
GET THE MOST
OUT OF YOUR
LATE-CYCLE
REVIEW MEETING
ECG®

# Get the Most Out of Your Late-Cycle Review Meeting

As part of its emphasis on transparency and communication, PDUFA V introduced "the Program,"[1] which contains three meetings between sponsors[2] and FDA review teams that frame the first review cycle for NME NDAs and novel BLAs: the pre-submission meeting, the mid-cycle discussion, and the late-cycle meeting (LCM). Each provides important opportunities to identify review concerns and issues and to clarify them.

The ultimate goal of these three milestone consultations is to increase the number of applications approved during the first cycle without lowering rigorous assessment standards. Of the three, the LCM is particularly important as it is often the final official interaction between the sponsor and the FDA review team before the approval decision. Accordingly, preparing for this meeting has become an essential step in the path to approval.

## THE NATURE OF THE LCM

The LCM was designed as a formal opportunity for the applicant to hear and understand issues that had emerged from the review and either to explore ways in which they might be addressed in the final stages of the review or how they might be addressed in an advisory committee meeting (AdComm)[3], if the Agency chooses to hold one.

For applications that will not be discussed in an AdComm, the meeting comes approximately three months prior to the PDUFA date, giving both the Agency and the sponsor sufficient time to act on the issues discussed in the LCM. The scope of the meeting can include any review issue: CMC, choice of assays, trial design and conduct, toxicology, clinical results. The LCM, however, was not designed to discuss overarching topics like benefit/risk and approvability.

For applicants who will present at an AdComm, the meeting must take place "not less than 12 calendar days before the date of the AdComm." In this case, the meeting can focus on a range of issues like those described above; however, the FDA is more likely to place the greatest focus on how the issues will be approached in the AdComm, and these issues are generally clinical. In addition, although the FDA will not generally discuss overarching topics at this meeting, it will often include questions of benefit/risk and approvability for consideration by the members of the advisory committee.

For complete details, see this guide on PDUFA V.

---

[1] See "Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMP), dated April 2005," and process requirements described in the PDUFA V agreement entitled: "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017."

[2] "Sponsor" is a common term for the filing company; the company that "sponsors" the submission

[3] This term, "AdComm," will be used throughout the document to refer to an FDA advisory committee **meeting** but not to the committee itself.

Developing a plan to prepare for this meeting, with or without a subsequent AdComm, requires considerable rhetorical skill because of the meeting's communication context. First, the process is relatively new for both the FDA and the sponsors. Most filing teams will not have members who have participated in one of the meetings, so planning based on experience is limited. The nature of the LCM is still evolving as a step in the approval process. In addition, the FDA makes no claim about being a monolithic enterprise with a book of hard and fast rules for its drug approval processes. Indeed, the review teams at the FDA interpret processes and guidelines according to the team's experience, expertise, and even character, therefore leading to variations on exactly what a sponsor team might expect at any given LCM.

For an example, including an agenda, see this LCM Background Package.

In practice, LCMs have been held in person and by teleconference, have lasted less than 30 minutes, have lasted more than two hours; there's neither rule nor guidance for actual team preparation. As mentioned above, their focus has varied from CMC issues only to clinical issues only. Their outcomes have been equally varied.

At some meetings the Agency and sponsor have identified steps the company could take to resolve issues. Others have reduced the impact of an issue. Some have even resulted in issues being resolved. Some have consisted only of a direct reading of issues from the FDA's briefing package, with no discussion and no movement from the FDA. In addition, the scope and quality of the briefing package varies widely from team to team. Guidelines call for this briefing package to be sent to the applicant not less 12 days before the LCM if no AdComm is planned, so in theory it's possible to prepare to discuss the FDA's position, but, since there's not always discussion, preparation must be guided by what the sponsor team has learned from interacting with the review team and what regulatory can learn from its FDA contacts.

## PRINCIPLES AND PRACTICES: PREPARING FOR AN LCM

To understand how to plan, rehearse, and take full advantage of the LCM, the team needs to begin with a general understanding of the Program's stated goals for the LCM and its participants. Though not designed as a debate, the LCM does provide a setting in which opposed perspectives can be shared and aligned, and, though not decisional, the LCM can lead to agreements and set the tone for subsequent deliberations. Issues can be relegated to secondary status and can occasionally be resolved.

