Processa Pharmaceuticals

Benefit-Risk Analysis for FDA Approval Requires More Than a Pivotal Trial

20th ORPHAN DRUGS & RARE DISEASES 2023 AMERICAS
November 16, 2023

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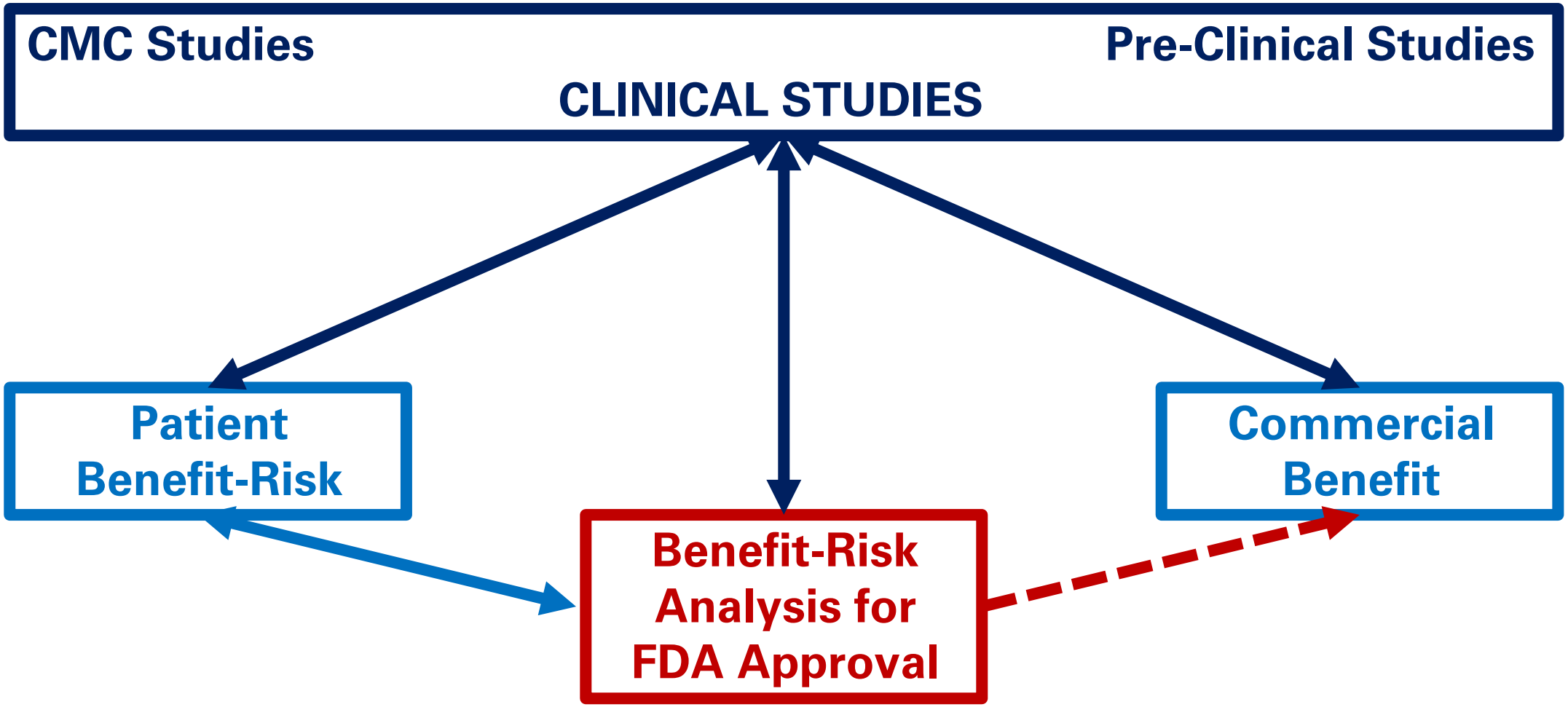
How Do You Approach Drug Development?



Benefit-Risk Assessment: Foundation for FDA's Regulatory Review/Approval

FDA States

"For a drug to be approved for marketing, **FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This assessment is informed by an extensive body of evidence about the drug's safety and efficacy submitted by an applicant**."

