Avoid Having to Turn Lemons into Lemonade:

The Review as a Continuation of the Development Process

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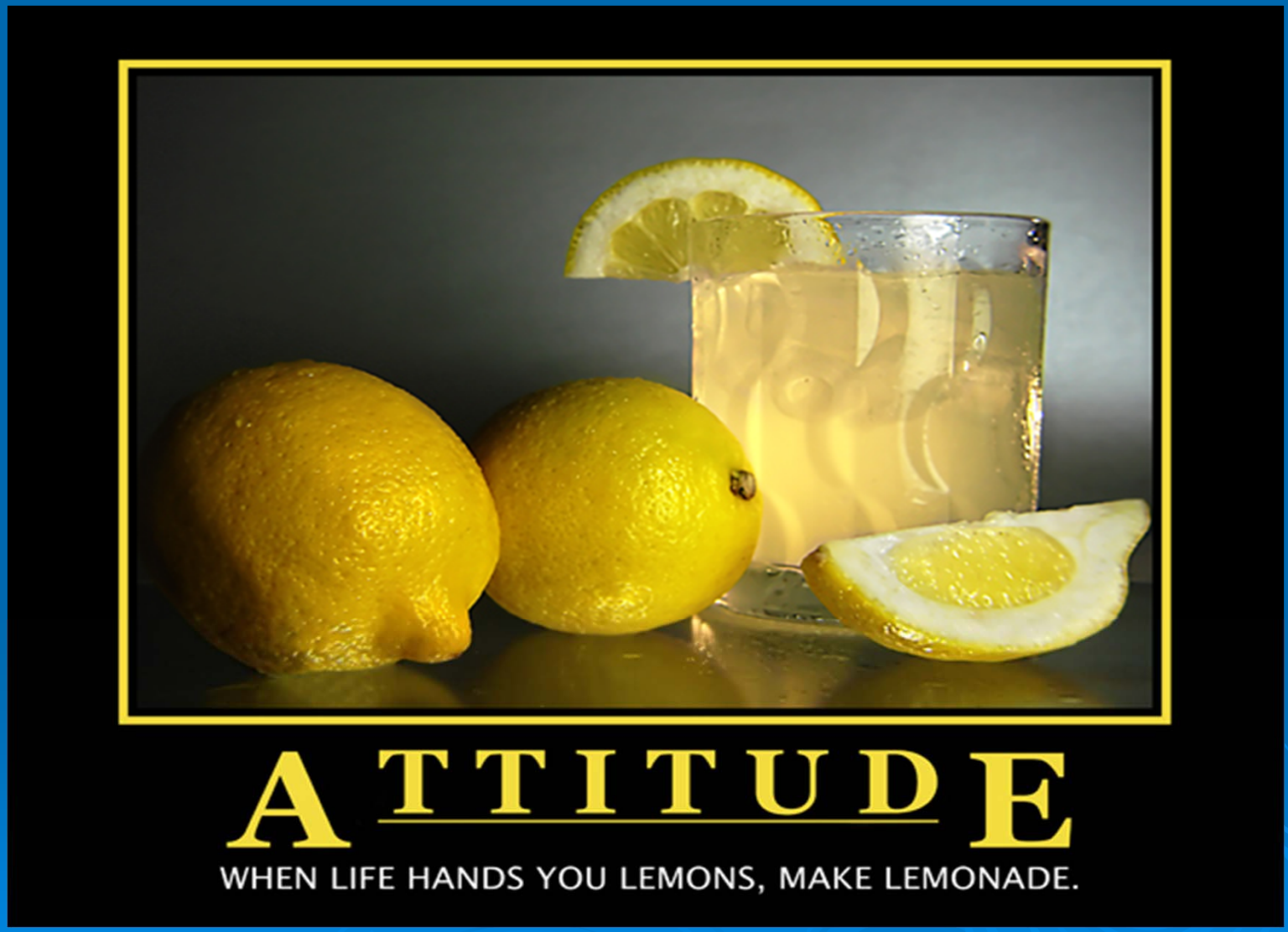
Disclaimer

- I am an employee of Abbott. My travel expenses travel are being paid by Abbott.
- I worked at the U.S. Food and Drug Administration (FDA) in various capacities in the past.
- I am a member of FDA Alumni Association (FDAAA). The following are my views and not necessarily the views of FDAAA or FDA.