*The LCM provides an important opportunity to work with an extended FDA review team to resolve or at least fully understand issues.*

The participants in the meeting reflect its potential. In the Program, the FDA committed to documenting "substantive concerns" from all disciplines that had emerged during the review in the briefing material for the LCM. Accordingly, the array of FDA members required to participate at the LCM gives special weight to the agency summary of review issues. FDA representatives at the late-cycle meeting are expected to include the signatory authority for the application, review team members from relevant disciplines, and appropriate team leaders and/or supervisors from disciplines for which substantive issues have been identified in the review to date.

Sponsors should know as they approach the meeting that they are likely to be facing an aligned FDA. The LCM requires internal discussions within the FDA to align positions so that the Agency is speaking with one voice. In any case, for the sponsor of a submission with unresolved issues, the LCM provides an important opportunity to work with an extended FDA review team to resolve or at least fully understand these issues.

One mistake some companies make is considering the FDA-identified issues a portent of the final decision. Though the impulse is understandable, using the meeting as a crystal ball misconstrues its intended function. The communication goal of the LCM is not to announce or lay the groundwork for approval or a Complete Response. The meeting is focused on identifying and clarifying each current issue, not on weighing them collectively to see if the approval scale tilts one way or the other. It's not a benefit/risk assessment meeting. Rather than trying to predict the future, work to understand the present. How your team addresses these issues will determine the future, both what will happen and when.

## SCIENTIFIC ADVOCACY

Ideally, sponsors start developing their sense of scientific advocacy[4] early in the development process, even before creating a Target Product Profile. After filing, however, the process intensifies as the end goal comes into view. To get the most of their late-cycle consultation, sponsors need to employ an ongoing and nimble approach to scientific advocacy. The sponsor's strategy for scientific advocacy should focus the filing's positioning—it begins with a consensus on the core messages that need to be conveyed convincingly; it guides the team's preparation plans and informs every interaction with the Agency. It evolves with the identification of issues that could challenge credibility and matures when the data is organized to support arguments for the company's positioning. The strategy needs to be fine-tuned through, and for, each interaction with the FDA to take full advantage of the increased communications opportunities that PDUFA V offers. It continues to evolve until the Agency has reached its decision.

Its evolution should incorporate input from scientific advisors, new data and analyses from studies, external publications, and the increasing clarity of the team's own thinking. Because the process of honing advocacy involves multiple disciplines within the sponsor's organization, teams must develop an effective decision-making structure involving senior management as appropriate. It's important that the sponsor team enter the LCM speaking with one strong voice while advocating for its position.

[4] We define "scientific advocacy" as advocating for a position by providing scientific evidence structured and delivered with persuasive effect. A sponsor's submission advocates for approval by providing scientific evidence obtained largely from trials but also from other external scientific sources. In a workshop in 2011 AAAS defined advocacy as "attempting to influence a specific outcome, to tell an external stakeholder, 'This is what you should do!' It is a deliberate, purposeful . . . expression of an opinion or point of view. In this understanding, it is using one's scientific position and expertise to accomplish a specific . . .goal . . . . "
http://www.aaas.org/sites/default/files/reports/Advocacy_Workshop_Report_FINAL.pdf

## TECHNIQUES OF ADVOCACY

Implementing the strategy will engage the team in a variety of preparation activities throughout the review process. Since one of the basic components of any advocacy involves careful listening, in this case carefully hearing what the review team is saying in meetings and in correspondence, teams should actively work on this primary skill. Every meeting with the review team, but especially the pre-submission meeting, provides an opportunity to learn what's driving the review, provides a sense of how the reviewers are responding to the team's position. The most successful teams work to ensure that they have fully understood the issues documented in advance of the meeting and to elicit any additional concerns or amplifications that might have emerged during the interim.

*During meetings and teleconferences, sponsor teams need to practice patience.*

During meetings and teleconferences, sponsor teams need to practice patience, at minimum, and ideally develop techniques to learn as much as possible from the review team: supportive silence, verbal checking for accuracy and completeness, subtle probing for nuance, and controlling the instinct to debate. A*ctive listening* doesn't always come easy for company experts who have become ardent advocates for a prospective medical treatment. The team's initial goal is to see how the agency sees the data—to empathize, as it were—to understand how intelligent people may reach different conclusions.

Teams should also regularly test their evolving approach to advocacy through simulation exercises that hone not only the team's approach but also the ability to employ it effectively. Such exercises allow teams to experiment with alternative approaches, testing different ways of conveying a core message and also different messengers. It is important to learn how to establish an open, collaborative atmosphere. An argumentative or defensive team with a contentious tone is far less likely to learn exactly what is needed to reach agreement.

