FDA Advisory Committee Meetings: What they are, why they happen, and what they mean for regulatory professionals

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Abstract
The US FDA convenes panels of external experts or Advisory Committees to provide advice on product-specific and general questions. These meetings are generally open to the public and can be attended in person or by webcast. Advisory Committee meetings provide a challenge and an opportunity for regulatory professionals and their organisations.

Competitive intelligence from previous Advisory Committee meetings can be a valuable tool in the design of a development programme for a novel agent, identifying key issues, experts, and unanswered questions.

Many new agents are reviewed by an Advisory Committee prior to approval, and preparation for these sessions is critical. Strategic selection of speakers, authoring briefing documents, compiling presentation slides and backups, and responding to queries may be the deciding factors in the approvability of the compound and the prescribing information, post marketing commitments, and risk mitigation activities that will be imposed. Preparation is resource-intensive and careful planning is the key to success.

The significance of FDA Advisory Committee meetings

Bringing a medical product to market today has never been so complex or costly. While most people focus on the US$1 to $2 billon cost of research, development and commercialisation, there is one component to this process in the US that is often overlooked, and which has a tremendous impact on whether a product actually ever makes it to market – the US FDA Advisory Committee. For those unfamiliar with this, an FDA Advisory Committee meeting is a panel of outside experts convened by the FDA to advise the agency on key scientific issues and questions. These issues commonly include whether a product should be approved and, if so, under what labelling conditions or constraints. The Federal Advisory Committee Act became law in 1972, and is the legal foundation defining how Federal Advisory Committees operate (Pub. L. 92-463, Sec. 1, Oct. 6, 1972, 86 Stat. 770). Advisory Committee meetings are public and are typically attended by rival pharmaceutical or device companies, the media, and key stakeholders, including patient and advocacy groups.

Because the FDA usually follows the recommendations of its Advisory Committees, the success of a product is largely dependent on this meeting. In addition to product approvals, the FDA also calls general topical meetings to discuss scientific issues for a class of drugs (eg, cardiovascular issues with glitazones) or indications (eg, endpoints for accelerated and full approval of oncology agents). Advisory Committee meetings typically include: a 60–90 minute presentation by the drug/biologic or device sponsor; a presentation by the FDA; a public comment period; a question and answer (Q&A) period; a discussion session among the panellists; then, most often the committee votes on the safety, effectiveness and approvability of a product, as well as making general comments or recommendations for the record. The closest parallel to this forum in the EU is the Oral Explanation, where a small number of sponsor representatives respond to specific questions from the Committee for Medicinal Products for Human Use (CHMP). This, however, is a very different experience from the questions sponsors have to field from the panel of experts at a public Advisory Committee meeting.

Panel members consist of outside experts who are invited and vetted to become "Special Government Employees" while they serve on the committee. Because of increasingly stringent conflict-of-interest rules, and the time commitment of serving, it is becoming more and more difficult for the FDA to fill the committees with qualified panel members. Each panel generally has a dozen or more experts, including a patient advocacy representative and a non-voting industry representative. The FDA will often convene two or more panels for the same meeting if a product cuts across various areas, such as a drug with an associated diagnostic, or cardiovascular safety of a metabolic agent. While these meetings are not new, they are playing an increasingly significant role in FDA's review and approval process.

The history of FDA Advisory Committee meetings

The FDA began convening Advisory Committees in the 1960s to evaluate drugs and then expanded their use in the 1970s to review biologics and devices. A few key events have helped shape the need for, and dependency on, Advisory Committee meetings. These include the 1962 Amendments to the Federal Food, Drug and Cosmetic Act (FD&C Act) following thalidomide tragedies in Europe, Canada and other countries. These amendments required drug manufacturers for the first time to establish that a medication was safe and effective before going onto the market. This new standard helped evolve and improve the drug development process in the US, but it also raised the bar on both sides of the regulatory aisle, resulting in the review and evaluation of more scientific data. Over time these same standards were applied to devices. While new agents can be approved without Advisory Committee hearings, since

Table 1: Committees and panels used by the FDA to review the safety and efficacy of medicinal products.

