Processa Pharmaceuticals

Science

# Thinking Regulatory First: Considerations for the Effective Development of Rare Disease Therapies

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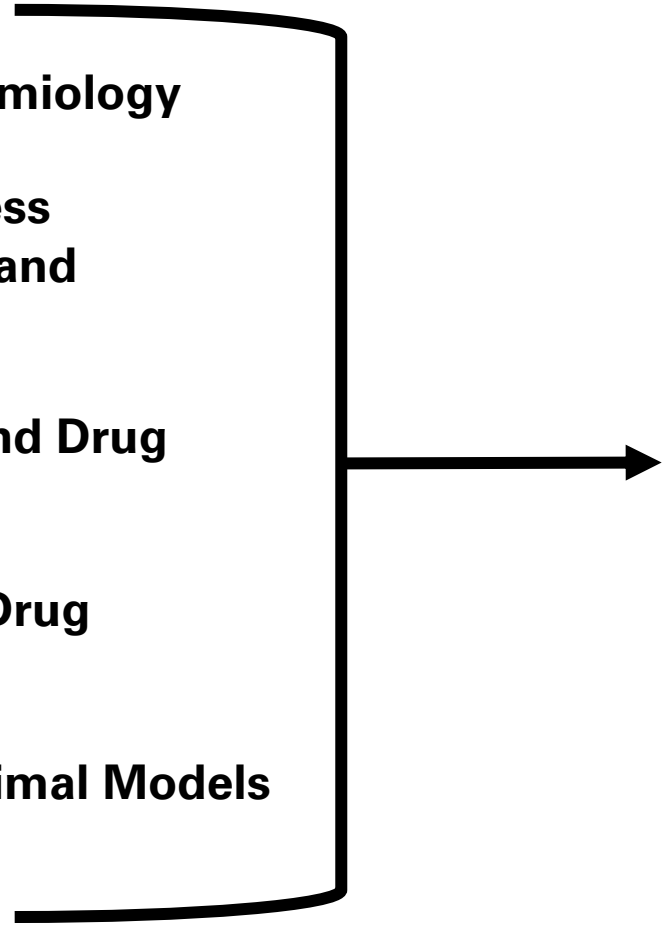
# In Drug Development – How do you Approach Development? Science vs Regulatory vs Regulatory Science

- **Understanding the Disease**
  - Natural History and Epidemiology
  - Pathophysiology, Clinical Manifestations, Seriousness
  - Present Standard of Care and Therapeutic Options
- **CMC of the Drug Substance and Drug Product**
- **Nonclinical Evaluation of the Drug**
  - MOA
  - ADME and PK
  - Efficacy in Appropriate Animal Models
  - Toxicology



- **Clinical Evaluation of the Drug**
  - Natural History and Standard of Care
  - Efficacy Endpoints
  - Evidence of Efficacy and Safety
  - Clinical Study Design
  - Study Conduct

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

## FDA States:

**"Simply put, 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. "**

## Think Regulatory 1st

**Although the benefit-risk analysis used by FDA for an Orphan Designated drug is the same as other drugs, "Think Regulatory 1st" considerations:**

- **Risk assessment includes more than drug safety in Orphan Diseases**
- **Approval is based on benefit-risk in a definable target population**
- **FDA must view the primary endpoint as clinically relevant**
- **Other considerations**



"Benefit-Risk Assessment in Drug Regulatory Decision-Making"
Draft March 30, 2018

# 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<br>• Benefit-risk of present options |
| Benefit of New Approved Treatment | • Identify and measure clinically meaningful endpoints for the patient and FDA<br>• 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<br>• Risk includes both safety & potential of not having approved treatment option |

