Calculating Benefit/Risk Assessment for New Drugs

Introduction to Drug and Device Law and Regulation for Patient Organizations

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Benefit-Risk Analysis

To approve a drug, FDA considers “whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.” (21 CFR § 314.84(a))

Benefit-Risk Analysis

Three key concepts:

1. Benefits
2. Risks
3. Risk Mitigation

These are evaluated stepwise

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BENEFITS

Demonstrating Clinical Effectiveness

Clinical Effectiveness (FD&C Act § 505(d))

"Substantial evidence…consisting of **adequate and well-controlled investigations**, including clinical investigations," such that "experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved" could "fairly and responsibly" conclude that "the drug will have the effect it purports or is represented to have **under the conditions of use...in the labeling** or proposed labeling…"

Clinical Effectiveness (cont.)

- FDA has interpreted this standard to mean, generally, a minimum of 2 such adequate and well-controlled clinical studies
- FDA has promulgated regulations defining the types of trial designs that are ‘‘adequate and well-controlled studies” (21 CFR § 314.126)
- Traditionally, FDA has accepted 2 adequate and well-controlled trials when each meets its primary endpoint by its prespecified primary analysis and is statistically significant (a P-value of ≤ 0.05)

Single Study Approval Authorities

Two formal single-study approval authorities:

- “Data from one adequate and well-controlled clinical investigation **and confirmatory evidence**” (FDAMA 115)
- When there exists a “statistically very persuasive finding [that is]…a very low p-value” on the primary endpoint and this is applicable almost always only where to conduct a “second trial would be practically or ethically impossible” (May 1998 Evidence of Effectiveness Guidance)

Historical orphan drug flexibility

- Challenges for rare disease drug development:
  - Natural history is often poorly understood/characterized
  - Diseases tend to b progressive, serious, life-limiting and life-threatening and lack of approved therapy
  - Small populations often restrict study design and replication
  - Phenotypic (disease presentation) diversity within a disorder adds to complexity, as do genetic subsets
  - Well-defined and validated endpoints, outcome measures/tools and biomarkers are often lacking
  - Lack of precedent for drug development
  - Ethical considerations for children in clinical trials

Historical orphan drug flexibility (cont.)

- Quantum of effectiveness evidence would not either:
  - Satisfy the usual and traditional showing of effectiveness
  - Be considered either a single-study approval or an accelerated approval

Historical orphan drug flexibility (cont.)

Table 6. Analysis of Orphan Drug Efficacy Evidence by Decade.

Orphan Drug Efficacy Evidence Time Period	Conventional, n (%)	Total Flexibility, n (%)	Administrative, n	Case-by-Case Flexibility, n
1983[a] to 1989	7 (33.3)	14 (66.7)	5	9
1990 to 1999	21 (35.6)	38 (64.4)	13	25
2000 to 2009	13 (26.5)	36 (73.5)	13	23
2010 to 2014[b]	12 (36.4)	21 (63.6)	15	6
Total	53 (32.7)	109 (67.3)	46	63

[a]Beginning in January 1983, the date of enactment of the Orphan Drug Act.
[b]Through June 30, 2014.

Sasinowski, Panico, & Valentine, 2015 (http://www.hpm.com/devitem.cfm?RID=1908)

Quantum of Effectiveness Evidence in Summary

Substantial Evidence of Effectiveness		
	Quantum of Effectiveness Evidence Needed	**Source of Authority**
1	Two Adequate and Well-Controlled Studies	21 U.S.C. § 355(d) [1]
2	One Adequate and Well-Controlled Study with "Confirmatory Evidence"	21 U.S.C. § 355(d) as amended by FDAMA 115 [2]
3	One Study Providing Statistically Very Persuasive Evidence and Where a Second Study Would be Difficult to Conduct on Practical or Ethical Grounds	May 1998 Guidance [3]
	Types of Therapies in which FDA Has Exercised Flexibility	
A	Accelerated Approval/Subpart H/Fast Track Therapies	Historical FDA Precedents [4]
B	Orphan Drug Therapies	Historical FDA Precedents [5]

1. Federal Food, Drug, and Cosmetic (FDC) Act § 505(d)
2. FDA Modernization Act § 115
3. FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)
4. FDC Act § 506
5. FDC Act § 526

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RISKS

The Safety Database

Safety Requirement for Approval (FDCA § 505)

