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# FDA Advisory Committee Meetings– A Statistical Programmer's Survival Guide

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## ABSTRACT

Supporting your company's presentation to an FDA Advisory Committee Meeting may be one of the most important and high-profile things you will do during your career. As a statistical programmer, you will have to do a lot of preparation and be able to provide analyses to answer any questions during the meeting. This paper explains what to do in the months leading up to the meeting in order to be fully prepared based on my experience as the Lead Statistical Programmer for two FDA Advisory Committee Meetings. Although this paper is aimed at statistical programmers, it is useful to all involved in the preparation for the committee meeting, including statisticians and project managers.

## INTRODUCTION

Preparation is the key to a successful committee meeting, also called a panel, and for your ability to support it. Knowing what to expect plays a big part of that. You cannot prepare if you do not know what you are supposed to do! You should be familiar with what an advisory panel is, who is there and what happens so that you can provide support to your company, referred to at the meeting as 'the sponsor'. Prior to the meeting, you will be doing a lot of analyses for your team members who will be writing the primary presentation and briefing document. Keep a log of everything you have done with program and output locations and to track validation. On the day of the panel, you need to be prepared for anything. Ensure everyone you may need is ready at a moment's notice to assist you and that you are ready to provide any analysis at short notice. Redundancy is part of that preparation. Failure is not an option, so server or internet reliability issues are not an excuse for not getting something done.

Not everything listed in this paper needs to be done by statistical programmers. In many cases, statisticians will take the reviewing tasks and perhaps some of the validation and programming, but particularly at smaller companies, roles may not be so fixed. However, everything described in this paper needs to be done by someone, so if no one else is doing them, statistical programmers should step up and do it.

## WHAT IS AN FDA ADVISORY COMMITTEE MEETING (PANEL)?

The FDA uses advisory committee meetings to obtain independent expert advice on scientific, technical, and policy matters. Not all submissions require an advisory committee meeting but the FDA may call one following the receipt of a company's submission for new or controversial indications that require expert advice or public scrutiny. The advice from the panel is not binding, but its purpose is advising the FDA by bringing in experts to help them make a decision on new therapies.

In his 2013 presentation[1] at the Biopharmaceutical Applied Statistics Symposium (BASS), Michael Proschan describes how an advisory committee is analogous to a criminal trial.

- Sponsor is like the prosecution (must prove case beyond reasonable doubt)
- FDA is like the defense (makes sponsor prove their case)
- Advisory committee is like a jury but of experts, not peers and sees evidence ahead of time
- Each side has its own experts
- Each side presents case separately

## WHO IS THERE AT AN FDA ADVISORY COMMITTEE MEETING?

The committee is usually made up of at least nine experts in the area of the drug, vaccine, or medical device that is under consideration for approval and at least one statistician and/or epidemiologist, all of whom have voting rights at the end of the meeting. There may additionally be a patient representative, an industry representative and a consumer representative who would normally not be voting members but can contribute to the deliberations.

Anyone else can attend the meeting as it is a public event and may even speak to the committee during the public hearing. Journalists and stock analysts will almost certainly be there.

## WHAT IS THE USUAL AGENDA OF AN FDA ADVISORY COMMITTEE MEETING?

The meeting will start with an introduction by each of the committee members where they explain their credentials, disclosures and the role they are fulfilling (expert, statistician or representative), followed by the chair stating the procedure and rules of the meeting. All panelists will have been provided with the briefing documents from both the FDA and sponsor ahead of the meeting. The FDA presentation will include their own review and determination of the submission and highlight the questions or concerns that the agency has, and which they will like the committee to consider. It will also state the voting questions for the end of the day. The sponsor presentation will outline the clinical data and should attempt to answer the FDA's concerns. Following the presentations, the committee members will ask questions to the sponsor which may be answered immediately or later if it requires additional analyses.

Example Agenda

- FDA Presentation
- Sponsor Presentation
- Questions
- Answers
- Public Hearing
- Committee Deliberations
- Committee Voting

## WHAT IS THE ROLE OF A STATISTICAL PROGRAMMER BEFORE THE MEETING?

You will be notified approximately 55 days[2] before the meeting is scheduled but if you anticipate this is going to happen, you should start the preparation ahead of the formal notification. In the time leading up to the meeting, your team will need to fully understand the data so that they can put the best case forward for the committee to recommend approval. As a statistical programmer, you will need to provide whatever analyses are required by your team. The basis of the panel will be the data submitted to the FDA in the NDA for drugs and vaccines, or PMA for medical devices. If multiple studies were included in the submission, the panel preparation should include all of these, and you should be prepared to answer questions on any of them.