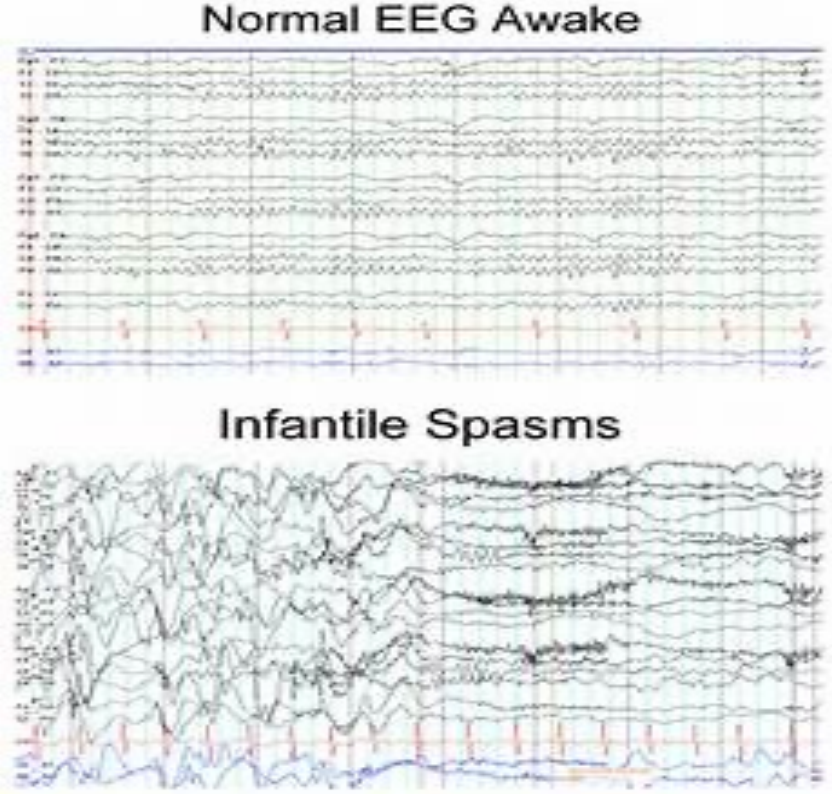
# Examples of Think Regulatory 1st - Critical to Development and Approval

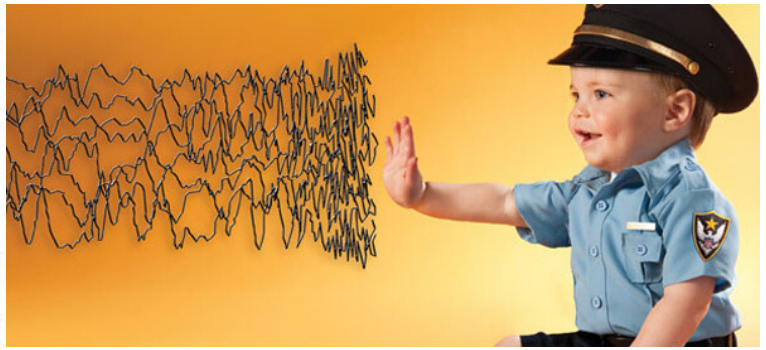
- **Evaluate and Minimize Risk**
  - Acthar FDA approval - Risk is more than the safety of a drug (Questcor sNDA approval in 2010)

- **Define Clinically Meaningful Endpoint in a Targeted Population**
  - PCS499 development in ulcerated Necrobiosis Lipoidica (uNL) vs all Necrobiosis Lipoidica (NL) patients (Processa presently running a Phase 2B trial)
  - PCS3117 development for the treatment of pancreatic cancer (Processa presently planning a Phase 2B trial)

# Case 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.

# Case 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

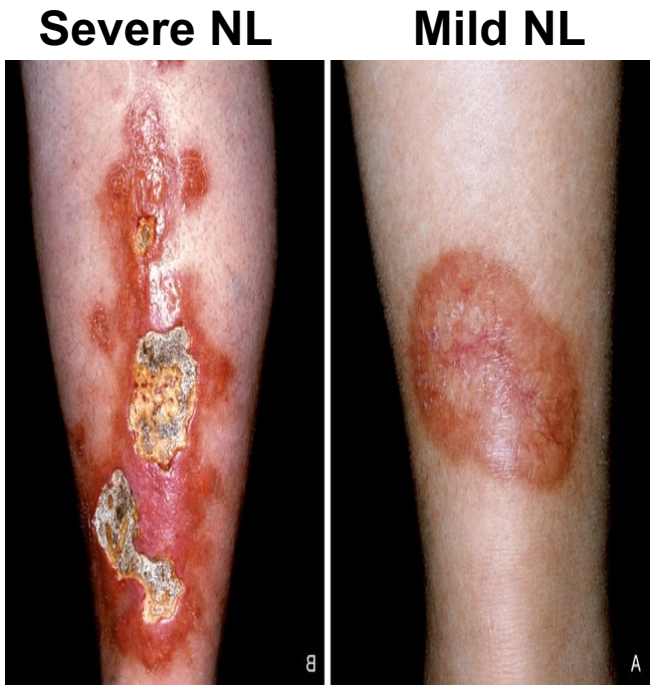
- Negotiated new, updated Acthar label with FDA
- Questcor desired to eliminate many of the over 50 indications and obtained a modernized label with 19 indications by providing the data supporting each of the 19 indications
- FDA appropriately evaluated more than the efficacy and safety data from a clinical 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

