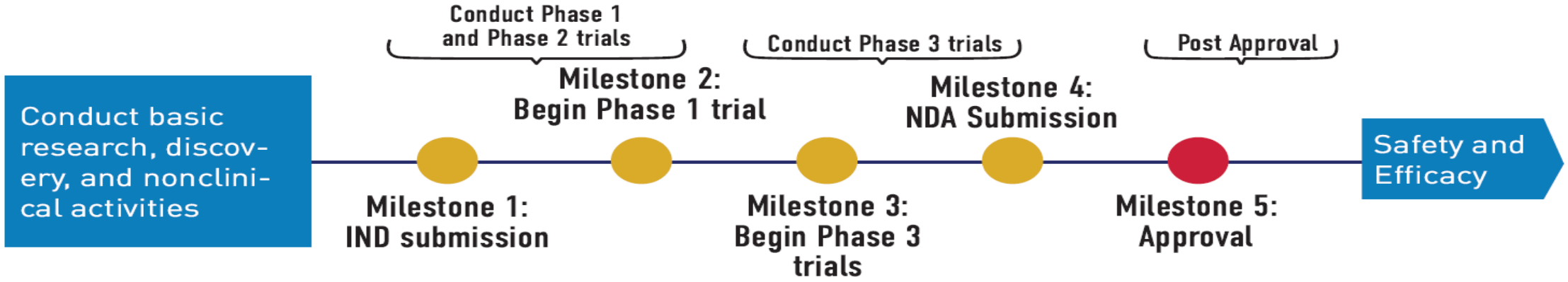
Regulatory Strategy for Ultra Rare Diseases

If Content is King, Context is GOD

Latika Kohli
Global Regulatory Affairs, Ultragenyx
November 2024

The Typical Regulatory road to a Drug approval



- For a drug to be found effective; the standard is **"substantial evidence of effectiveness"** for treatment of the proposed indication:
  - Defined as evidence from adequate and well-controlled investigations (21 CFR 314.126)
  - Usual standard is two adequate and well-controlled clinical studies
  - ***Critical element of these studies is the control group***
- Demonstration that the **benefits of the drug must outweigh its risks** for the patient population for which the drug is indicated (21CFR 314.50)
- Adequate manufacturing methods to ensure product identity, strength, quality (and purity)
- Evidence-based drug labeling that guides providers and patients on using the drug safely and effectively

Reference: FDA Case Study. Drug Approval – Bringing a new drug to the market

FDA's benefit risk framework as basis for drug approvals

- Core task of regulators is to balance desirable effects (benefit) and undesirable effects (risks)
- **FDA applies a Structured Benefit-Risk framework** to the approval process:
  - Analysis of the target indication and available treatments
  - Assessment of benefits and risks based on results of clinical studies
  - Strategies for managing risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Reference: FDA Guidance for Industry. Benefit-Risk Assessment for New Drug and Biological Products. Sep 2019

See Appendix for additional details

Regulatory Framework for Rare Diseases

- **Orphan Drug Act (ODA):** To promote development of drugs for rare diseases with unmet need (fewer than 200,000 people total in the US)
  - **Eligibility**: Previously unapproved drug or a new orphan indication for an already marketed drug
  - **Incentives**: 7yrs of market exclusivity, tax credits, PDUFA fees waiver etc
- **Rare Pediatric Disease (RPD) Designation and Priority Review (PR) Voucher:**
  - Incentive program to encourage drug development for rare serious/life threatening pediatric conditions. RPD drug approval (if addtl conditions are met), grants eligibility for a PR voucher for future drug OR sold to a different company
- **Expedited Pathways**
  - Fast Track
  - BTD
  - Accelerated approval
  - RMAT

ODA does not alter the statutory standard/requirements for drug approval

No distinction between rare and "ultra rare" diseases (diagnosed in 2000 or fewer patients)

Regulatory Flexibility for Ultra Rare Diseases

Strategies to enable drug development even when N=1

Evidence bar for establishing safety and effectiveness in ultra rare diseases – *Expectations vs Reality*