ATTITUDE
WHEN LIFE HANDS YOU LEMONS, MAKE LEMONADE.

What are the Attributes of a Good Review?

- The review document demonstrates
  - Thoroughness
  - Clarity
  - Insight
- The review document provides clear conclusions and allow third parties to understand the basis for these conclusions
- The review process is efficient

Internal Processes to Support Good Reviews

- Review template
- Periodic meetings to allow different disciplines/reviewers to discuss issues
- Support and involvement of more senior management
- Agreed upon and adhered to timelines to allow adequate assessment by signatory authorities

What About the Material You are Reviewing?

- Can you have a good review if the data submitted is incomplete?
- Can you have a good review if dose-finding is inadequate?
- Can you have a good review if the study is not designed to answer the relevant questions?
- Can you have a good review if the analysis plan is lacking?
- You might have a complete review even with the above but would it/could it be a good review?

You Can’t Make a Silk Purse out of a Sow’s Ear

How Can You Avoid the Preceding Situation?

- Good internal processes will identify the preceding problems, but if this occurs when the dossier is submitted for review it is unlikely that these problems can be fixed in that review cycle
- What steps can avert this situation?

The Review as a Continuation of the Development Process

- The time to fix problems in dose, design and analysis is during development
- Conducting clinical studies with a product of uncertain quality leaves those studies as having potentially limited or no value
- A stepwise approach to safety assessment provides the best opportunity to collect the most relevant data in Phase III studies

When are Interactions between Sponsor and Agency of Greatest Value?

- For certain innovative products before the IND/CTA is submitted
- At the time of the submission of the IND/CTA
- At the time the plan for the principal studies to support marketing is being developed
- At the time the marketing application is being compiled

Pre-IND Meetings

- Novel products/indications
  - Toxicologic Studies
  - Proof of concept studies (POC) in pre-clinical setting
  - Initial dose finding in humans and perhaps early POC in humans

Submission of IND/CTA Interaction

- Review of pre-clinical package
- Initial review of quality attributes
- Range of doses in initial human study
- Safety monitoring

Before Principal Studies Initiated (FDA EOP-II)

- Agreement on study design, endpoints and analysis plan
- Final alignment of clinical program with desired labeling
- Opportunity to pilot certain risk mitigation plans

Before Submitting Marketing Application (FDA pre-NDA/BLA)

- Top-line review of data to be included in marketing application
- Opportunity to address issues that are identified during data assessment while compiling application
- Discussion of format of the application

EMA Scientific Advice

- Available during much of the development cycle (except just before submission)
- Covers quality, pre-clinical and clinical issues
- Special provisions for orphan medical products
- Clear timelines for Agency and sponsor

Interactions with Sponsors Should be a Two-Way Process

- It is important to provide clear actionable answers to the sponsor questions
- It is also highly desirable to address important issues identified by the agency that the sponsor should have brought forward but didn’t
- The goal is to avoid playing a game of “gotcha” at the time the marketing application is submitted

Minimize Surprises to the Sponsor

- Provide a heads up particularly for unfavorable news
- Although it is often thought that government agencies represent the height of bureaucracy, this is not necessarily the case
- Pharmaceutical companies, particularly the larger ones, have complex reporting structures and need time to share news, especially if it is unexpected and/or unfavorable

Why Isn't Advice Clear?

- There was no meeting held
  - Sponsor and agency perspective
- The appropriate questions were not asked
  - Sponsor and agency perspective
- What was said and what was heard were not identical
  - Sponsor and agency perspective
- The questions and/or answers were not clear
  - Sponsor and agency perspective

Are there Frameworks that Can Help the Dialogue?

- Questions and answers supplied ahead of time
- Use the proposed labeling to assess the adequacy of the proposed studies
- Use benefit-risk tools or paradigms to help make assumptions explicit

Does the Desired Labeling Align with the Proposed Studies?

- Sponsors generally know fairly early in development what they would like to say about their product
- Reviewing this in the context of their development program when the principal studies are being discussed helps ensure alignment. This in turn can facilitate a successful review

Can Some of the Newer B-R Paradigms Facilitate the Review Process?

- Both qualitative and quantitative approaches to demonstrating B-R are being developed
- They share the critical attribute of requiring that the assumptions for benefit and risk be spelled out
- This approach allows a comparison of the assumptions from the sponsor and agency and helps focus the review

FDA B-R Framework

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		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