A successful journey through FDA review Sharing experience in a Vaccine Submission

Gabriele Filippo Di Domenico GSK - IX Italian CDISC UN Day 12-MAY-2023

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Objectives	1. CBER agency
	2. Submission Preparation
	3. Post Submission Comments
	4. Take home messages
Owner	Gabriele Filippo Di Domenico

CBER

Center for Biologics Evaluation and Research

The Center for Biologics Evaluation and Research (CBER) is one Center within the Food and Drug Administration, an Agency within the United States Government's Department of Health and Human Services (HHS).

CBER's mission is to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies.

The Center for Biologics Evaluation and Research (CBER) regulates vaccine products.

Main official Guidance are:

- **Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (v2.1 December 2019)**
- **Study Data Technical Conformance Guidance (v5.0 October 2022)**

Center for Biologics Evaluation and Research (CBER) | FDA

GSK roadmap

The Vaccine and the Submission Plan

Vaccine in scope was already available in US market.

A newly improved formulation was created and **two Ph2 studies** were conducted to support a sBLA (supplemental Biological License Application).

SAC study #1
October 2020

SAC study #2
December 2020

Wave 1 Comments
February 2021

ISS
March 2021

Wave 2 Comments
March 2021

Submission
Q3 2021

During completion of activities in preparation of Submission, CBER raised concern on our data standards in the context of other Vaccines projects…

CBER comments

Pre Submission - how to react to comments related to other submissions?

Wait
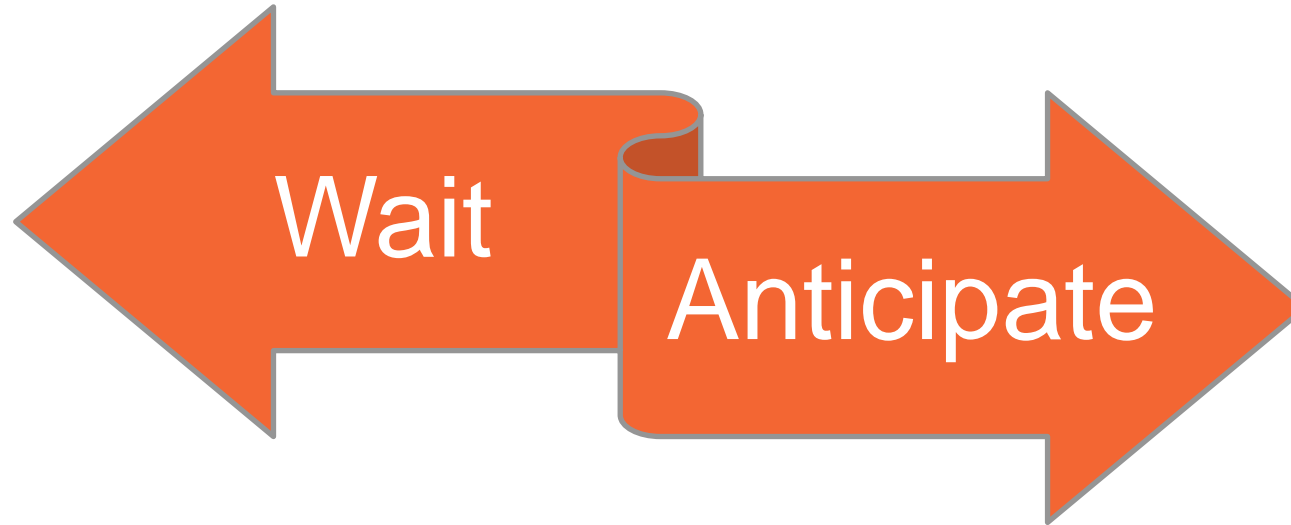
Anticipate

Company position was to **anticipate** future questions for this sBLA and to update proactively the datasets

(SDTM & ADaM)

SDTM package of 2 studies amended in 7 weeks

ADaM package of 2 studies amended in 6 weeks

ISS ADaM package amended in 2 weeks

ADaM Update

What to do with Summaries?

SDTM were updated with new structure in some domains, and as a consequence also ADaM were updated to reflect SDTM changes.

But Clinical Study Reports were completed already in January 2021, so tables wouldn't be amended...

ADaM were updated in specifications and in programming, but the final outcome (since source data were untouched) shouldn't be changed.

Team decided to document that ADaM datasets after the update were exactly equal (proc compare) to those of Final SAC, so tables wouldn't be re-generated and CSRs were untouched.

Company submitted as per plan in September 2021…

What happened next?

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Information Request #1

09 February 2022

20 Questions arrived from CBER review, divided as below:

- 11 on SDTM

- 2 on ADaM

- 1 methodology for Reactogenicity Events

- 4 on new summaries based on new definition of Reactogenicity Events

- 2 on other topics (e.g. general clarifications)

Team wanted to mitigate CBER requests and many cross-functional meetings were done to agree on how to proceed.

Statisticians and Stat Programmers were involved in such discussions to bring ideas and way of workings.

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Information Request #1
GSK Strategy

First bunch of replies in 10 working days days as per standard timeline in relation to Information Requests from CBER.

In case of need the Company could use additional 2 calendar weeks as additional time for Response to Questions completion

Information Request #1

GSK position - Example of **acceptance** of a new standard in **SDTM** without amendment of the package

While we agree that EPOCH is not a required variable, we prefer that it be utilized in all of your datasets in future submissions. Please acknowledge

GSK confirms that a mapping which automatically populates EPOCH in all relevant domains has been added to its data standards as of the start of this year.