- **Establishing benefit via a clinical endpoint which is defined by the "feels, functions or survives" paradigm**
  - Challenging in studies of **small/heterogeneous patient populations** or in diseases with limited historical data or long periods with subclinical or slow progression and/or that have substantial irreversible damage at the time of diagnosis
  - **Lack of regulatory precedents for endpoints**. Disease may not readily fit into existing clinical models and previously identified clinical endpoints may not be applicable
  - **Limited knowledge/awareness and/or misconceptions around disease** can pose a challenge in alignment on "study parameters" with regulators

- **Evidence requirement from adequate well controlled trials**
  - Lack of available patients impacting a study's ability to reach a reasonable level of power to detect a statistically significant change

Reference: Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints. Emil D Kakkis et al, 2015

Navigating Endpoint Negotiations: Ultra Rare Diseases

Aspect	Potential strategies
Misconceptions around, • Disease manifestations • Feasibility of measuring proposed EPs or outcomes in population of interest	Creating awareness on the disease and relevant aspects, via • Physician/KOL presence at meetings • Patient Listening Sessions • Supplement justifications with patient/caregiver quotes, illustrations of patient experience (videos etc)
Disagreement on primary/co-primary endpoints	• If sponsor proposed EP is subjective/considered to be prone to bias, leverage POC/early phase data to speak to anticipated strength of data/treatment effect [if applicable] • Propose a totality of evidence approach acknowledging that efficacy assessment for drug approval would hinge on a composite of outcomes from the study (including primary, secondary, tertiary EPs) [Sponsor's risk]
Heterogeneity in clinical manifestations as an impediment to aligning on an EP/sufficiently powering a study	• Propose individualized EPs with a baseline control strategy [case study]

Individualized endpoints 1/2

CASE STUDY

- **Drug**: Xuriden (uridine triacetate), Wellstat Therapeutics Corporation
- **Indication**: Pyrimidine analog for uridine replacement indicated in adult and pediatric patients for the treatment of hereditary orotic aciduria (HOA)
- **Disease context:** Inborn error of pyrimidine metabolism. Characterized by rapid onset of severe hematological disorder in affected newborns, leading to developmental delays. Approx. 19-20 documented cases
- **Approval date**: Sep 4, 2015. Received Rare Pediatric Disease Voucher
- **Clinical Trial Design**: 6 week single arm open label study in 4 patients followed by 6 months extension phase. Pts 1-3 had prior treatment with uridine. Pt 4 was treatment naive

Table:
Baseline Demographics

	Patient			
	1	2	3	4
Sex	Male	Female	Male	Male
Race	White	White	White	White
Age (years)	6	19	7	3.5

Individualized endpoints [2/2]

CASE STUDY 1 contd.

Clinical evidence

- Changes in patients pre-specified hem parameters during initial 6 week + extension phase
  - Patient 1: Neutrophil count and % neutrophils
  - Patient 2: WBC count
  - Patient 3,4: Mean corpuscular volume
- Primary EP:
  - Patients 1-3: Stability in specified parameters
  - Patient 4: Improvement of hematological parameters
- Supportive evidence:
  - Case reports (n=19) of patients treated with exogenous uridine

Table:

Prespecified Hematologic Parameters

Patient	Pre-specified Hematologic Parameter (Age-specific reference range)	Baseline (Day 0)	6 Weeks (% Change from Baseline)	24 Months (% Change from Baseline)
Patient 1	Neutrophil Count (1.5 to 8.0 $x10^3/mm^3$)	0.95	0.81 (-15%)	0.61 (-36%)
	Neutrophil % (26 to 48%)	21	23 (10%)	13 (-38%)
Patient 2	White Blood Cell Count (3.8 to 10.6 $x10^9/L$)	7.8	7.4 (-5%)	8.6 (10%)
Patient 3	Mean Corpuscular Volume (75 to 91 fL)	109.9	108.5 (-1%)	108.8 (-1%)
Patient 4	Mean Corpuscular Volume (72 to 90 fL)	114.6	113.4 (-1%)	112.9 (-1.5%)

Navigating Endpoint Negotiations: Ultra Rare Diseases….. contd

Case Study

- Drug: Tysabri
- Indication: Relapsing forms of multiple sclerosis.
- Basis of approval (2004):
  - Accelerated approval based on a large therapeutic effect on relapse rate through approximately 13 months of treatment
  - Confirmatory study: Continue the existing trials into the post-marketing period to confirm the durability of the observed effect at 2 years.