The two deliverables from the sponsor for an advisory committee meeting are the briefing book and a presentation. The former is a document provided approximately a month ahead of the meeting which generally contains the following[3].

- an executive summary
- disease background

- unmet medical need
- product background
- overview of clinical development
- safety and efficacy from key studies
- risk management plan
- benefit-risk conclusion

Despite its name, the briefing book is rarely brief and may run into hundreds of pages although this is discouraged. It is provided to the committee members ahead of the meeting, and is made public via the FDA's website, so proprietary material should be excluded. With a document of this size, many tables and figures will be required, and it is the job of the statistical programming team to create these outputs, validate them and review the final version to ensure no editing has occurred that has changed the numbers. The briefing book will be the first time the committee members see the study results, so it is imperative that they are accurate. A discrepancy between this document and anything else the committee members will subsequently see, will lead to embarrassment and a distrust of all analyses.

The sponsor presentation will contain some of the same information as the briefing book but should also try to directly address the voting questions which will be known only a few days before the meeting. Therefore, the presentation will still be worked on in the days and even hours before the meeting so statistical programmers need to be available to provide last-minute outputs, validate them and validate the final slides until the presentation is complete.

In the preparation of the briefing book and presentation, many analyses may be requested that may not make the final version, but these are not to be discarded. If a member of your team thought to ask about something, a member of the committee may have the same request, so these analyses can be placed in back-up slides which serve as a repository of answers to potential questions that may be asked during the panel. Additionally, back-up slides should include any subgroup analyses performed during any study mentioned in the briefing book and analyses on alternative populations (e.g., As Treated and Per Protocol). It is not uncommon to have in excess of 1500 back-up slides so this will require dedicated resources for a considerable amount of time leading up to the panel. As well as the original programming, validation of the output and the slides is essential.

## WHAT IS THE ROLE OF A STATISTICAL PROGRAMMER DURING THE MEETING?

On the day of the panel, the only role of statistical programmers is to provide answers to unanticipated questions. Anticipated questions will already have back-up slides available, but no one can predict every line of inquiry, so the programmers need to be ready to provide any additional analysis at short notice.

Panelists questions that require additional analysis or statistical programming input will normally fall into these categories

- Clarification of something that was unclear
- Clarification of a discrepancy between briefing books or presentations
- Clarification of a discrepancy between tables or figures
- Request for a subgroup analysis of a presented table

In order to provide all requested analyses before and during the meeting, statistical programmers should develop some tools to make their job easier, more efficient and reduce the reliance on last-minute

programming. Creating patient profiles and listings and developing macros for subgroup analyses will help get answers to questions quickly during the panel preparation. This is not an exhaustive list but is a starting point for programmers and details of these tools are discussed below. It may be the case that these tools or other ad hoc analyses are easier to create using RStudio or any other programming language. However, care must be taken to ensure consistency with your original regulatory submission to avoid any unintended discrepancies.

## PATIENT PROFILES

A very useful tool for understanding your data on a patient level is to create patient profiles. These are quick summaries of key patient data and can take many forms from listings to annotated figures. Many examples are available online but for the purposes of panel preparation, it is a quick way to understand what happened to an individual study participant. It is not intended to be part of the presentation, and so should be as simple as possible yet include all important information. The exact content can be customized according to your team members' preferences, but as a starting point, the demographics and primary and secondary endpoints should be included. It is recommended to keep it to a single page of output otherwise it loses its effect as a 'simple' patient guide. Once programmed (and validated of course), the profiles should be shared with those involved in writing the presentation / briefing book so they can use them for reference without having to ask the programmers every time they want to know about a particular patient.

For things like adverse events or laboratory measurements which may run to more than one page for an individual patient, you can still output individual lists but in separate files so that if a particular subject's data is being scrutinized, your colleagues do not need to open a large listing and filter to the patient of interest. However, a note of caution, ensure that where a patient does not have any data for a listing, create an output stating "Patient has no data" rather than an empty or missing file to avoid any confusion. These profiles are meant to make life easier for the preparation team, not to sow confusion, frustration, or additional questions.