CDER	CDRH	CBER
Anesthetic and Analgesic Drug Products Advisory Committee	Anesthesiology and Respiratory Therapy Devices Panel	Allergenic Products Advisory Committee
Anti-Infective Drugs Advisory Committee	Circulatory Systems Devices Panel	Blood Products Advisory Committee
Antiviral Drugs Advisory Committee	Clinical Chemistry and Clinical Toxicology Devices Panel	Cellular, Tissue and Gene Therapies Advisory Committee
Arthritis Advisory Committee	Dental Products Panel	Transmissible Spongiform Encephalopathies Advisory Committee
Bone, Reproductive and Urologic Drug Advisory Committee (formerly Reproductive Health Drugs Advisory Committee)	Ear, Nose and Throat Devices Panel	Vaccines and Related Biological Products Advisory Committee
Cardiovascular and Renal Drugs Advisory Committee	Gastroenterology–Urology Devices Panel	
Dermatologic and Ophthalmic Drugs Advisory Committee	General and Plastic Surgery Devices Panel	
Drug Safety and Risk Management Advisory Committee	General Hospital and Personal Use Devices Panel	
Endocrinologic and Metabolic Drugs Advisory Committee	Hematology and Pathology Devices Panel	
Gastrointestinal Drugs Advisory Committee	Immunology Devices Panel	
Medical Imaging Drugs Advisory Committee	Medical Devices Dispute Resolution Panel	
Nonprescription Drugs Advisory Committee	Microbiology Devices Panel	
Oncologic Drugs Advisory Committee	Molecular and Clinical Genetics Panel	
Peripheral and Central Nervous System Drugs Advisory Committee	Neurological Devices Panel	
Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee	Obstetrics and Gynecology Devices Panel	
Pharmacy Compounding Advisory Committee	Ophthalmic Devices Panel	
Psychopharmacologic Drugs Advisory Committee	Orthopedic and Rehabilitation Devices Panel	
Pulmonary-Allergy Drugs Advisory Committee	Radiological Device Panel	

PDUFA IV (Prescription Drug User Fee Act) and more recently FDASIA (Food and Drug Administration Safety and Innovation Act), Advisory Committees are more often the rule rather than the exception.

The current reality

The standards the FDA applies to the approval of medical products are an ongoing source of debate among all of its stakeholders. The agency is continuously faced with criticism from all sides – from those who believe it does not do enough to protect patient safety, to those who want the agency to approve products faster. Throughout the past decade, the FDA has relied more on Advisory Committee meetings to help balance these voices and assess key questions regarding a product's safety and efficacy in an open and transparent manner. Today there are 44 committees and panels to review the safety and efficacy of medicinal products. In the Center for Drug Evaluation and Research (CDER), there are 18; the Center for Device and Radiological Health (CDRH) has 18; and the Center for Biologics Evaluation and Research (CBER) uses five committees (see Table 1).[1]

In the past five years the FDA has held more than 400 Advisory Committee meetings. While the agency is not required to follow the Advisory Committee's ruling, it generally does. In fact, a recent review of FDA Advisory Committee outcomes showed that the FDA followed the recommendation of its Advisory Committee around 87% of the time.[2]

How meetings impact on companies' development plans

The potential impact of an Advisory Committee meeting on a sponsor

is very clear if its product is being discussed. But these meetings can also benefit regulatory professionals and their organisations in a number of ways. Here are just a few examples:

- **Competitive intelligence.** The Advisory Committee documents, slides and sessions can provide useful details on studies that have been conducted and insights as to how they are viewed by the FDA and experts. The documents and slides for each meeting are available electronically on the FDA website for recent meetings (after 2009) and are an invaluable tool in planning a development programme (see www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm). It should be noted that these meetings are also a time for team members to be on their guard. The meeting site and surrounding venues (including airports and rail/metro stations) are filled with competitors, members of the press, and representatives of the financial community. It's important to be aware of what is being discussed, what can be seen on computers, tablets, and/or phone screens.
- **Trends in approvals and guidance.** In some therapeutic areas, it is clear what challenges are facing the regulators and the regulated industry, such as measures of efficacy, risk tolerance for the indication, appropriate comparators, etc. However, for those who are not immersed in the field, there may be surprises in the issues raised by the FDA. Advisory Committee meetings often provide useful insight into the "behind the scenes" discussions and changes that are on the horizon. Thus, they can be very helpful for companies in the process of developing a compound or even when designing a target product profile for future agents.
- **The human factor.** Although Advisory Committee meetings have been available as live feeds and recordings for many years, there is no substitute for attending in person. They provide a unique opportunity to observe the FDA staff and key committee staff in action. Often the most useful information is picked up through casual interactions at these meetings. In addition, they are a great opportunity to meet up with colleagues in the field, as well as others who are addressing the same challenges with their own development programmes.
- **Public forum.** Speakers in the public forums represent a wide range of constituencies and provide insight into the challenges facing patients and their families, the view of medical practitioners, and the strongly-held beliefs of advocates and groups. Remember, all of these people can (and often do) contact legislators and media, which may lead to new pressures on the FDA and/or the healthcare system.
- **Critical review.** Taking the time to review the proceedings by a team that is well versed in the issues is critical. With the decline of scientific journalists, many of the live feeds, blogs and tweets from Advisory Committee meetings may not focus on the underlying issues.
- **Transparency.** The open discussions of issues with sponsors, the FDA, and Advisory Committee members provide an opportunity for the public and the medical profession to have a view of the complex decisions involved in the approval of drugs, devices and biologics, and to provide some input via the public hearing and comment session.