Aspect	Potential strategies
Timepoint for measurement not deemed sufficient to assess durability	Explore potential for Accelerated Approval on premise of “Intermediate clinical endpoints”

External Controls (ECs) as a Tool to enable Regulatory Decision Making

- While valid comparison to an internal concurrent control remains the gold standard, external controls may be leveraged to enable regulatory approval

Type	Description
Prospective Natural History [Concurrent External Control]	Data collected at same time as treatment arm but in different setting (generally preferred by regulators but not always feasible) "initiation of prospective natural history studies should not delay interventional testing otherwise ready to commence for a serious disease with unmet medical need" *
Historical Data	• Retrospective Natural History (sources: Patient charts, registry) • Published Data (literature – no access to subject level data or data collection methodology) • Previous Clinical Study • Baseline-controlled study (data collected from pt over period of time prior to treatment

**FDA guidance "Rare diseases: common issues in drug development"*

Justification for External Controls: Setting up a successful negotiation

Key Points For Inclusion

- Ethical concerns (w) placebo control, and/or lack of available comparator
- Disease course can be reliably predicted
- Objective outcome measures [e.g., survival] with well characterized covariates
- Large treatment effect that may not be impacted by bias, temporally associated and can be reasonably predicted by clear MoA (supported by non clinical models)

Desired attributes of Control Group

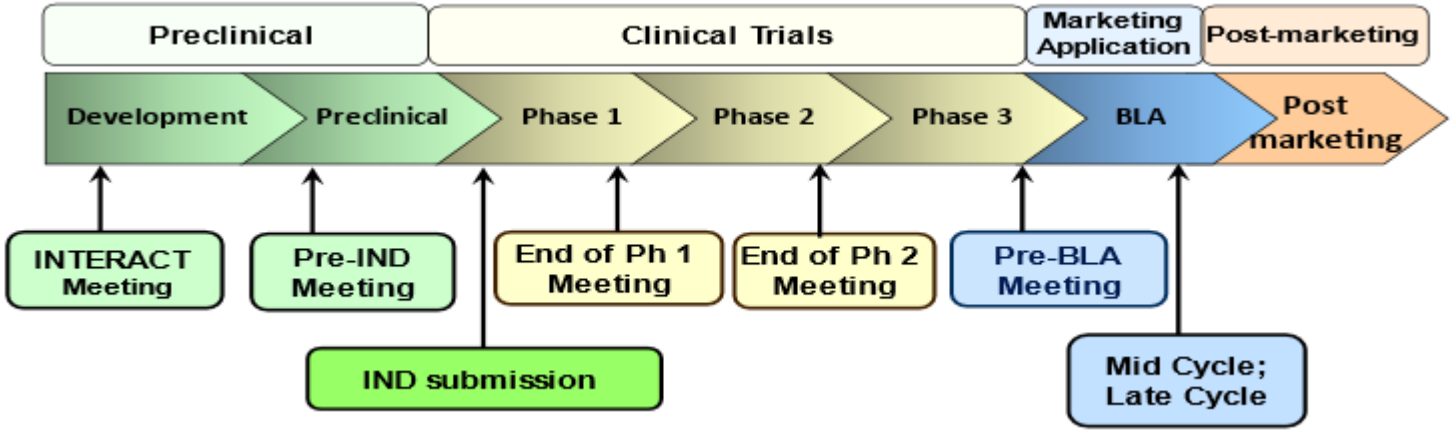
- Control group population must be similar to subjects on treatment arm
  - Demographics,
  - Baseline disease characteristics
  - Prior treatment history
  - Concomitant therapy
- Well documented population with patient level data