## LCMs PRECEDING AN ADCOMM

PDUVA V also states that the Agency will inform sponsors in the 74 Day Letter if there will be an AdComm. This notification can contain some ambiguity. Language stating "at this time no review issues have arisen that would require an advisory committee meeting" leaves the door open to a meeting being scheduled when such an issue arises later. In other words, unless the sponsor with an NCE or novel biologic receives a definite commitment from the review team, and perhaps even from the Division, the prudent sponsor combines the principles of preparing for a LCM with the practices of preparing for an AdComm.

If a sponsor has been told that there will be an AdComm, it is a mistake to attempt to use the LCM to debate the issues. Rather than position the FDA and the company on opposite sides of an argument, it is better to focus on their shared goal of getting meaningful guidance from the advisory committee. This focus requires a collaborative, not a combative, approach in which the participants gather around a planning table instead of volleying back and forth across it. On the other hand, the review team and the sponsor do not always share the same goals. For the Agency, the purpose of the meeting might be to **plan** the final stages of the review and **prepare** for the AdComm, not **pre-empt** the identified issues.

But for the sponsor, even though the meeting is not "decisional," placing all the identified issues without qualification in front of an independent committee leaves open the possibility that issues might become even more embedded in the review. This is the last chance to persuade the FDA to consider the potential resolution of an issue before it becomes a heated meeting topic, but sponsors must have reasonable expectations. In general, the best outcome of the LCM would be that the Agency modify its position on one or more issues. Letting the FDA know what the sponsor might be saying at the AdComm about an issue could lead the review team to reconsider its tone for raising the issue and the analyses they use to introduce it. Nevertheless, the company should not try to win its arguments but rather to set the stage for success by working **with** the FDA to plan an effective AdComm – one that will allow its independent panelists to make informed, data-based judgments about the scientific issues at stake.

The team facing an AdComm can make the most of its time by considering preparation for the meeting and preparation for the LCM as part of the same intellectual activity. The AdComm, in contrast to the LCM, allows the sponsor to tell its entire story, to advocate for its position about its product. Consequently, getting ready for an AdComm includes preparing a presentation and briefing document that contribute to the development of an umbrella case for approval and for the acceptance of a well-defined benefit/risk profile.

Both meetings, however, also center on issues and the sponsor's goal of resolving the most critical ones. For the AdComm, the sponsor wants the resolution of issues to lead to an overall acceptance of the company's position; for the LCM, the focus remains on individual issues and not on overall approval. Nevertheless, the focus on resolving issues creates a useful overlap of effort beginning with the first preparation meeting identifying target messages, inherent issues, responses to issues, and potential support for both messages and responses.

This overlap gives AdComm Q&A preparation a dual purpose. As companies prepare an issues compendium for the meeting, they can maintain an awareness that any of the potential issues they've identified and any responses to issues they've developed might well provide content to the team as it prepares for the LCM. To avoid repeating work, teams should prepare their issue books in a sortable format, thus facilitating both retrieval of slides at an AdComm and isolating content for the LCM.[5]

*The review team and the sponsor do not always share the same goals.*

AdComm preparation also provides sponsors the opportunity to test its responses to issues through various forms of internal and external rehearsals. The most powerful of these is the Mock Advisory Committee. Carefully selected mock audiences provide penetrating feedback on the team's response to and handling of the issues, but rehearsals are revealing even when the team simply views itself critically. What's the message inherent in the team's body language and attitude? Does the team project credibility? Is there consistency between the team's oral and written communication? Such rehearsals show how well intentions correlate with impact when theory is put into practice. The data gleaned from these trial runs offer vital counters to the dangers of *groupthink*, in which teams steadily reinforce their own beliefs without soliciting contrary contentions and new perspectives.

[5] The issue book prepared during this process can also be used to answer questions from the review team or questions from other health authorities, for example the Day 120 questions from the EMA.

When an AdComm is pending, the FDA will also provide sponsors a complete briefing book and a list of potential questions/points of discussion for the LCM. As mentioned, guidelines call for this briefing package to be sent to the applicant not fewer than 20 days before the meeting if an AdComm is to be held and 12 days before the meeting if no AdComm is planned.