Benefit-Risk Analysis

The **benefit-risk analysis is more than the efficacy-safety evaluation** in a pivotal trial for orphan and non-orphan designated drugs:

- **Risk assessment includes more than drug safety in Orphan Diseases**
- **Benefit assessment includes more than the magnitude of efficacy**
- **FDA must consider the existing standard of care if it exists**
- Other considerations

Benefit-Risk Integrated Assessment

Added Importance for Orphan Disease

Dimension	Disease and Drug
Analysis of Condition	• Identify patients and the seriousness of their condition while recognizing and measuring what matters most to patients
Current Treatment Options	• Define standard of care and therapeutic treatment options • Benefit-risk of present options
Benefit of New Approved Treatment	• Identify and measure clinically meaningful endpoints for the patient and FDA • Benefit includes efficacy of the drug as well as having clinical trial-based evidence of efficacy rather than case study off-label evidence
Risk & Risk Management of New Approved Treatment	• Identify and measure the safety risk of new and existing treatments • Risk includes both safety & potential of not having approved treatment option

Examples from Processa Founders and Processa Pipeline

- **Evaluate and Minimize Risk**
  - Acthar FDA approval - Risk is more than the safety of a drug (Questcor sNDA approval in 2010)

- **Next Generation Cancer Drugs with Proven Cancer-Killing Mechanisms and Superior Benefit-Risk Profile**
  - Next Generation Chemotherapy – Capecitabine (NGC-Cap)
  - Next Generation Chemotherapy – Gemcitabine (NGC-Gem)
  - Next Generation Chemotherapy – Irinotecan (NGC-Iri)

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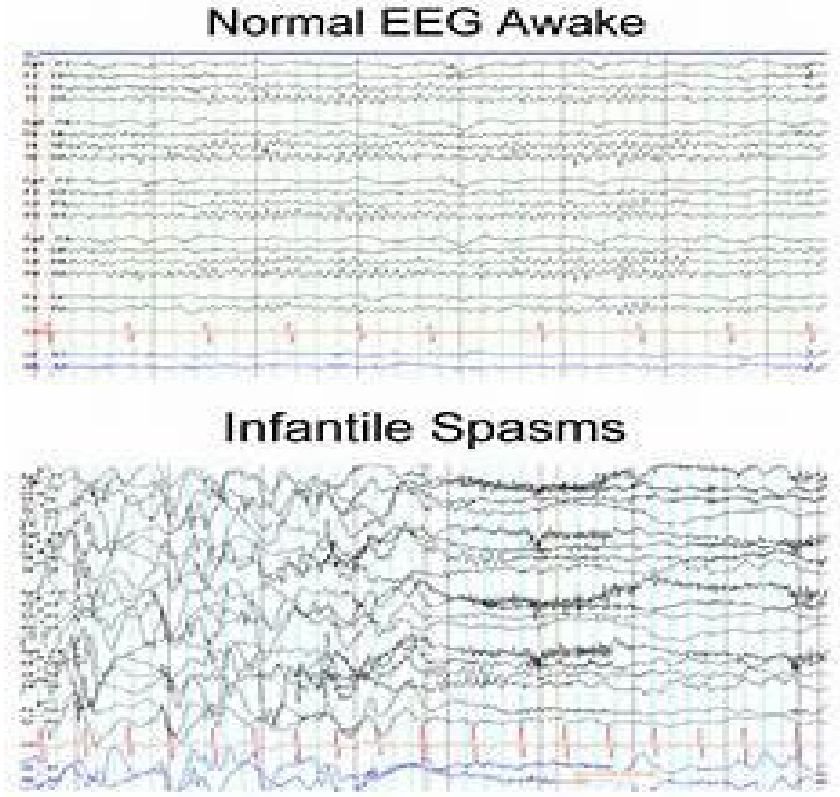
Example 1:

Acthar Approval for Infantile Spasms (Questcor sNDA approval in 2010)

Risk = More Than Drug Safety in a Clinical Trial

Example 1: Risk is More than Safety of Drug

- Typically occurs in children less than 2 years old; occurs in 2,000 – 2,500 children per year
- Premature death rate of 5-31% and > 60% of untreated/inadequately treated patients have serious mental/physical disabilities with other types of seizures developing over time
- Characterized by seizures (“spasms”) and abnormal EEG called hypsarrhythmia



- In order to improve cognitive development and mortality rate, therapeutic objective is to rapidly control seizures and normalize EEG.

Example 1: Acthar Gel Used Off-Label for IS

Acthar, a purified preparation of adrenocorticotropic hormone in a gel, was used off-label for treatment of IS for over 30 years with IS sales in 2006-2007 representing almost 100% of sales

Acthar was approved in 1952 and became a DESI (Drug Efficacy Study Implementation) drug in 1962. Prior to being acquired by Questcor Pharmaceuticals, the Acthar label included over 50 indications including 1978 approval for multiple sclerosis flares

In 2007 Questcor received an FDA Complete Response Letter for the IS sNDA

(Tried to Obtain Approval Based on Need without Efficacy-Safety Clinical Data)

In 2010 FDA approved Acthar for IS

(Approval Based on Benefit of Acthar Treatment Outweighing Acthar Safety Risks and Risks of Patients Having Off-Label Use or Not Treating Patients)