Precedents for Drug Approvals Built on External Control Strategies

Drug	Indication	Trial Design
Zolgensma	Spinal Muscular Atrophy (pediatric pts. <2). Infants with SMA develop progressive muscle weakness and atrophy with mortality of 30% at 2 years of age	Retrospective Natural History Single arm, open labeled trial using natural history controls (n=22; ≤6 months of age). Outcomes – survival and developmental motor milestones
Veopoz (complement inhibitor) 2023	Chaple Disease (pts 1 yr and older) (<100 global cases). CD55-deficient protein-losing enteropathy (PLE) characterized by hypoalbuminemia	Baseline control Single arm Ph2/3 study (n=10; **3-19** age range); primary outcome (serum albumin concentration within normal range) compared to pre-treatment data in patients; secondary outcomes – albumin transfusions, hospitalizations

Communication with Regulators is Key

- **INTERACT** (INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs meeting): Specific topics or issues that are critical to early product development
- **Patient-Focused Drug Development (PFDD) Meetings**
  - Disease-specific, FDA-led or externally-led PFDD Public Meetings
  - Designed engage patients and elicit their perspectives on their condition and treatments
- **Patient-Focused Listening Sessions (PFLS)**
  - Hosted by FDA's Office of Patient Affairs
  - Small, informal, non-regulatory, non-public meetings



Prescription Drug User Fee Act (PDUFA) Meetings

- **Type A**: To help restart a stalled development program. For example, discuss and resolve responses to a clinical hold.
- **Type B**: Milestone advice meetings, including EOP2 and pre-NDA/BLA meetings.
- **Type C**: Any other meeting between FDA and a sponsor regarding the development and review of a product.
- **Informal interactions**: For clarifications. Requests considered on case-by-case basis

Current Rare Disease Pilot Programs at FDA

Pilot Name	Short Description
CDRP	Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot Program *Facilitate CMC development of products with expedited clinical development timeframes*
CID	Complex Innovative Trial Design Paired Meeting Program *Facilitate and advance use of complex adaptive, Bayesian, and other novel clinical trial designs*
Clinical Holds *(OTP internal Only)*	Identify and flag deficiencies in INDs to sponsor proactively before a product is placed on hold *Internal to OTP*
CoGenT Global *(CBER Only)*	Explore concurrent collaborative review of new gene therapy applications with other global regulators. *Internal to OTP*
MIDD	Advancing Model-Informed Drug Development Paired Meeting Program *Apply exposure-based, biological & statistical models derived from preclinical & clinical data sources in drug development & regulatory review*
RDEA	Rare Disease Endpoint Advancement Pilot Program *Support novel efficacy endpoint development for drugs that treat rare diseases*
RWE	Advancing Real World Evidence Program *Seeks to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products, or to satisfy post-approval study requirements*
STAR	Split Real Time Application Review Pilot Program *Shorten the time from the date of complete submission of efficacy supplement to the action date, to allow earlier patient access to therapies that address an unmet medical need. Accepted STAR applications are submitted in a "split" fashion, specifically in two parts submitted approximately two months apart*
START	Support for clinical Trials Advancing Rare disease Therapeutics Pilot Program *Help further accelerate the development of novel products for rare diseases with more frequent communication with FDA staff to provide a mechanism for addressing clinical development issues.*

Impact of Patient Voice in Drug Development

Case Study: Epidermolysis Bullosa (EB) [defective epithelial integrity in the skin leads to chronic and relapsing wounds that predispose patients to repeated]

- Failed clinical development program on a topical cream; did not meet primary EPs on time to wound healing and proportion of pts. with complete closure of target wounds
- At FDA PFDD Meeting for EB, patients contrasted their symptom endpoints (like reduction in pain medication or fewer bandages) to wound measurements; comments supporting time to wound healing as a EP but questioning whether 100% wound closure was truly important
- FDA acknowledged patient concerns with the failed results and the interest in making the endpoints more accurately reflect patient treatment objectives (beyond wound healing) and reflected the feedback from the PFDD meeting in a Guidance document on EB drug development
- Final Guidance states that “there is “not yet sufficient clinical trial experience to establish effective endpoints” and that endpoints can include effects on patients’ signs or symptoms such as itching, pain, blister prevention, wound healing.
- In 2023, Vjuvek, a GT, was approved for EB treatment [Ph3 double blind, placebo controlled intra patient trial – primary wound pairs identified in each patient were randomized 1:1 to receive drug or placebo; Note: Ph1/2 pts were allowed to participate in Ph3 after a 1 yr washout period]