# Case 1: 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<br>**IS - Very Serious Orphan Condition** |
| Current Treatment Options | • Define standard of care and therapeutic treatment options<br>• Benefit-risk of present options<br>**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<br>• Benefit includes efficacy of the drug as well as having clinical trial-based evidence of efficacy rather than case study off-label evidence<br>**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<br>• Risk includes both safety & potential of not having approved treatment option<br>**Risks associated with both off-label use of Acthar & not treating patients** |

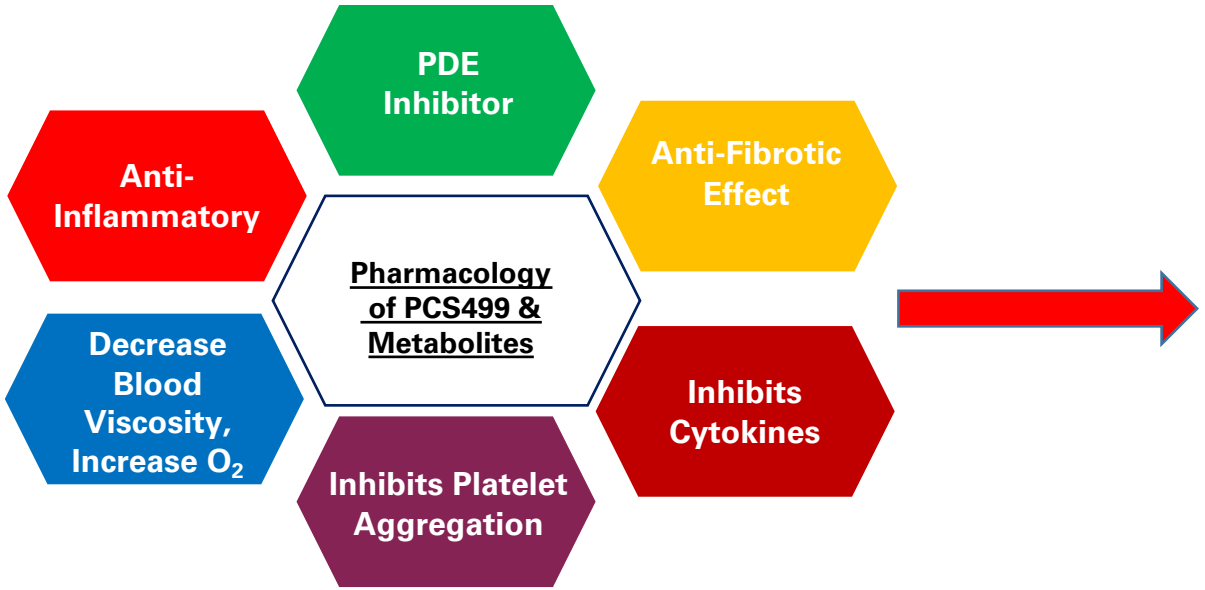
# Case 2: Select Clinically Meaningful $1^0$ Endpoint in Targeted Population

- **Skin and tissue below skin becomes necrotic**, can last from months to years with complications such as infections, amputation, and cancer
- 70% of the patients are women between 20 – 60 years old; 60% of NL patients are diabetic but NL is not dependent on glucose control and is **not the same histologically as diabetic ulcers**
- **Clinically beneficial endpoint has not been well defined for patients with mild NL**
- 30% of NL patients have painful ulcers occurring naturally or from contact trauma to the lesion; **the clinically beneficial endpoint of complete wound closure has been previously defined by FDA in the Ulcer and Wound Guidance**
- 75,000 – 185,000 NL & 22,000 – 55,000 uNL patients in the U.S.
- **Natural complete healing of moderate to severe ulcers** during the first 1-2 years after onset occurs **in less than 5% of these patients**