Benefit Outweighed Safety Risk & Risks Associated with Off-Label Use

- Negotiated with FDA what was to be included in the sNDA given conducting a trial when patients are treated off-label for IS was not ethical
- BENEFIT
  - Emphasized that approval would provide consistent guidance on Acthar IS treatment given the different regimens that were used off-label
  - Evaluated Acthar in a previous academic trial of 29 patients (Acthar vs prednisone), not powered to FDA standards; Combined endpoint of spasms and EEG improvement was statistically better in the Acthar treated group than prednisone group; other smaller studies supported the efficacy and regimen
- RISK
  - Safety supported through evaluation of 311 patients on Acthar (134 patients on proposed labelled regimen, 177 on different regimens than proposed)
  - Safety profile was acceptable to FDA, but a Risk Evaluation and Mitigation Strategy (REMS) drug safety program was required

Acthar FDA Approval

- Negotiated new, updated Acthar label with FDA
- Questcor desired to eliminate many of the over 50 indications and obtained a modernized label with 19 indications by providing the data supporting each of the 19 indications
- FDA appropriately evaluated more than the efficacy and safety data from a clinical trial, they evaluated all aspects of the drug, the orphan condition, seriousness of the IS, existing approved treatments, and the off-labelled use of Acthar

Example 1: Benefit-Risk Integrated Assessment of IS

Dimension	Disease and Drug
Analysis of Condition	• Identify patients and the seriousness of their condition while recognizing and measuring what matters most to patients **Very serious orphan condition resulting in death or severe mental disabilities**
Current Treatment Options	• Define standard of care and therapeutic treatment options • Benefit-risk of present options **No approved drug, Acthar used off-label with various regimens**
Benefit of New Approved Treatment	• Identify and measure clinically meaningful endpoints for the patient and FDA • Benefit includes efficacy of the drug as well as having clinical trial-based evidence of efficacy rather than case study off-label evidence **Conducting a new trial not possible, approving Acthar provided guidance,**
Risk & Risk Management of New Approved Treatment	• Identify and measure the safety risk of new and existing treatments • Risk includes both safety & potential of not having approved treatment option **Risks associated with both off-label use of drugs & not treating patients**

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Example 2:

Next Generation Cancer Drugs with Proven Cancer-Killing Mechanisms and Superior Benefit-Risk Profile

Benefit = More Than Demonstrating Efficacy, More Patients Treated

Next Generation Chemotherapy – Capecitabine (NGC-Cap)
Next Generation Chemotherapy – Gemcitabine (NGC-Gem)
Next Generation Chemotherapy – Irinotecan (NGC-Iri)

Example 2: NCE Next Generation Chemotherapy (Not New Formulations)

- NCE Next Generation Chemotherapies (NGCs) are designed to **improve the efficacy and safety profile for more cancer patients than their currently FDA-approved counterparts**

- The cancer-killing metabolites of the NGCs are either the exact same as their counterparts or analogs such that the **MOA of killing cancer cells is the same**

- The major difference is that the **metabolism and/or distribution of the NGCs are different resulting in an improved side effect profile and/or greater efficacy given more exposure to the cancer cells**

Example 2: Oncology Opportunity

- **The FDA-approved counterpart of each NGC is used to treat multiple types of cancers with more than 200,0000 new patients diagnosed in the US with these cancers**
  - Orphan-designated cancers presently treated (e.g., pancreatic, ovarian, gastric, biliary, small cell lung)
  - Other types of cancers (egg, colorectal, breast, bladder)
- **35%-85% of the patients receiving the existing FDA-approved counterparts:**
  - **Require a decrease in their dose or discontinuation of the drug because of side effects or**
  - **Are resistant or become resistant to their treatment**
- If NGCs **improve the efficacy-toxicity profile and allow more patients to receive treatment at an optimal dosage regimen**, the NGCs will be different from their existing counterparts
- Processa's **Regulatory Science Approach seeks to find the optimal dosage regimen (ODR)** based on the evaluation of the exposure-response relationship (FDA's Project Optimus Oncology Initiative and draft oncology guidance on finding the optimal dosage regimen)

Benefit-Risk Integrated Assessment

Dimension	Disease and Drug
Analysis of Condition	• Identify patients and the seriousness of their condition while recognizing and measuring what matters most to patients **Serious condition with 35%-85% of treated patients not receiving ODR, poor survival**
Current Treatment Options	• Define standard of care and therapeutic treatment options • Benefit-risk of present options **Approved drugs but poor survival, high % of patients receive sub-optimal dose, high % of non-responders**
Benefit of New Approved Treatment	• Identify and measure clinically meaningful endpoints for the patient and FDA • Benefit includes efficacy of the drug as well as having clinical trial-based evidence of efficacy rather than case study off-label evidence **Treat more patients with ODR, improve benefit-risk profile**
Risk & Risk Management of New Approved Treatment	• Identify and measure the safety risk of new and existing treatments • Risk includes both safety of new treatment but also safety of existing treatment **Side effect profile may change requiring further evaluation of the seriousness of side effects as well as the prevalence**

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