How to prepare for an Advisory Committee meeting

An Advisory Committee meeting is one of the most important days in a product's lifecycle. Whether a product eventually receives FDA approval often hinges on the outcome of the meeting and the discussions may impact whether, or how, a therapy is accepted by the medical and patient communities after approval. Not surprisingly, it takes a tremendous amount of preparation and resources to get ready for an Advisory Committee meeting. Since the FDA usually only gives companies 90 days' notice for their meetings, it's too late to wait until that notification for a company to begin preparing. Companies that have successfully mastered the preparation process usually start preparing while they are developing their new drug application/biologics license application/premarket approval (NDA/BLA/PMA).

There are some key steps companies can take to prepare for this meeting. The best preparation starts with listening to the regulators. Engage with the FDA and listen to its feedback, concerns, and questions. In fact, an analysis of approvable and non-approvable letters from the FDA indicate that not listening and communicating with the FDA during the drug development process can derail a product approval.[3] In addition, global regulators have frequent discussions about products and issues – any concerns raised by other agencies, such as the European Medicines Agency (EMA), Health Canada or Australia's Therapeutic Goods Administration may become a stumbling block with the FDA as well.

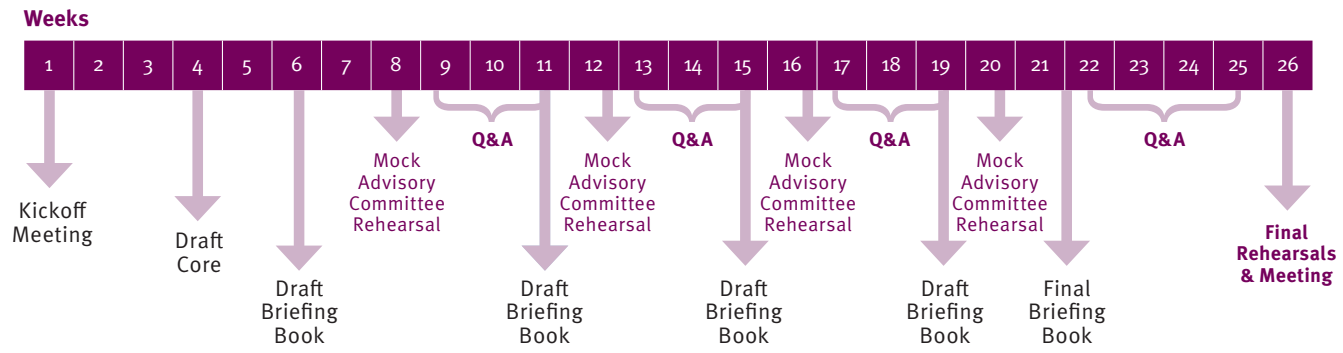
Preparing for an Advisory Committee is a full-time job. The first step in the preparation process is to organise a smart, focused and dedicated team that is fully supported by management. Because of the time commitment needed, it is critical to designate a team of people who can, and will, prioritise the Advisory Committee preparation over all other work. The ideal team should include representatives from a variety of areas: regulatory, medical, clinical, toxicology, statistics, pharmacovigilance, chemistry, manufacturing and controls (CMC), marketing, and commercial. In addition to the core internal team, it is important to start identifying external experts who can provide support for the company at the meeting, as well as experts who can serve as critical reviewers during the development of the materials. As these experts usually have very demanding schedules, it is important to secure their availability and commitment early in the process. Carefully considering who may be called on by the FDA may assist in the selection process.

It is recommended that sponsors allocate around six months to prepare for their Advisory Committee meeting. A sample timeline with key milestones is shown in Figure 1, including drafting the core slide presentation, briefing book for panellists, four mock rehearsals, and several Q&A practice sessions. Scheduling these dates and keeping to this timeline is not an easy task. Assigning a top-notch project manager is very important in making sure timelines are met.