# Case 2: Why PCS499 for the Treatment of uNL?

- **Drugs used off-label with mixed success given their side effect profile and/or limited efficacy** (for example; pentoxifylline (PTX), immunomodulating agents)
- **PCS499 is the deuterated analog of a major metabolite of PTX**; has identical metabolites and pharmacological targets but **PK of 499 + metabolites is different than PK of PTX + metabolites resulting in a better 499 safety profile and allowing the administration of a higher dose of 499**

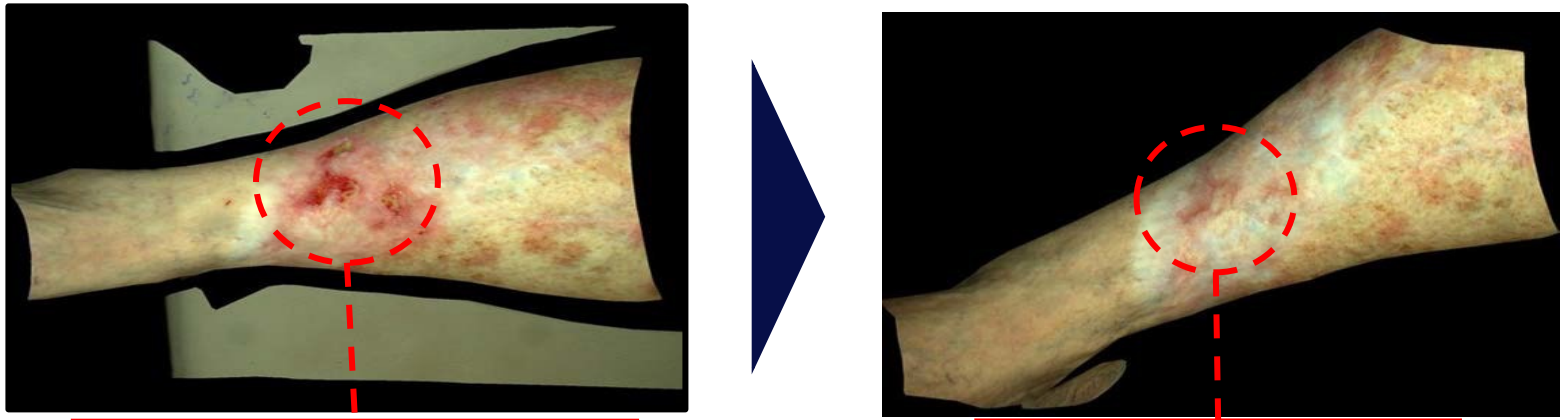



**Pathophysiological Changes in NL**

- **Decrease in blood flow & Oxygenation**
- **Decrease in platelet survival**
- **Increase inflammation**
- **Increase fibrosis**
- **Increase cytokines**
- **Degeneration collagen**
- Alters fat deposition

# Case 2: PCS499 Safe and Efficacious in NL and uNL Patients

- In open labelled trial of 10 NL and 2 uNL patients, **all ulcers closed** in the 2 uNL patients, **including new contact trauma ulcers &** non-ulcerated patients reported an improvement
- **1.8 gm/d of 499 was well tolerated in the 12 patients**



Open Ulcers at Baseline



Complete Closure

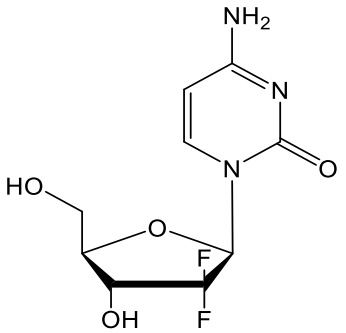
- Now conducting 20 patient Phase 2B ulcerative NL **randomized, double-blind, placebo-controlled trial, primary endpoint = proportion of patients with complete ulcer closure**
- **One adequately powered pivotal Phase 3 trial initiated in 2023-2024** with a supportive phase 2B may be sufficient to demonstrate the benefit-risk profile is approvable given the lack of treatment options and the seriousness of the condition

