# FDA Initiative to Integrate Pre and Post-Market Review Lifecycle Approach to Drug Review

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# Recommendations at Issue:

3.4 Appoint OSE staff member to each NDA review team and assign joint authority to OND and OSE for post-approval regulatory actions.

4.4 Assure timely and valid evaluations (internally or by industry) of Risk Minimization Action Plans (RiskMAPs).

4.5 Develop systematic approach to R-B analysis for use both pre- and post-approval.

4.13 CDER analyze and make public all post-market study results as well as our assessment of them with respect to R and B.

5.4 Evaluate all NMEs within 5 years post-approval, based on sponsor submission of additional data, including peer-reviewed publications and status of distribution conditions.

# Plan

Dr. Unger and I will highlight specific aspects of FDA's extensive Response to the IOM Report, particularly where we have specific involvement or relevant experience.

# FDA Responses and Comments

3.4 OSE participation in NDA review team and joint authority for regulatory actions.

FDA's response to the Report emphasizes several pilot programs that Dr. Unger will describe, as well as 1) plans to clarify responsibility when post-marketing safety issues go to a specific Division's (they really all belong to the Commissioner) Advisory Committee, and 2) plans to assure a "strong voice" for OSE in pre- and post-marketing safety decision making.

I want to take note of a Process Improvement initiative to introduce a safety focus in the OND review divisions. Dr. Unger will describe the initiative further.

# 3.4 (Cont): Division Safety Focus

The proposal has created a safety focus in each review division, including at least the Deputy Director with project manager support, but with possible further staff. There has been a long-standing example of this in the Neuropharm (now Neuro and Psych) Division, with a "Safety Group" responsible for both pre- and post-marketing evaluation. The group has had about half a dozen clinical reviewers.

Rec 3.4 is in the "Culture" chapter of the report which, among other things, suggested a clash between the "controlled trial" oriented ODE reviewers and epidemiologically oriented safety reviewers.

While I don't believe this particular clash exists (beyond recognition of the limitations of each method), the Neuropharm experience is very encouraging, perhaps in unexpected ways.

# 3.4 (Cont) – Division Safety Focus

1. Focus on post-marketing safety

We have created an electronic system for post-marketing safety issues, a significant advance that will allow us to develop timelines and action plans similar to those we use to monitor and assure timeliness of application reviews.

Neuropharm has tracked its safety issues for years, has had written status lists, and has discussed them at monthly meetings with OSE.

By all (OND, OSE) accounts, the perceived larger culture clash (subject of chapter 3) did not exist there, perhaps because the Safety group was plainly focused on safety, had epidemiologic skills, and made use of epidemiologic approaches.

# 3.4 (Cont) – Division Safety Focus

2. Benefits in pre-marketing review.

Safety data from controlled trials is relatively straightforward, but much safety data in an application (most long-term data) is in open, often uncontrolled studies. The safety group has used epidemiologic approaches that gave pre-marketing review a new dimension, quite eye-opening to me, including

- Cross NDA comparison for a QT prolonging anti-psychotic
- Time-related assessments of melanoma rates for a Parkinson's Drug.

# 3.4 (Cont) Division Safety Focus

The safety group (now serving two divisions) model calls for a number of specifically dedicated physicians, generally with epidemiologic experience, who contribute to both pre- and post-marketing evaluation.

Their role both within the review Division and in interactions with OSE has been very fruitful.

# 4.4 RiskMAP Evaluation

Dr. Unger will address this

# 4.5 Systematic Approach to Risk-Benefit Analysis

FDA is response was a commitment to examine quantitative benefit-risk assessment and a description of several initiatives to deal with safety issues.

# 4.5 Systematic Approach to B/R

Whether quantitative R-B, i.e., somehow getting R and B onto the same scale, is going to work remains to be seen but my reading of the IOM report suggests that, although the Committee thought such analyses might have a role, they were far more focused on better quantitation/assessment of benefit and risk (and subset differences), and close and explicit attention to all of the factors that go into a benefit-risk assessment

- Severity of disease
- Alternatives available
- Better assessment of QOL impact

The report, in addition to urging rigorous assessment and study design, calls for wider availability of our analyses with explicit recognition of all of the factors going into decisions and our uncertainties.

# 4.5 Systematic Approach to B/R

FDA Review Template

The clinical review template, used by all reviewers, already has many elements clearly calling for explicit weighing of, and discussion of, benefit and risk.

1. The Executive Summary calls for evidence of effectiveness, safety for its intended use (noting that this is a risk-benefit comparison) and asks that. If not apparent, the risk/benefit analysis should be described briefly. The Summary also addresses adequacy of data, limitations of the data, areas of safety, uncertainty needing resolution by more pre-marketing data or post-marketing efforts, all, I think, what the Report seeks more of.

Details are in the body of the review.

While it remains to be seen whether quantitative B/R assessments will be useful, I have no doubt at all that we can improve our attention to the details of the specific benefits and risks, and limitations of data that go into our thinking.

# 4.13 Evaluate post-marketing studies and make results public

See FDA response. The desirability of this seems clear to me, but how to do this in the face of confidentiality and on-going discussions is not clear. We also do not necessarily get detailed reports of studies not intended to support labeling change, unless they have clear safety implications.

# 5.4 Evaluate NME post-marketing data no later than 5 years post-approval

I believe 5 years is far too late. An ODEI/OSE pilot will examine methods for doing collaborative systematic reviews at 1, 2, 3 years post-approval for 4 NME's. We will review all available data (AERs, further trials, literature reports, epi studies, sponsor periodic reports) and use tools such as data mining to generate signals.

I am very excited about this but we need to know about

- Personnel costs
- Advantage over less intense alternatives, e.g., data mining plus review of serious cases
- How to extract from AERs the critical cases for further discussion
- OND/OSE roles and interactions