Partnering with health authorities

- Duchenne muscular dystrophy community (led by Parent Project Muscular Dystrophy) created a proposed draft guidance document for submission to FDA in June 2014 [**first patient advocacy-initiated draft guidance for a rare disease**].
  - Preceded by, preference studies involving caregiver and patients views on willingness to to accept considerable risk and uncertainty for a therapy that stops or even slows the progression of Duchenne; preferences for non skeletal muscle benefits; risk tolerance in gene therapy interventions
  - FDA advised PPMD that a well proposed draft guidance could serve as the basis for–and hasten the development of–FDA's own version of an industry guidance for Duchenne
- FDA finalized guidance in 2018

Closing Remarks

- Try to approach regulators with a Proposal vs Open ended questions
  - Do not limit the proposal to expectations outlined in guidance docs OR precedence
  - Use regulatory precedents to justify/guide your proposals, BUT, Do not feel limited by the absence of precedence while proposing a unique scientifically sound strategy to regulators

- Data driven conversations can yield better outcomes – strength of data can impact the nature, tone and outcome of meetings with regulators
  - Large treatment effects can often overcome existing challenges/gaps in a program

- Do not feel discouraged if you cannot “check every box”
  - Regulators can/will take a “Totality of evidence” approach if warranted [seriousness of disease, unmet need, biological plausibility]

Rare Bootcamp™

Sponsored by Ultragenyx

Thank You

Appendix

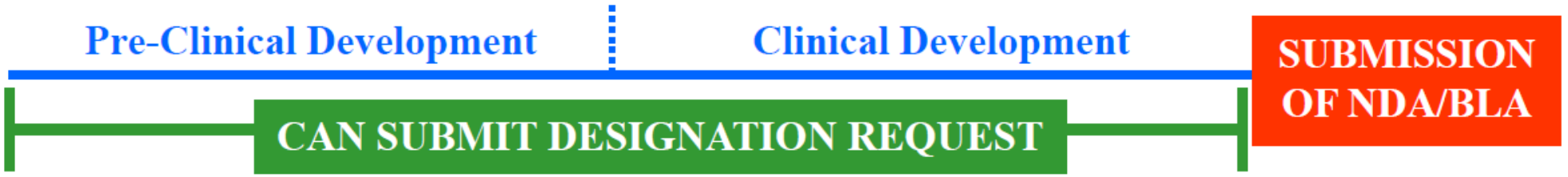
FDA ORPHAN DRUG ACT and ORPHAN DRUG DESIGNATION (ODD)

- Orphan Drug Act (ODA) of 1983 designed to promote development of drugs for rare diseases with unmet need
- A disease or condition is classified as **"rare" if it affects fewer than 200,000 people total in the US, or if the cost of developing a drug and making it available in the US will exceed any potential profits from its sale.**
- Orphan drug is a **drug or biologic intended for use in a rare disease or condition**
- Since inception:
  - 4,500 orphan designation requests have been granted
  - > 730 drugs and biologic products approved > 250 rare diseases
- ODA does not alter the statutory standard/requirements for drug approval
- **Eligibility:**
  - Previously unapproved drug or a new orphan indication for an already marketed drug
  - Based on disease prevalence and scientific rationale for use of the drug

ODD Incentives

- **What does Orphan Designation provide?**
  - Seven years of marketing exclusivity to sponsors of approved products
  - 25% federal tax credit for expenses incurred in conducting clinical research within the United States
  - Waiver of Prescription Drug User Fee Act (PDUFA) fees for orphan drugs
    - A value of approximately $2.9 million in 2021
  - Ability to qualify to compete for research grants from the Office of Orphan Products Development (OOPD) to support clinical studies for orphan drugs
  - Eligibility to receive regulatory assistance and guidance from the FDA in the design of an overall drug development plan

When to submit an Orphan Designation Request



- No IND is required

Review of a Designation Request:

1. What is the disease/condition?
2. Is the disease rare (prevalence)?
3. Is there sufficient scientific rationale that demonstrates "promise" that the drug/biologic will treat, diagnose or prevent the disease/condition at issue?

