Negotiating Stasis and Achieving Meaningful Public Participation in Pharmaceutical Policy-Making

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“What endpoint then is sufficient for your approval? Months, years? Despite potential side effects from Avastin, metastatic breast cancer has only one, death. Certainly, Avastin can do no worse.”

“...the absence of evidence is not evidence of absence.”

In February of 2008, Avastin (bevacizumab) was approved for the treatment of metastatic breast cancer under the Food and Drug Administration’s (FDA) accelerated approval program. But after her review of “thousands of pages submitted to a public docket, data from several clinical trials, and the record from a two-day hearing held in June, 2011,” on November 18, 2011, FDA Commissioner Margaret A. Hamburg, M. D., announced that she was “revoking the agency’s approval of the breast cancer indication for Avastin” (FDA News Release). Specifically, Commissioner Hamburg states that “there was not, at the time of approval, credible evidence of
increased overall survival or increased quality of life, and there is no such evidence now. Instead, CDER (the Center for Drug Evaluation and Research) based its accelerated approval on a different measure, referred to as ‘progression free survival’” ([Hamburg, 2011](#)). Commissioner Hamburg has argued definitively that Avastin is neither safe nor effective.

This article reports on a portion of a broader analysis of the FDA’s deliberative procedures. Questions regarding the appropriateness of the Avastin revocation or the validity of the arguments that lead to that revocation are beyond the scope of this article. Rather, this article takes as its object of analysis the FDA’s inclusion of the public in the two day public hearing. This hearing was convened on June 28th and 29th, 2011 in order to offer a final appeal to Genentech—the makers of Avastin. The public’s call for participation has been embraced by the FDA, and they now include a patient representative on each drug advisory committee as a matter of course (Lewis). The regular inclusion of patient voices in drug policy hearings is a strong indicator of the FDA’s commitment to key stakeholder participation in policy decision-making.

However, we question the degree to which stakeholder testimony from the public and among other non-researching participants (e.g., clinical oncologists) was meaningfully incorporated into the FDA’s deliberations. Invoking contemporary stasis theory and conducting rigorous rhetorical analysis of the two-day trial provides the grounds upon which we make suggestions about how to improve cross-stakeholder deliberations like those of the FDA’s.

**Pharmaceuticals policy-making from a rhetorical studies perspective**

Traditional stasis points include questions of fact, definition, quality, and jurisdiction. Stasis theory suggests that, in the course of any public debate, points of contention will arise that need
to be adjudicated before the overall issue for which said debate was called can be decided. These stases--or stopping-points--constitute the basic framework upon which the ultimate decision will be made.

Contemporary scholarship in rhetorical theory (Prelli; Fahnestock and Secor) has updated points of stasis to account for the nature of debate in healthcare and health policy. Recent scholarship in rhetorical studies has focused on taxonomizing the argumentative styles and procedures used in healthcare and health policy (Graham and Herndl). Generally speaking, contemporary medical stasis points evaluate questions at the core of evidence-based medicine, e.g., 1) what is the appropriate form of evidence in determining which drugs are safe? 2) what are the appropriate forms of evidence for determining which drugs are effective, etc. In the case of the Avastin hearing, the lack of common definitions for the terms of the debate may be responsible for the deliberative stalemate.

**Stasis in Action: The Avastin Hearings**

We invoke contemporary stasis theory as a way to better understand the degree to which breast cancer patients’ and non-researching clinicians’ testimonies were effectively and meaningfully incorporated into the FDA’s deliberations. Transcripts from the two-day Avastin hearing were coded for the kinds of grounds upon which witnesses made their claims for or against Avastin. These codes were then analyzed alongside both the explicitly-stated key issues articulated by the Presiding Officer in the Opening Statement and the final voting justification statements made by members of the advisory board.
Thirty-five, three-minute public presentations were made by so-called “non-parties;” among them were practicing clinicians who had prescribed Avastin, breast cancer survivors and their family who had been or were currently being treated with Avastin, and representatives from relevant breast cancer survivor and support organizations. Other key stakeholders also engaged in deliberations. Among them were industry representatives on behalf of Genentech, the Center for Drug Evaluation and Research (CDER), and the FDA Advisory Committee.

Rhetorical analysis of the transcripts from the two-day FDA trial suggests that the testimony of some stakeholders (in particular, those who are not researchers) was, albeit unintentionally, discounted due to the disciplinary and definitional scope of the four decision-making aims outlined at the outset of the trial (listed below, emphasis ours).

1. Do the AVADO and RIBBON 1 trials fail to verify the **clinical benefit** of Avastin for the breast cancer indication for which it was approved?

2. Does the **available evidence** on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

3. Does the **available evidence** on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved and that Avastin has not been shown to present a **clinical benefit** that justifies the risks associated with use of the product for this indication?
4. If the Commissioner agrees with the grounds for withdrawal set out in Issue 1, Issue 2(a) or Issue 2(b), should the FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug’s clinical benefit?

Each of the above four decision-making aims cites “clinical benefit” and/or “available evidence” as key terms in the debate. When attending to questions that concern “clinical benefit” and “available evidence,” credentialed researchers and members of the FDA advisory board deliberated almost entirely about what constituted a proper clinical endpoint in the Avastin trials. That is [insert sidebar quotes 1-3 from Appendix here], they asked if progression free survival could be considered a viable alternative to overall survival. What counts as “available evidence” and “clinical benefit” for credentialed, researching stakeholders, therefore, was based only in scientific literature; alternate definitions of available evidence presented by non-researching stakeholders (clinical oncologists, breast cancer survivors, etc.) were implicitly excluded. Preoccupation with whether or not overall survival was a more meaningful measure of clinical benefit than progression-free survival actually served to if not discount, then distract from other kinds of evidence presented by non-researching clinicians, patients, and their families [insert sidebar quotes 4-6 from Appendix here].