- “include all tests reasonably applicable to show…drug is safe…under…proposed labeling”
- “results of such tests show…drug is safe under such conditions”

Safety Assessment During Drug Development

- Safety data is continuously evaluated at all stages of drug development
- Non-clinical identify target organs of toxicity/determine safety margins for clinical trials
- Before progressing to phase 3 trials, non-clinical data and Phase 1-2 safety data are reviewed
- Predict possible AE in phase 3 trials
- Allow design safety assessment for phase 3 trials
- Rarely identify serious AEs due to limited exposure (a few hundred patients)

Goals of NDA Safety Review

- To assess the adequacy of the testing for safety
- To determine the significance of the adverse events and their impact on the approvability of the drug (risk/benefit analysis)
- To describe the safety issues that should be included in product labeling should the drug be approved
- To decide whether additional safety studies and /or risk-management plan is needed

What are the data sources?

- Randomized controlled trials
- Open label trials
- Postmarketing experience
- Medical literature
- Safety profile of other drugs in the
- class (inclusive of other indications)

What events are most concerning?

- Deaths
- Serious adverse events
- Discontinuations due to adverse events

3

Risk Mitigation

Tipping the scales

When a drug's risks may outweigh the benefits

- Risk management/mitigation may help tip the balance so that risks are minimized to allow approval
- FDA has tools to minimize risks while preserving benefits
- Primary tool: communicating through FDA-approved product labeling, which includes summary of essential information needed for safe and effective use
- Labeling alone is sufficient for most drugs to ensure benefits outweigh risks

Safety Labeling

- Boxed Warning (so called “Black Box”)
- Limitations of Use
- Dosing and Administration
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drugs Interactions
- Use in Specific Populations

When Labeling Isn’t Enough: Risk Evaluation and Mitigation Strategies

- While all drugs have labeling to inform stakeholders about risks, only a few require a REMS
- REMS are designed to help reduce the occurrence and/or severity of certain serious risks, by informing and/or supporting the execution of the safe use conditions
- REMS are not designed to mitigate all the adverse events of a medication
- Rather, REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event

Components of a REMS

- Most REMS include a communication component (e.g., Medication Guide)
- Some REMS also include “elements to assure safe use” (ETASU), which require activities to be undertaken before the medication can be prescribed, dispensed, or received
  - Require prescribers/dispensers become certified and agree to carry out set of activities designed to mitigate risk (e.g., only dispense at hospital, monitoring, register patients)
  - Require prescribers/dispensers/patients to document a “safe use condition” (e.g., monthly lab test)

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Role of Patient Input

Calibrating FDA’s scale

Benefit-Risk Analysis

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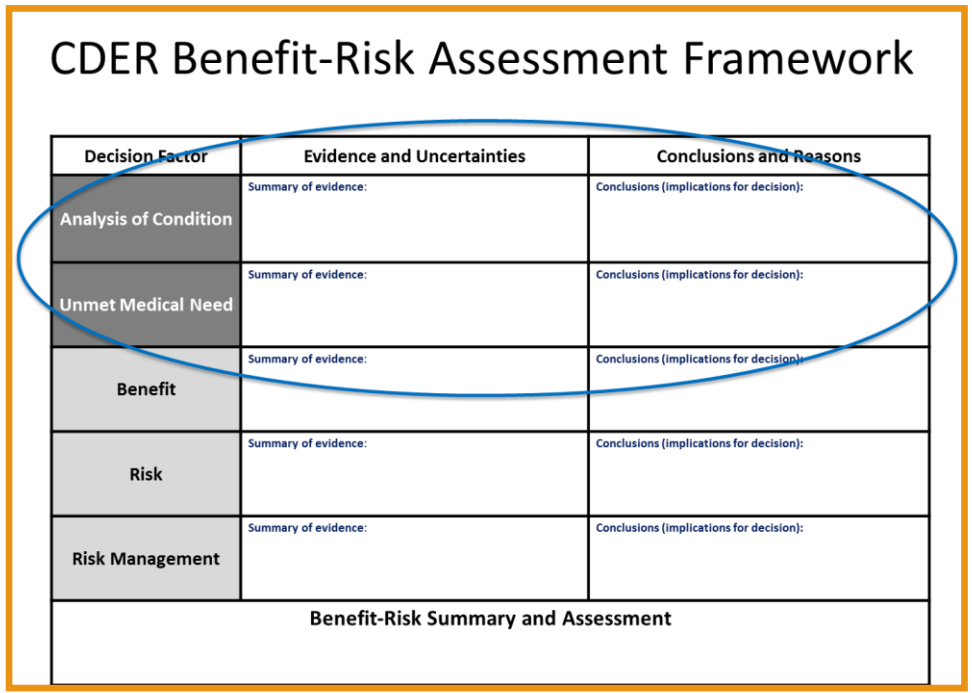
Benefit-Risk Assessment