EPOCH will therefore be present in all relevant domains for all studies which started SDTM set up using this latest version of the data standards. Due to the complexity of this mapping update, it may not be feasible for all studies currently ongoing to implement this change prior to their submission, however this change will be applied to new studies.

Information Request #1

GSK position - Example of **acceptance** of a new standard in **ADaM** without amendment of the package

We note that you are using ACAT1 (grade 3, leading to hospitalization, medically attended, overall, related, related medically attended and serious) and ACAT2 (day 1 30 mins, days 1-29, days 1-181, days >181 and overall) to further flag unsolicited adverse events in ADAE instead of adding additional columns to flag each one and keeping the rows consistent between AE and ADAE.

The Company acknowledges CBER's request aimed at simplifying and streamlining data review. As for the current structure the traceability is maintained using SRCFL (Source Record for ACAT1/ACAT2), which is derived from the original AE rows; for future submissions we will ensure adherence to CBER's feedback.

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Information Request #1

GSK position - Example of **push back** answer

It also appears that you may be reporting investigator obtained reactogenicity events in the AE domain that are not necessarily ongoing but are terms synonymous with solicited reactogenicity events and occurring during the prespecified assessment period. As previously conveyed to you, these events should be reported in the FA/FACE domain for day-to-day information (with EVAL=investigator) and as part of the summary in the CE domain as per the FDA guidance "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review." […]

Please see other attached document "Reporting reactogenicity data" for an example.

The company confirms that the investigators have used the study eCRF to provide details about events which occurred during the post-vaccination observation period, and which from the verbatim terms entered, can be assumed to be solicited events.

For data integrity purposes we consider that only data recorded directly by the subject (or delegate) in the eDiary device can be considered to be reactogenicity data. […]

The company does not consider reporting by site staff in the eCRF as an adequate replacement for this process as ALCOA-compliance cannot be ensured.

For future studies GSK will ensure that additional training and guidance is provided to site staff/investigators to ensure that the eCRF is not used to record their interpretation of reactogenicity events.

Information Request #1

GSK position - Example of **accomplish** request with **extended** timeline - part 1

Please provide a summary table that lists the proportion of participants across study groups who reported safety events that are synonymous with prespecified solicited adverse reactions with day(s) of event occurring during the 7-day (but not on Day 7) assessment period and then reported again on or after Day 8. Please include the severity grade of the reported adverse reactions, as defined in the study protocol. a. Please provide another summary table that lists the duration (mean, median, and range in days) of each adverse reaction. b. Please comment on the proportion of participants for whom each adverse reaction was considered resolved, ongoing, or unknown (information not provided).

o What do *synonymous* mean?

o How could we determine those?

o Which severity has to be reported?

o Why do not consider different events instead of one but intermittent?

Information Request #1

GSK position - Example of **accomplish** request with **extended** timeline - part 2

The Company is working on the analyses herein requested. The safety summary tables listed above will be provided in a separate document as mentioned before.

To address this question:

i. A table will be generated to summarize the proportion of participants who reported AEs that are identified as synonymous of solicited local and systemic reactions and that started between Day 1 and Day 6 and were also reported from Day 8 onwards. Source of the data will be eCRFs.

ii. A second table will provide the AE duration expressed in days.

If an AE was reported more than once during the study participation, this will be considered as a unique event. In that circumstance, duration will be calculated assuming that the event occurred continuously from the first day of onset to the last day it was reported (i.e. duration= last day– first day + 1, as per CBER' request), regardless of how many days the event was documented in between.

iii. A third table will provide by AE the proportion of subjects with the adverse event being resolved, ongoing or unknown.

Information Request #2

29 March 2022

3 Questions arrived from CBER review, concerning:

o Immunogenicity Assay Limits

o Immunogenicity Analysis

The same cross-functional meeting (including Statistician and Statistical Programmer) was held and the Team decided to use a similar approach to previous IR:

- Challenge the main feedback on Assay

- Respond to the analysis questions not related to the Assay limit

- Prepare in advance the responses and the analyses in case of CBER disagreement on the challenge (work at risk)

Information Request #3 and final outcome

The 19th of April, CBER came back…

[…] *Thus, it is our position that the data presented do not support your position.*

Accordingly, please acknowledge and comply with our requests conveyed on 29 March 2022 and submit revised immunogenicity analyses.

The activity was already completed in previous wave of questions, so it was just a matter to send what was already prepared, accepting CBER comment.

🕐 17 October 2022

FDA APPROVED

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What did we learn from this?

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Conclusions (1/4)

Take home messages and actions taken

Team Work

Statisticians and Stat Programmers were considered key roles in all meetings.
For every RTQs round, 7 meeting on average were held.

Meetings were:
a. Done at project level (Managers, Clinicians, etc..) to agree on strategy
b. Technical calls to align with Data Management
c. Done with Regulatory members on responses

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Conclusions (2/4)

Take home messages and actions taken

Be proactive

Instead of waiting comments and then replies,
Team decided to anticipate as much as possible
future questions in order to speed up the review.

We got green light in one year, using Ph2 data for
a license and during pandemic!

Conclusions (3/4)

Take home messages and actions taken

Negotiate

Do not always accept Health Autorithies comments.
As our client (acting as a filter for population medical needs) we have to please them and also try to <u>understand their needs but clarify our points</u>.

Conclusions (4/4)

Take home messages and actions taken

Learn & Improve

- ❑ Centralize Questions and Answers across projects
- ❑ Create specific Vx Support Team in Stat Programming function
- ❑ Create CBER Task force, across Data Management and Biostatistics

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Thank you

Conflict of Interests: Gabriele Filippo Di Domenico is employee of GSK group of Companies.

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