## DATA LISTINGS

Having said that single-patient listings are useful, it does not replace the need for full listings. These can be used to answer simple questions by using the filter functionality or pivot tables and can be done without programming, reducing the burden on the statistical programming team. If you have not already created these as part of your original submission, a starting point would just be to list the ADaM data sets but add as many 'common variables' as necessary. As mentioned, anyone can use these for their own 'analysis' but it must be documented and independently validated. Their main use is to allow others to answer simple questions themselves (e.g., how many males under 65 had a particular adverse event within 30 days) during the preparation phase, or to quickly answer questions on the day of the panel. It will also help in the unlikely event that you are unable to program on the day of the panel (see Redundancy section).

## SUBGROUP ANALYSES

A common thing to do whilst trying to fully understand your data is looking at subgroups to see if the results differ for some subset of patients. During the extensive preparation of my second panel, I was asked to analyze over 100 subgroups and therefore, if I was to do it again, I would immediately create macros that could produce tables for the primary and secondary endpoints by any subgroup. I'd also create similar macros for the baseline characteristics, as upon discovering that one group has different

outcomes to another, the next question was always “Were the patients in these groups significantly different at baseline”.

One subgroup might be of such interest that it may be required to produce all tables, figures and listings (TFLs) for that group. In this situation, it would be better to copy the whole submission to a separate folder, create the subgroup in ADSL and update outputs to use macro variables for the subgroup variable and labels. This may seem like a lot of work initially but after you have been asked to create all TFLs for 10 different subgroups, and the last 9 of these only required a change to a macro call, you will be glad you did. Do not under-estimate the amount of analysis your team will need and use every labor-saving trick that you have!

## TRACKING LOGS

It is essential to keep track of all outputs created during the preparation phase in case of follow-up questions on them at any time by your team, or by the committee members on the day of the panel.

Include at a minimum,

- Program name and location
- Output(s) name and location
- Production programmer name
- Validation programmer name
- Validation status

Other logs should be created that reference all data in the primary presentation and briefing books. When questions come on the day of the panel, the slide or page number will often be referenced, and you will need to know which output was on “slide 78”.

## VALIDATION OF SLIDES / BRIEFING BOOK

If the numbers in the presentation slides are incorrectly entered, all previous work is done for nothing so possibly the most important job is to validate the slides. This should be done on an ongoing basis as it benefits no one to see the wrong numbers at any time. Ideally this should be done as new data is being entered but that is often not realistic, so you need a method of identifying updates. PowerPoint does not have track changes, but you can compare files[4] so as long as the team is informed when updates are made, you can check the newly entered values. It is recommended that updates are entered in a different color until after they have been verified, or a symbol placed on slides that have been updated so they are clearly identifiable. The symbol can then be removed once the checks are complete. This is an example of where a task may be performed by someone other than a statistical programmer, like a statistician, but if no one else is doing it, you should step up as it is imperative that it is done by someone.

As with the presentation, every number needs to be checked in the briefing book, a document that will be the first chance for the panelists to see that data and which will be publicly available. However, unlike the slides, you will be able to use track-changes to identify updates because it will likely be developed in Word. Ensure consistency between the briefing book and presentation and be prepared to answer questions on where things deviate deliberately.

## VERIFICATION OF FDA BRIEFING BOOK

The FDA will provide you with a draft of their briefing book 2-3 weeks ahead of the panel. This gives you a chance to review and compare their analysis to yours and give feedback on any discrepancies. Check, verify and note the source output for every number reported. Create a log that references your TFLs with all data in the document so that you can prove where everything came from and be ready to answer follow-up questions related to anything. The final version will be made available 7 days before the committee meeting. The panelists will receive both the sponsor and FDA briefing books and will certainly ask questions on differences between them and you need to have answers prepared.

## TEAM SELECTION

The size of the programming team required for the panel preparation will depend on how much time you have to prepare, the complexity of the submission and how many people of other roles, such as statisticians, are able to assist you. At an absolute minimum, you need three dedicated programmers but twice this number would be preferable. Late nights and weekends will be common during the process, so it is important to allow time for people to take breaks. Do not allow team members to be siloed into tasks so that they become the only person to be able to work on a particular thing. On the day of the panel, you may get a lot of requests related to one thing, so you do not want the situation that one person is scrambling to get a lot done whilst others are idle.