The four decision-making aims outlined at the outset of the trial, therefore, invite and validate only certain kinds of testimony or debate—none of which include the testimony of non-researching experts fully versed in the scientific specifications of the disease. The FDA did not include as part of its deliberations an opportunity for all participants to agree upon (a) what
would count as a clinical benefit, and (b) what kinds of evidence would be deemed meaningful. How, then, might the FDA account for the expertise and experiences of all stakeholders—even those who may lack formally recognized credentials in medical and scientific disciplines?

**Concluding Thoughts**

Rhetorical analysis of the trial’s stases suggests that cross-stakeholder consensus about the definitions for “clinical benefit” and “evidence” was not achieved. Argumentative power lies on the side of those who are privileged with the authority to define the terms of the debate. A lack of consensus among both researching and non-researching stakeholders about key definitions—definitions upon which the terms of the debate hinge—leaves little room for meaningful public participation in policy-making. In future FDA deliberations, therefore, it may be of value to incorporate a kind of pre-trial hearing wherein the very terms upon which the deliberation hinges are negotiated and successfully defined.

The United States Supreme Court provides one model for achieving pre-trial agreement about definitions for key terms. For instance, in cases where a plaintiff alleges patent infringement, a pretrial hearing is held wherein a judge determines the definitions for relevant key words that will be invoked during the actual trial. This pre-trial event is often referred to as a “Markman Hearing,” or a “Claim Construction Hearing.” Judges in Markman Hearings yield to Federal Rules of Evidence in selecting experts to help construct claims and definitions. According to said Federal Rules of Evidence, expertise may come from “knowledge, skill, experience, training, or education” (Federal Rules of Evidence). A similar model with similar rules would be of great benefit to the FDA.
Stasis analysis of the transcripts from this two-day hearing suggests that once deliberations about pharmaceutical policy move into the public sphere, the decision-making mechanisms by which the FDA makes final recommendations must be revised. These revisions should account for the expertise and experiences of the patient and other non-researching, expert stakeholders. Such revisions, at least in the case of Avastin, must begin at the level of definition. Future public participation in pharmaceutical policy debates, therefore, may be improved were the FDA to include as part of its deliberative process an opportunity for stasis points to be negotiated and agreed upon in a pre-trial hearing.
Works Cited

FDA News Release. Available at:


Federal Rules of Evidence document:


Hamburg 2011. Available at:

Lewis, C. Advisory committees: FDA’s primary stakeholders have a say. FDA.gov Web site. 
http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/PatientInvolvement/ucm123870.htm

Appendix A. Sidebars

Note: The following sidebars have been included as an appendix for the purposes of the initial submission. If accepted for publication, we imagine these would be included as true sidebars once the document was converted to html.

Stasis Debate Quotes

1. One, progression-free survival is an endpoint that benefits women with metastatic breast cancer only if it predicts overall survival or demonstrates improved quality of life. Avastin has done neither. What use is there for a drug which, in this population, does not extend life and has more toxicities, some very serious, than the present standard of care? (I:81, Helen Schiff, Advocacy Organization Rep)

2. Unfortunately, the existing evidence from randomized controlled trials conducted by the drug’s manufacturer has demonstrated that Avastin has not lived up to the initial hype. Trials completed demonstrated some improvement in progression-free survival. We remain convinced that it is not enough to justify FDA approval for treating metastatic breast cancer. (I:97, Vernal Branch, Advocacy Org Rep)

3. I think all of us would agree that clinical trials are intended to be pure scientific experiments which must have valid endpoints. Progression-free survival or PFS is often the most objective and, hence, most valid endpoint in a clinical trial. (I:46, Robert Berger, Clinician)

Metastasis Quotes
4. I wish I could provide more than my individual case, as I know there are many variables. However, I hope the committee will consider individual experiences presented today as we represent the story behind the numbers. (I:30-31, Nancy Hauty, BC Survivor)

5. Avastin has been shown to be unsafe and ineffective for breast cancer patients. The FDA’s decision on Avastin must be based on scientific evidence from well-done trials and cannot be based on any one individual story, no matter how compelling. This decision cannot be driven by anecdotes. It must be driven by science. This decision must be made for the greater good and on a public health basis. (I:91, Christine Brunswick, Advocacy Rep, BC Survivor)

6. While we acknowledge the pain and suffering caused by cancer, our job in making decisions about drug approval is to focus on the available scientific evidence. Our regulatory decisions are based on data from adequate and well-controlled clinical trials. They are not based on consideration of the drug’s cost or decisions by third-party payers regarding reimbursement. (I:126-127, Richard Padzur, CDER)
Appendix B. External Links

Avastin (bevacizumab) description

http://en.wikipedia.org/wiki/Bevacizumab

Details about the FDA’s accelerated approval process

http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm

Details about the role of the FDA’s Office of the Commissioner

http://www.fda.gov/AboutFDA/CentersOffices/oc/default.htm

The FDA news release that describes Commissioner Hamburg’s decision to revoke Avastin for the treatment of metastatic breast cancer

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm

A PDF of Commissioner Hamburg’s written decision to revoke Avastin for the treatment of metastatic breast cancer


Transcripts from the two-day Avastin trial

http://www.fda.gov/newsevents/meetingsconferencesworkshops/ucm255874.htm
Additional information about Markman hearings

http://en.wikipedia.org/wiki/Markman_hearing

PDF that details the United States Federal Government’s “rules of evidence”