This advanced notice of the FDA's positions potentially provides the team sufficient time to structure its approach to the LCM and to review and revise its material for the AdComm. Some companies schedule Mock LCMs during the week before the meeting. Others schedule Mock AdComms during this time in order to discover how the mock panel responds to the FDA's positions and the company's responses. Still others use an internal rehearsal before the LCM and schedule a Mock AdComm for the time between the LCM and the AdComm with the idea that after the LCM the team has the most complete idea of how the FDA will approach the committee.

Once again, however, because of the variable usefulness of the FDA's package, the best prepared team will be the one that uses the best targeted resources to explore its potential issues and develop persuasive responses to them.

When companies construe the LCM as an adversarial encounter, they are inclined to be less transparent and to hold back their planned arguments for the AdComm. This strategy, although perhaps based on the sponsor team's interaction with members of the extended review team, makes it impossible to leverage the expert advice the company has received during the mocks. The FDA is sensitive to external pressure and the knowledge that the best experts in the field have helped the sponsor shape its responses can have an impact on the FDA's tone and approach at the meeting. By communicating results, the preparation process can be used at the LCM to gain alignment around the most effective approach to addressing issues with the members of the actual committee. This knowledge can alert the FDA to dangers of framing the discussion in different ways and suggest alternatives that focus the committee on the heart of the problem.

*Careful positioning and discussion with the Agency can take some issues off the table.*

Another consideration for the sponsor team is the company attendance at the meeting. The meeting should be a priority for face-to-face attendance for the key decision makers on the sponsor AdComm team; such attendance builds comfort and collaboration and allows direct communication with FDA senior staff members (they are required to attend the meeting). The interaction with the review team and division leadership at the LCM can help sponsors shape their final preparations for the AdComm.

Careful positioning and discussion with the Agency can on occasion take some issues off the table; the FDA can still structure the AdComms discussion and voting questions to reflect the absence of an issue. Even more frequently, these discussions can lead the Agency to soften or modify its position on an issue, making it less likely that the issue will become dominant for the committee members.

Some review teams will share their draft AdComm presentation slides, usually after the LCM but sometimes during or prior, and will modify their presentations. This level of collaboration and openness can help both the review team and the sponsor team narrow the focus of their final preparations, homing in on the critical issues and spending less time on minor or resolved issues. It allows both parties

to agree on points that don't need belaboring as well as streamline presentations and explain roles and responsibilities when it comes to clarifying or responding to certain topics. As OND Director Jenkins asserts, "Planning for AC meeting will avoid redundancy of applicant/FDA presentations in areas of agreement and allow focus on areas of disagreement or need for committee input."

The LCM can also facilitate discussion about the meaning or intent behind FDA questions to the committee and whether the draft questions provided in the FDA briefing document are the same ones that will be utilized at the meeting or if edits are already occurring. This knowledge allows the team to fine-tune its approach to the AdComm. Sometimes, as a result of the meeting, sponsors have been able to run analyses that more directly address a particular concern that became apparent during the LCM. On rare occasions, sponsors have received permission to introduce data that completely seals a hole in the application prior to the AdComm.

After the LCM, sponsors should debrief and conduct at least one dress rehearsal or mock to make final adjustments consistent with commitments made to FDA in the LCM or that are tuned to FDA guidance about the topics and concerns to be surfaced at the meeting.

## THE IMPACT OF PDUFA V AND THE LCM

PDUFA V has had a dramatic effect on the approval process. It's too soon to know if the rate of first cycle approvals will increase; however, there appears to have to have been a reduction in the number of AdComms held. It's impossible to ascertain a direct cause and effect relationship, but it is possible to suggest that improved communication between the review teams and the sponsor teams has decreased the number of open issues late in the review process. In any case, early responses from the industry suggest that the addition of the formalized LCM is a beneficial step for both sponsors and FDA, one that should be exploited for maximum benefit for both parties, as both parties share the same goal—a wise decision that will allow the public to receive important, new medical products.

**Additional References**:

CDER 21st Century Review Process Desk Reference Guide: New Drug Application and Biologics License Application Reviews (NDA/BLA Review Process)

New Drug Review: An Update and a Look Ahead – FDA/Investor Meeting presentation by John K. Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research

**About the Authors:**

ECG is a strategic communications consulting company. We have worked with most of the leading international healthcare companies to help them develop and refine their communication strategies, documentation, and presentations for critical health authority meetings. Our Principals have helped prepare teams for over 140 FDA Advisory Committee Meetings and recently, the crucial late-cycle meetings that precede them.

Michael J. Vivion, PhD.
Steven Cohen
Frank J. Carillo
Richard Barr, PhD., LCSW

ECG®
The Communication Strategy Company.