## MOCK PANELS / PRACTICE

A mock panel is an opportunity for the whole team to practice for the real thing but without the pressure. In order for it to be optimally useful, everyone should take it seriously and use it to learn about gaps in your preparation and potential questions that the panelists may ask. There are consulting companies who can help arrange the mock panel and bring in outside experts to test your preparedness or you can select independent people (people not involved in this project) from your own company to act as the panelists.

If mock panels are not organized, as statistical programmers, you can still practice using previous panels available online to witness the process, so you know what to expect. You can also see which type of questions are asked and how long you would have to answer them. Remember that any analysis needs to be created, validated, put into slides, and loaded for presentation so you do not have very much time to do the programming. This is why tools such as patient profiles, listings and created anticipated analyses ahead of time should be utilized and ready to use as soon as questions are asked.

## REDUNDANCY

The importance of the panel to your company dictates that this is a zero-fail mission and so all scenarios should be considered and mitigated for so that you are able to provide whatever data analysis is required. Therefore, you need to be able to cope with internet, VPN or server issues and be able to work despite any outage. It is vital that statistical programmers are present at the location of the advisory panel to be able to collaborate in person with the team to provide timely answers to questions raised during the meeting, and the same is true of preparation meetings and mock panels too. However, programmers need to make contingencies for any technical issues and should have support personnel elsewhere who are ready and able to help out at a moment’s notice. This includes other programmers who can be directed to run programs and IT professionals who can quickly address any issues. Phone these people before the meeting and have them standing by.

Additionally, have some redundancy in your hardware and software. It is recommended to have at least

one standalone laptop with its own version of SAS® and all data sets saved on its local drive so that you can still run programs in the event of connectivity issues. Your team will not be sympathetic in the middle of the meeting to “The server is down so I can’t run my programs”. Also have all outputs, including patient profiles and listings, and all study documentation, saved on a local drive on all laptops and have printouts of major documents such as the protocol, analysis plans and briefing books for quick reference by anyone.

As everyone in your company will have a stake in the outcome of the panel, you can request that other people refrain from running large programs (e.g., simulations) on the day of the meeting. Nothing anyone else is doing that day will be more important than your work.

## FUTURE WORK

This paper focuses on FDA panels for US approvals, but many other countries have a variation on the same theme. In Japan for example, the PMDA holds similar meetings except that questions are not answered on the day but instead answered in writing after the meeting. Regardless, the main message of preparation and knowing what to expect applies to any such meeting so it is hoped that this paper is of use anywhere in the world. Please let me know if you have any experience of this and it could be included in a future version.

## CONCLUSIONS

Give yourself as much time as possible. Start the preparation as soon as you *think* there *may* be a committee meeting for your submission. If you wait until it is confirmed, you have already lost a lot of valuable preparation time. Choose reliable and dedicated team members and instill in them the importance of the job as well as the personal reward the opportunity to work on a panel means. Many people go through their entire careers without working on one, so this is an honor as well as a lot of work.

Anticipate lines of questioning. If you have been asked for a breakdown of the primary endpoint by several subgroups, you may be asked for the secondary endpoints by those same subgroups, so prepare the programs ahead of time. On the day of the panel, you can be asked anything, but the most likely questions will be related to something they have already seen. It is better to have the programs ready and not need them than to try and do the programming on the day in a high-pressure environment.

On the day, have redundancies and back-ups. The server going down or having a problem with SAS®, RStudio or your own laptop is no excuse for not providing answers so be prepared for anything. Have a separate laptop with its own version of all required programming software installed and all data saved on the local drive so that you can continue in the event of internet, server or even power outages. Also have anyone you might need (e.g., IT or other programmers) available to you from the beginning of the meeting which normally start at 8am Eastern Standard Time, so you may need to get people out of bed early!

Practice, practice, practice. Drill the team to be able to answer questions quickly and work under pressure by having mock panels. Your whole panel team should be involved but at the very least, watch some previous meetings on YouTube and try to answer the questions that they are asked in real-time.

## REFERENCES

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[4] https://www.howtogeek.com/690222/how-to-track-changes-in-microsoft-powerpoint/

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