Once the logistics have been organised, the next step is developing the content. That begins with analysing the audience. As with any presentation, companies need to know who they are speaking to, their background and interests and likely questions they will ask. This is critical in both preparing an effective presentation and for the Q&A session. Studying past votes and discussions around similar issues is a vital step in the preparation process. While all of this information is public, and transcripts can be accessed online, there is nothing like experiencing a meeting "live". An important component of preparation is for the company team to experience an Advisory Committee in person.

The first impression of a product will be gained from the panel's review of the background packages (briefing documents) prepared by the FDA and the company. It is essential to ensure the document is clear, succinct, and drives home key messages. Careful selection of the writer is crucial. External writers or a medical writer who has participated in the review of the dossier(s) may assist in preparation, and it is important that the briefing document mirrors the messages in the sponsor's presentation, and the desired labelling language. This document should be critically reviewed and carefully quality-checked as it will be available to the public: competitors, prescribers,

Figure 1: Example of a "typical" FDA Advisory Committee or Device Panel preparation timeline.



payers and patients can access the document long after the Advisory Committee meeting has been held. The FDA will provide its own background package for the sponsor's consideration 14 business days before the meeting (to correct any factual errors and redact any sensitive information, the final sponsor background package must be submitted 22 business days prior to the meeting), and it is wise to review this document with an eye to what questions it may raise for the panel. If time is limited, Advisory Committee members are more likely to read the FDA's briefing document than the sponsor's.

In addition to the briefing book, sponsors need to prepare for their presentation at the Advisory Committee meeting. Every company's presentation should do one thing – tell a clear scientific story that will lead to the approval of the product, with a label that supports appropriate use. A good presentation not only accurately conveys the data, but puts those data into context so they are meaningful to the audience. While there is no substitute for good data, without a clear, concise and compelling story, even the best data can be misunderstood. Great presentations are based on a credible strategy, clear, consistent messages, and data and slides that support that story. Because time is limited, every word in the core presentation must count towards a successful vote.

While the presentation to the panel is critical, how a sponsor handles the Q&A portion of the meeting can be the deciding factor. A published survey of Advisory Committee members showed that the Q&A session of the meeting had a significant impact on their vote.[4] This is often the most time-consuming aspect of preparing for an Advisory Committee. The goal of preparation is to predict all or most questions and have well-prepared answers. At the heart of a successful Q&A session is a well-skilled triage team. These are team members who identify and organise the data and develop hundreds, if not thousands, of backup slides. Identifying the questions most likely to be asked and most controversial issues early in the preparation process – and the appropriate responders for these issues – are important steps in successful preparation. Because an Advisory Committee meeting is the wrong time for an original thought, it is essential to identify all questions and develop credible answers with clear messages ahead of the meeting. It should also be noted that the sponsor may not be able to control the message at an Advisory Committee meeting. Any question can be asked, and the FDA and panel members may opine freely. Careful planning will help to steer the topic back to the desired message, but that may not always be possible. Contingency plans for damage control after the meeting should be considered.

Throughout the preparation process, company teams should always practice, test, and retest. Ideally, three mock panels of experts should be used to practice delivering a clear presentation and answering questions. Mock practice sessions should be designed to mimic the look and feel of an actual Advisory Committee meeting. That means mock panel members should be selected to match the expertise and background of the actual FDA panellists and be briefed to ask questions as the real members will. In addition, the room for the mock meeting should be set up to look exactly like the panel meeting. Speakers and responders should remain in role throughout the mock meeting, delivering their presentation and responding to mock members' questions, as they would at the actual Advisory Committee meeting.

While the steps outlined above are the foundation to any successful meeting, there are external factors that can affect the tone and tenor of the FDA questions and presentations, and the outcome of an Advisory Committee meeting. Just as these meetings have evolved over time, they may continue changing to reflect the current environmental and political landscape. Increasing quality problems and large-scale safety issues with any product can dramatically affect the level of risk the FDA and Advisory Committee members are willing to take. Importantly, companies should be aware of the environment in which they are seeking to bring a product to market, and be prepared to address how these external factors may influence their product's approval.

Conclusion

FDA Advisory Committee meetings are here to stay and almost every company attempting to market a medicinal product or medical device in the US has experienced, or will experience, this process. Being as prepared as possible and treating this meeting with the respect it deserves will increase the opportunity for achieving a successful outcome. Ultimately, companies should bear in mind that Advisory Committee meetings provide more than product approvals or resolutions of key issues. They also serve as public forums for exchanging important scientific information. And that can benefit everyone.

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