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SUMMARY

It is not common for a drug to go before two FDA Advisory panels before a final decision is made to approve or disapprove a drug. However, the decision is not random chance, and the FDA may take a drug to a second panel if for drugs when:

- They are first-in-class.
- There are questions of science.
- The company requests it.
- The first panel recommends it.
- Something new or controversial came up.
- A political issue in the medical community is involved.

MedImmune's FluMist nasal spray flu vaccine would appear to be a perfect case of a drug that is likely to need a second panel.

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FDA Advisory Panels: When One is Not Enough

Many new drugs are approved by the FDA without being considered by an Advisory Committee, but more often the FDA seeks the advice of an expert Advisory panel before approving a new agent, particularly something that is first-in-class or has safety or efficacy questions. A few drugs even go before panels twice before the FDA makes a final decision.

FDA officials, speaking on background, discussed when a drug or device might need a second Advisory Committee meeting, and they said the reasons can vary substantially. They emphasized that advisory panels are just that, advisory, and that it is the FDA which makes the decisions, and the advisory panel recommendations are only one data point. Sources said there is no set protocol for determining whether a panel is needed – either a first panel or a second panel – and each panel is determined on a case-by-case basis. Furthermore, there is no historical pattern that can be used to determine the likelihood of a second panel.

However, there are some cases when a second panel is unlikely. An FDA official said the agency probably would **NOT** require a second panel if the first panel found a drug efficacious but not necessarily safe **AND** any of the following were true:

- **The agency disagreed with the first panel's finding.**
- **Additional data was presented to the agency after the first panel meeting that clearly resolved the safety issue.** An official explained, "If the appropriate supportive data was submitted, and our scientific experts reviewed it and found it (post-advisory committee) to be adequate, we might not choose to present that to the committee for review…Ultimately if the company can submit supportive data that addresses the advisory committee concerns adequately, then it is fair to say the agency would, after completion of its review, have to take a look and determine the level of need for a follow-up advisory committee. And the data would have to be supportive in the FDA's opinion, not just the industry's opinion or the company's opinion."
- **The safety question dealt only with one age or population subgroup** (e.g., pediatrics). An official said, "If an advisory committee did not approve an agent based on safety, what are the specifics? There are so many different levels that could be involved. Was it just some age groups or was it across the board? What is the panel's definition of 'not safe'? I wouldn't want to definitely say that if a firm submitted sound scientific data in support of an advisory committee recommendation -- and was able to derive and compile the necessary data for approval – there would be no need for a second advisory committee."
- **The issue is related to manufacturing** because those issues are rarely if ever taken to a panel.
- **Efficacy questions applied to only subgroups and could be resolved with additional data.** An official said, "If an advisory committee said that, based on the data to date, we think a product is safe but efficacious only in some age groups and not others – or that the safety data is not conclusive – the committee may say the data is not overwhelmingly supportive of efficacy, and it may recommend the FDA require more data. Then, the FDA probably would ask for more data. The FDA may not agree with the advisory committee, but if we do agree with the committee, then, at that point, we would work with the company, and hopefully, it would derive the supportive data to support licensure. And if the company submitted that information over the course of the next several months – whatever it takes to drive the data or compile the data – then, we may not need to bring it back to the panel."

Officials said the FDA **would be likely to require a second panel in** the above scenarios (first panel pro efficacy, con safety) if:

- **This were a first-in-class agent.**
- **There were a political issue with the medical community.** For instance, when Warner Lambert (now Pfizer) withdrew its oral diabetes agent, Rezulin (troglitazone), from the market, the FDA held a panel to allow a full and open discussion of the decision. Doctors and patients loved the drug, but the agency had concluded it was not safe, and FDA officials felt a need to explain their decision publicly.
- **There were questions of science.** An FDA official in the Centers for Biologics Evaluation & Research (CBER) said "CBER is very science-based – probably more so than the other centers within the FDA," though he insisted he wasn't casting aspersions on the other FDA centers.
- **The company requested it.** A company can request a second panel if it feels the panel will help convince the agency to approve its drug.
- **Something new or controversial came up.**
- **The first panel said it needed more information** to make a recommendation.

CASE STUDY: MedImmune's FluMist

FluMist, an influenza vaccine delivered as a nasal mist, was first submitted to the FDA in October 2000 by Aviron (which was later acquired by MedImmune). The Antiviral Drugs advisory committee was convened in July 2001, and the panel voted the drug was effective, but members were not convinced it was safe. An FDA official said, "When (FluMist) went before the advisory committee, the committee did not recommend approval. They strongly indicated – overwhelmingly – that it had great promise, but they weren't recommending it because there was a need for sound data. At that first panel, the chair discussed that a great deal of safety data was being analyzed by the FDA and being integrated, so he joined against approval, but with the caveat that this was a 'work in progress.' The committed voted in favor of efficacy in adults aged 18-64, but it was a close vote. And there were concerns and unanswered questions about safety when given to children, so they voted no against safety."

Does FluMist need a second panel? MedImmune officials had insisted that FluMist would not require a second panel, but more recently they have admitted it is likely to need a second panel, though no date has been announced yet for a second panel.

Why is FluMist likely to have a second panel meeting? A look at the transcript of the first panel makes it clear that panel members wanted a second opportunity to consider and discuss FluMist. The transcript can be found at:
http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3769t2_03.pdf

Among the interesting comments in that transcript are these statements by the Chairman of the first advisory panel:

- "There are 10 No's and 4 Yeses. Of the 10 Nos, 6 people commented that they view this as a work in progress situation and would like to hear and review the data when the processing part has been finished. So, that's an important qualification, I think, on a large part of the No vote. And I think that it's important to convey to the sponsor that there is a lot of interest in the progress of this vaccination and that we feel like more data on these safety issues, particularly that have been raised, would be very important."

- "There is a great deal of data that bear on safety that are in the process of analysis and being integrated into the database here at the FDA. So, I must join the people who voted No, but with the caveat that it be sort of a work in progress kind of No."

- "I would love to have a chance to revisit this issue when all of the data that are available have been processed by both the sponsor and the FDA…I'm, on the whole, excited about the prospects for this vaccine being part of our armamentarium in the future."

- "I believe that there is a risk for – at least potential for risk – for a flu-like illness in the days following vaccine, and I'd like to hear more about that. I mean, we've sort of heard about it in Houston children when cultures weren't really being encouraged in that period, and I'd like to see that studied in a little more detail."

- "The transmission issue is an important one, although I suspect from what I've heard today it's not going to turn out to be an important clinical problem. But I think in the climate we have today with vaccines and new vaccines, we've got to be very sure, perhaps even a priori sure, that it's not a problem."

- "The asthma issue, I think is an important one. I'm not sure that asthmatic children would accept this vaccine if they knew there was a higher risk for an exacerbation following its receipt. And I think that given the data we've had, they may be a tip of the iceberg phenomenon and biased against people who weren't able to report that their child had asthma. And I'd like to see some more systemic study of that."

- "Pneumonia and conjunctivitis and nasal congestion, I think there's more data that's in the mill and being processed. And, again, I'd love to hear those data when FDA and sponsor have finished reviewing them."

- "The annual dosing issue I think really hasn't been addressed and I think is an important safety issue. Although, again, I suspect that when it is addressed, it's going to be a safety concern. But without data, who can say for sure."

- "I feel very confident in the safety data I saw for healthy adults over 50, but many adults are not healthy over 50. And it would be, I think, important, although perhaps not directly germane to this indication, to have some sense of what happens when you immunize people who are not 100% healthy." ¨