# Case 2: Benefit-Risk Integrated Assessment

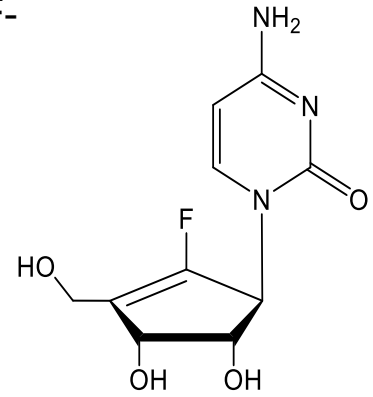
| Dimension | Disease and Drug |
|---|---|
| Analysis of Condition | • Identify patients and the seriousness of their condition while recognizing and measuring what matters most to patients<br>**Serious condition - affects QOL & may lead to other medical issues** |
| Current Treatment Options | • Define standard of care and therapeutic treatment options<br>• Benefit-risk of present options<br>**No approved drug, off-label drug efficacy & safety not adequate** |
| Benefit of New Approved Treatment | • Identify and measure clinically meaningful endpoints for the patient and FDA<br>• Benefit includes efficacy of the drug as well as having clinical trial-based evidence of efficacy rather than case study off-label evidence<br>**Clinical benefit and endpoint in uNL well defined, but not in non uNL** |
| Risk & Risk Management of New Approved Treatment | • Identify and measure the safety risk of new and existing treatments<br>• Risk includes both safety & potential of not having approved treatment option<br>**Risks associated with both off-label use of drugs & not treating patients** |

# Case 3: Select Clinically Meaningful $1^0$ Endpoint in Targeted Population

- Gemcitabine is a fluorinated deoxyribose analog of cytidine
- Gemcitabine is used as **first-line therapy in metastatic pancreatic**, advanced non-small cell lung, and metastatic breast cancer
- **55% - 85% of patients are inherently resistant to gemcitabine or acquire resistance – can be caused by one or more factors**
- PCS3117 is a ribose analog of gemcitabine but **inherent and acquired resistance to gemcitabine does not mean the cancer is resistant to PCS3117**
  - PCS3117 activated to the active nucleotide following a different pathway than gemcitabine
  - Mechanism of action in killing cancer cells for 3117 active nucleotide includes additional pathways beyond those for gemcitabine




Gemcitabine (dFdC)
IV Administration
(Cytosine + F,F-Deoxyribose)




RX-3117
Oral Administration
(Cytosine + F-Ribose Analog)

# Case 3: PCS3117 Evidence of Clinical Efficacy-Safety in Pancreatic Cancer

- In Phase 2A trial with gemcitabine naïve patients for **1st line therapy**, **response to PCS3117 was similar to gemcitabine**
- **As 3rd line therapy in patients with progressive metastatic pancreatic cancer** refractory to previous therapies of chemotherapy (including 93% **refractory to gemcitabine)**, PCS3117 response in a monotherapy Phase 2A trial was:
  - **31% (14 patients) had progression-free survival (PFS) for 2 months**
  - **12% (5 patients) had stable disease for more than 4 months**
  - **One patient had a tumor reduction of 40% after 28 days of treatment**

# Case 3: Clinically Meaningful $1^0$ Endpoint for Targeted Pancreatic Cancer Population

- Designing FDA approvable development programs by "Thinking like an FDA reviewer"
  - Are we selecting the correct endpoints? Overall Survival (OS), Disease Free Survival (DFS), Progression Free Survival (PFS), Objective Response Rate (ORR), Complete Response (CR)
  - Have we defined what would be a clinically meaningful result for the endpoints within the targeted population of patients for the label? May be different if the targeted population of patients on the label is $1^{st}$ line therapy vs $2^{nd}$ vs $3^{rd}$.

# Case 3: 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<br>**Serious condition with poor survival** |
| Current Treatment Options | • Define standard of care and therapeutic treatment options<br>• Benefit-risk of present options<br>**Approved drugs but survival still short and high % non-responders** |
| Benefit of New Approved Treatment | • Identify and measure clinically meaningful endpoints for the patient and FDA<br>• Benefit includes efficacy of the drug as well as having clinical trial-based evidence of efficacy rather than case study off-label evidence<br>**Endpoint and clinical benefit depends on targeted population** |
| Risk & Risk Management of New Approved Treatment | • Identify and measure the safety risk of new and existing treatments<br>• Risk includes both safety & potential of not having approved treatment option<br>**Risks associated with both off-label use of drugs & not treating patients** |

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