CDER 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		

- Assessment of a drug's benefits and risks involves first analysis of severity of condition and current state of the treatment armamentarium to understand the context in which a potential therapy will be used (the "therapeutic, or clinical, context")

Patient-Focused Drug Development

- Under PDUFA V, FDA convened 24+ meetings over 5 years focused on specific disease areas
- Each meeting featured a different disease area, reviewing the armamentarium for that indication and identifying areas of unmet need (i.e., establishing the therapeutic context)
- Participants included FDA review staff, the relevant patient advocacy community, and other interested parties
- In December 2015, FDA established the “externally-led” PFDD program to patient organizations to host meetings by submitting a letter of intent

Analysis of Condition: Disease symptoms and daily impacts that matter most to patients

- Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?
  - How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
- How has your condition and its symptoms changed over time?
  - Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
- What worries you most about your condition?

Unmet Medical Need: Patients' perspectives on current approaches to treatment

- What are you currently doing to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, and other therapies including non-drug therapies or lifestyle modifications)
- How well does your current treatment regimen treat the most significant symptoms of your disease?
- What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, need for multiple medications, etc.)
- Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?

Sample Benefit-Risk Framework for Lung Cancer: Analysis of Condition and Current Treatment Options

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	– There are more than 200,000 new cases and ~160,000 deaths from lung cancer every year. – Prognosis depends on the type and stage of lung cancer. The average 5-year survival rate for NSCLC is ~15%. Over 50% of patients are diagnosed at an advanced stage, once the cancer has spread (metastasized) to the brain, bones, and other areas. – Patients in early stages of lung cancer may not experience any symptoms. When symptoms do appear, they can include shortness of breath or difficulty breathing, coughing, coughing up blood, pain, weight loss, and fatigue. – Lung cancer and its treatment can have a significant impact on patients' ability to manage work and family life and their overall quality of life. Many patients live with uncertainty, fear, anxiety, and depression. – *See the Voice of the Patient report for a more detailed description of patients' perspectives on lung cancer symptoms and impacts.*	Lung cancer is a serious and life-threatening disease. It remains the leading cause of cancer deaths in the United States. It is a rapidly fatal disease, and prognosis is dismal. While symptoms vary depending of the type and stage of lung cancer, the disease and its treatment can have a debilitating effect on patients' lives.
Current Treatment Options	– The standard of care depends on the type and stage of the cancer. In early stages, surgery in combination with radiation therapy and/or chemotherapy can potentially be curative. In later stages, these treatments may be used to shrink or slow tumor progression or prolong life. – FDA-approved chemotherapy treatments include cisplatin, paclitaxel, gemcitabine, docetaxel, pemetrexed, and others. – Molecularly-targeted therapies are aimed at treating patients with specific genetic changes. FDA-approved targeted therapies include crizotinib, erlotinib, and afatinib. – Patients can develop resistance to chemotherapy and targeted therapies drugs after extended use, making some treatments less effective over time. – Side effects and risks vary depending on the type of treatment and can have a significant impact on patients' quality of life. Side effects of chemotherapy may include fatigue, nausea, nerve damage, cognitive impairment, hair loss, and increased risk of infection or bleeding. Side effects of targeted therapies may include rash, diarrhea, fatigue, high blood pressure, increased risk of bleeding, visual changes, lung injury, and liver injury. – Palliative or supportive care therapies include supplemental oxygen, pain medications, steroids, and non drug therapies such as breathing exercises and relaxation techniques. – *See the Voice of the Patient report for a more detailed description of patients' perspectives on lung cancer treatments and treatment decision making.*	There is a continuing need for additional treatment options for lung cancer patients. While some effective treatments exist, they can only be potentially curative if the disease is diagnosed in early stages. Most treatments are toxic and their side effects can have a significant impact on patients' daily lives. Emerging targeted therapies are promising for subsets of lung cancer patients. The potential development of resistance to chemotherapy or targeted therapies further supports the need for an expanded treatment armamentarium. Patients' treatment decisions often require making difficult tradeoffs between increasing the chance to prolong life and preserving quality of life.

