug approval implemented by the US, Japan, EU, and other countries allow faster approval of drugs for serious or life-threatening conditions and fill an unmet medical need. Different AP designations also provide various benefits to sponsors. 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. From statistical programming perspective, it is critical to understand the timing for rolling submission sequences and fully appreciate the different data requirements. Resources should be vigorously accessed in order to support accelerated timeline and rapid responses to agency queries. A harmonized approach to build in submission programming with clinical study programming will improve efficiency and quality for drug submission.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

LiFeng Good
Pfizer Inc
500 Arcola Road
Collegeville, PA 19426
USA
Work Phone:
Fax:
Email: LiFeng.Good@Pfizer.com