   *"**The scientific rationale is best supported by clinical data**; however, in the absence of human data, the application for orphan drug designation may be satisfactorily supported with **preclinical data using a relevant animal model for the human disease**."*

RPD Designation and Priority review voucher

- Additional incentive program to encourage development of drugs for rare pediatric diseases/conditions
- RPD must meet the following criteria:
  - The disease must be a serious or life-threatening disease **in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years**
  - The disease is a rare disease or condition (as defined by Section 526 of the FD&C Act)
- Approval of a Rare Pediatric Disease Product Application grants eligibility for a voucher that can be used to obtain priority review for another future drug application.
  - Vouchers can be transferred/sold
  - Priority review shortens FDA review from 10 months to 6 months.
  - Attractive to larger companies who will buy the vouchers for large sums (prior transfer value from $67-350 million)

See: FDA Guidance for Industry. Rare Pediatric Disease Priority Review Vouchers. July 2019

Expedited Pathways

- Goal is to facilitate and expedite drug development and review of applications
- Treatments for serious and life-threatening conditions for which there is high unmet need
- Help ensure that therapies for serious conditions are approved and available to patients as soon as possible
  - Evidentiary standards still apply
  - Preserve standards for efficacy and safety and “benefits justify their risks”
  - Flexibility on type of endpoint eg **surrogate endpoint** used in the **accelerated approval mechanism in the US**
  - Quantity of evidence eg **less comprehensive evidence** is considered in **conditional approval in the EU**

See: FDA Guidance for Industry. Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014

US/FDA Expedited Programs

Fast-Track

- Serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need or a drug designated as a Qualified Infectious Disease Product (QIDP)
- More frequent communications and rolling review

Breakthrough Therapy Designation

- Serious condition and when early clinical data show a substantial improvement on a clinically significant endpoint(s) over existing therapy.
- Extensive communications with sponsor and potential for expedited review; organization commitment; rolling review

Accelerated Approval

- Serious condition and a meaningful advantage over other therapies and surrogate endpoint likely to predict benefit or on a clinical endpoint that can be measured earlier than an effect on IMM or other clinical benefit.
- Approval based on surrogate or intermediate end point; rolling review

Priority Review

- Serious condition and will provide a significant improvement in safety or efficacy or pediatric labeling change or a QIDP or priority review voucher
- PDUFA review clock shortened

Additional expedited program for Regenerative Medicine Therapies for Serious Conditions

- **What is a Regenerative Medicine Therapy?:**
  - Includes cell therapies, therapeutic tissue engineering products, human cell and tissue products
  - Human gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues, may meet the definition of a regenerative medicine therapy
- **Regenerative Medicine Advanced Therapy (RMAT) Designation** applies if certain criteria are met :
  - Meets the definition of a regenerative medicine therapy
  - It is intended to treat, modify, reverse or cure a serious condition, and
  - **Preliminary clinical evidence indicates that the regenerative medicine therapy has potential to address unmet medical needs for such condition**
- **Benefits of RMAT** include all benefits of Fast Track and Breakthrough Designations
- Guidance encourages early interactions discuss surrogate or intermediate endpoints to support accelerated approval and satisfy post- approval requirements.

See: FDA Guidance for Industry. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions. Feb 2019

Guide to access FDA “Summary Basis of Approvals”

- Navigate to Drugs@FDA [Link: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm]
- Type the name of the drug in search bar

- Summary Review

Products on NDA 208169

CSV | Excel | Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
XURIDEN	URIDINE TRIACETATE	2GM/PACKET	GRANULE;ORAL	Prescription	None	Yes	Yes

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 208169

Labels for NDA 208169