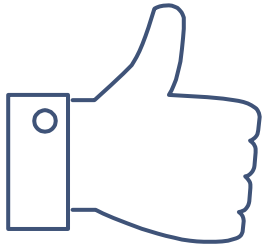
Patient Tolerance for Risk

- Two Types:

1. Risk tolerance (e.g., chemotherapy toxicities)
2. In certain settings, “a somewhat greater risk…of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced agains the risk of rejecting or delaying the marketing of an effective therapy…for an unmet medical need.” (FDA, Draft Guidance: Demonstrating Substantial Evidence of Effectiveness (Dec. 2019))

Patient Experience Data (FD&C Act § 505(y))

- Requires FDA to make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of an approved NDA or BLA
- This includes the following information:
  - Data that are collected to provide information about the patients' experiences with a disease or condition, including related to the impact of the disease on patients' lives and patient preferences with respect to treatment;
  - Information on patient-focused drug development tools (e.g., Patient-Reported Outcome measures); and
  - Other information FDA determines to be relevant
- This will apply to NDAs/BLAs submitted after June 12, 2017



THANKS!

Any questions?

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Hyman, Phelps & McNamara PC

Food and Drug Law Institute

Risk Mitigation

Wednesday, December 2, 2020

The FCS FOUNDATION

Who is the FCS Foundation and How Did We Start

- Who we are? What is FCS?
  - Co President/Co Founder, FCS Foundation in 2016
- We began our journey in the regulatory process in 2017 with a drug already in clinical trials. The Foundation is committed to sharing the story of Familial Chylomicronemia Syndrome and its impact on patients.
- Prepared a Voice of the Patient report, which we shared with FDA and can be found on their website.
- We've had one patient led meeting, we participated in the Advisory Board hearing regarding drug approval, one additional in person post CRL, one teleconference.
-

Volanasorsen/Waylivra
Pre-Advisory Meeting 2017-2018

- Through 2016-2017 patients enrolled in a clinical trial for Volanasorsen/Waylivra shared their story about:
  - Living with Pancreatitis
  - the burden of FCS on day to day quality of life.
- Volanasorsen/Waylivra is an injectable drug (biologic) that helps reduce the level of triglycerides in patients.
- This reduction in triglycerides lowers risk of pancreatitis, overall day to day chronic pain and discomfort.
- No other drug currently exists to treat FCS beyond a low fat (<15-20g of fat per day) diet.
- Patients testified to the benefit this drug had on their life, allowing them to stay out of the hospital, go back to work, finish school, attend birthday parties and graduations.
- While risks/side effects were identified by patients, patients also spoke to the benefit and positive impact on their lives.
- Patients want options

Advisory Hearing, May 2018

FDA Perspective

- Replacing one issue (Pancreatitis) with the risk of another (Thrombocytopenia)
- Concerns over drop out rate
- REMS (Risk Evaluation Mititgation Strategies) was too burdensome
- Injection site reactions

Patient Perspective:

- Many approved drugs have REMS
- Many approved drugs have a risk of thrombocytopenia

The Advisory Committee voted in favor of approving Waylivra/Volanasorsen, which was a huge win for our patient community.

Post CRL, August 2018
What We Learned

- Following the positive advisory committee hearing vote CRL (Complete Response Letter) was issued.
- In the end, the FDA felt the risks outweigh the benefits. However, the patient experience told a different story.
- As patients we wish we could have addressed concerns which include:
    1. what patients considered a burden in terms of monitoring and risk mitigation
    2. how serious and debilitating pancreatitis.
    3. why patient drop out rates were so high (in terms of sample size percentage)
- What felt like a very open two way dialogue early on was no longer accessible and as a patient group we had the best answers to these concerns and questions.
- No survey or data collection can preemptively answer every potential question that comes up in a clinical trial-especially in rare disease.

The Heart Act

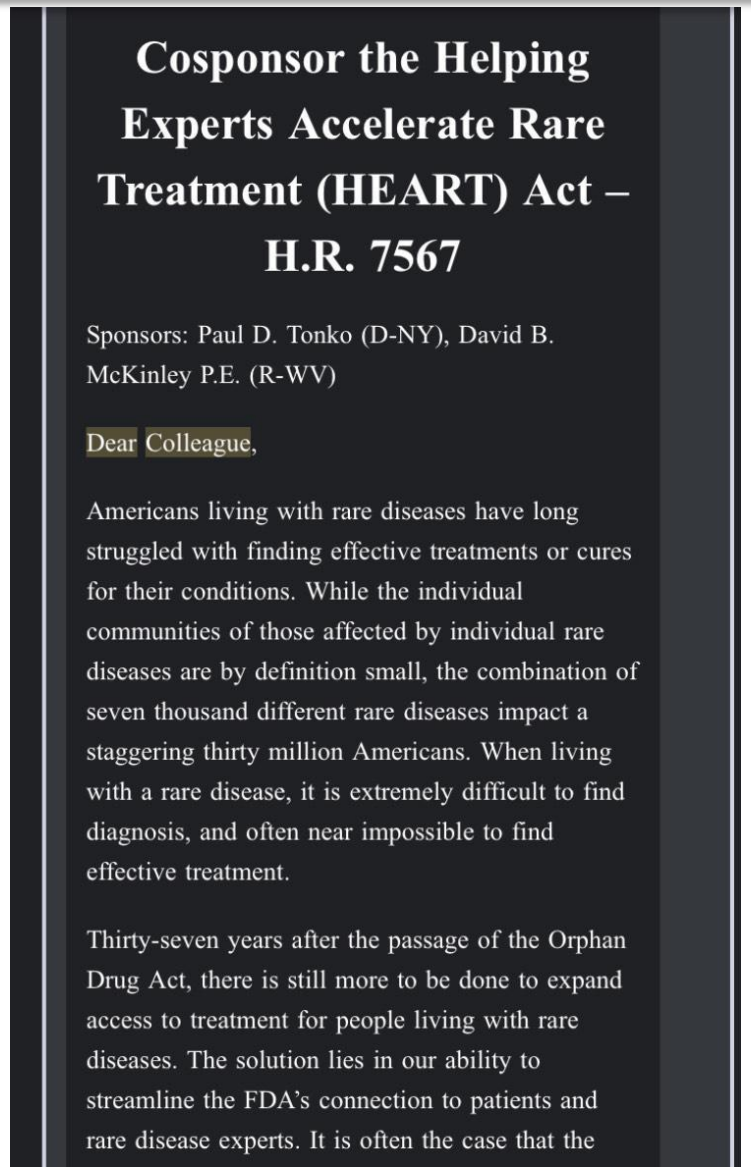
- The Foundation was devastated when the CRL was issued. We had to do something.
- When speaking with Hill offices they said we weren't the first group to share this concerns.They invited us to create this bill to support all rare disease drug approval process.
- Speaking with other rare disease groups about our experience and our ideas of how to move forward there was a lot of agreement and shared experiences.
- The HEART Act was introduced to Congress in July 2020 to help all rare disease groups find their voice in the regulatory process.

The Heart Act

While we are grateful for the work the FDA does and look forward to working with them in the future we do think:

- Advisory committee hearings should include rare disease experts and small sample experts to review data in a relevant way.
- Include patient input when assessing Risk Evaluation and Mitigation Strategies (REMS)
- Include patient input throughout the entire process of drug evaluation.
- Be accountable to congress by providing a report on how many rare disease drug applications they see per year
- Require a GAO study (Government Accountability Office) looking at procedures done in the European Union and how that data can assist the drug approval process in the US.

Support The Heart Act



Cosponsor the Helping Experts Accelerate Rare Treatment (HEART) Act – H.R. 7567

Sponsors: Paul D. Tonko (D-NY), David B. McKinley P.E. (R-WV)

Dear Colleague,

Americans living with rare diseases have long struggled with finding effective treatments or cures for their conditions. While the individual communities of those affected by individual rare diseases are by definition small, the combination of seven thousand different rare diseases impact a staggering thirty million Americans. When living with a rare disease, it is extremely difficult to find diagnosis, and often near impossible to find effective treatment.

Thirty-seven years after the passage of the Orphan Drug Act, there is still more to be done to expand access to treatment for people living with rare diseases. The solution lies in our ability to streamline the FDA's connection to patients and rare disease experts. It is often the case that the

Visit www.livingwithfcs.org/the-heart-act for more information

To send support for The Heart Act to your congressperson

https://haystackproject.org/act-now

or https://rareadvocates.org/take-action