RAPS 2021 Convergence

Pediatric Development: Increasing Success and Overcoming Obstacles

RAPS 2021 Convergence

Welcome to Pediatric Drug Development: Increasing Success and Overcoming Obstacles

Description:

- Product development in pediatrics is **challenging**, however bringing a product to market that addresses safety and efficacy in pediatrics is **tremendously rewarding**. Creation and coordination of the regulatory pathway which results in an approved product that address pediatric needs is grounded on engagement with the regulators early and often.
- This session will actively engage the audience through **scenario planning to highlight strategic imperatives, pitfalls, and insights into the FDA and EU policies**, regulations and guidances including some envisaged changes to the EU Paediatric Regulations as currently under discussion in 2021.

Learning Objectives:

- Describe the current **US and EU requirements**
- Understand and communicate the regulatory **risks and benefits for drug development in pediatrics**
- Identify **common pitfalls** to **increase probably of success** for a pediatric drug development program

Please use chat to ask your questions! We appreciate them being short and precise!
Join us at the “Meet the Speakers” for more detailed discussions

Session Speakers

- **Linda McBride, R.Ph., RAC,** Regulatory Consultant
- **Karl-Heinz Huemer, MD, PhD,** Medical Assessor, AGES (Austrian Agency for Health & Food Safety)
- **Kimberly Belsky, M.S.,** Executive Director, Regulatory Policy & Intelligence and AdPromo, Mallinckrodt Pharmaceuticals

Session Agenda

- Intro to Session (5 minutes)
- EMA and FDA Requirements (10 minutes)
- Common Pitfalls (15 minutes)
- Case Studies (30 minutes)
- Conclusions and Q&A (15 minutes)

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EMA and FDA Requirements

EMA Requirements
Regulation on Medicines for Paediatric Use – EC 1901/2006

Aims of the Regulation

- Better Medicines for Children by:
  - **High quality drug research** in paediatric patients
  - **Increased of approval** of drugs in EU member states
  - **Improved information** on drugs for paediatric use
- This should be achieved:
  - **Without exposing children to unnecessary clinical trials**
  - **Without delaying marketing application approvals for adult indications**

EMA Requirements
Regulation on Medicines for Paediatric Use – EC 1901/2006

Key Points of the Regulation

- There is a **legal requirement** to perform paediatric development, where applicable
- The proposal for such trials, Paediatric Investigation Plan (PIP), has to be **discussed early** (after FIH study) with the Paediatric Committee (PDCO) at EMA, prospectively
- The completion of the agreed upon PIP is **obligatory** with **key elements and timelines**, this also incudes **waivers** and **deferrals**
- **Compliance Check** during validation of the submitted MAA is necessary
- Generics, biosimilar, bibliographic applications, herbals & homeopathics exempted
- However: **orphan** medicinal products are **not exempted** from a PIP

EU Regulation Considerations

Forthcoming EU regulation changes *(in potentially 2 years …important to monitor for these changes)*

Possible changes (just a guess at the moment)

- Rewards system to be better adapted to effort/costs
- Better reflect the “unmet need” and “significant benefit” aspects
- Iterative agreement on detail during development
- Requirement to amend an agreed PIP regularly?
- Orphan and Paediatric Regulation will be better aligned

FDA Requirements – Code of Federal Regulations

TOPIC	SELECTED INFORMATION
Pediatric Patients	**Labeling regulations for prescription drugs: 0 to 16 years old** [21 CFR 201.57(c)(9)(iv)] Clinical trials: **Children means persons who have not attained the legal age for consent** to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. *[21 CFR 50.3(o)]*
General Principles for Pediatric Drug Development	**Ensure product development programs include pediatric studies** when pediatric use is anticipated Have information in the approved labeling that **reflects appropriate use to treat pediatric patients**
Evidentiary Standard for Approval	For approval, **same standard as adult product development** **A product approved in pediatrics must demonstrate substantial evidence of effectiveness/clinical benefit**: • The impact of treatment on how patient feels, functions or survives • Improvement or delay in progression of clinically meaningful aspects of the disease *21CFR 314.50: Content and format of an application*

FDA Requirements - Legislation

REGULATION	SELECTED INFORMATION
Pediatric Research Equity Act (PREA)	**Requires companies to assess safety and effectiveness** of new drugs/biologics in pediatric patients (Pediatric Assessment) **Studies must use appropriate formulations for each age group** The goal of the studies is to obtain pediatric labeling for the product
Best Pharmaceuticals for Children Act (BPCA)	Provides a **financial (exclusivity) incentive to voluntarily conduct pediatric studies** outlined in a Written Request issued by FDA
FDA Safety and Innovation Action of 2012 (FDASIA)	• Section 908, Rare Pediatric Disease Priority Review Voucher Program • Permanently reauthorized PREA and BPCA
FDA Reauthorization Act of 2017 (FDARA) - Title V - RACE for Children Act	• **Requires evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and** directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer." • Molecularly targeted pediatric cancer investigation: clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling." [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)] • Elimination of orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets - **Compliance began August 2020**

PREA versus BPCA

PREA *(the stick)*	**BPCA** *(the carrot)*

• Drugs and biologics
• **Mandatory** studies
  • **Limited to** indications proposed for adults for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration
  • No incentives
• Requires studies **only on indication(s)** under review
• **Orphan indications exempt** from requirements
• Pediatric studies **must be labeled**
• Pediatric Study Plan (PSP)
  • Sponsor submit PSP at end of Phase 2
  • Waiver and Deferral
	• Drugs and biologics
	• **Voluntary** studies
	• Studies relate to entire moiety and **may expand indications**
	• Studies **may be requested** for orphan indications
	• Pediatric studies **must be labeled**
	• Priority Review
	• Written Request (WR)
	  • Outline of study requested by FDA
	  • Proposed Pediatric Study Request (PPSR) can be submitted by sponsor for WR
	  • Rationale for studies and study design, Detailed study design, Appropriate formulations for each age group
	• Sponsors who submit studies to fulfill a WR **may be eligible to receive 6 months of pediatric exclusivity**

RACE ACT Implementation

- **The Research to Accelerate Cures and Equity (RACE) for Children Act went into effect on August 18, 2020** and impacts all cancer drug development.
- Under the RACE Act, **new molecularly targeted compounds for adult cancers need to be evaluated for children's cancers if** the molecular target or mechanism of action (MoA) of the drug, not the tumor type or indication, is relevant to the growth or progression of pediatric cancer.
- **Any NDA or BLA for a new active ingredient must have an agreed initial pediatric study plan before submission**.
- …even applicable to orphan drugs

Good to Know! EMA and FDA Cluster Calls – Position Paper

26 March 2021 Common Commentary - EMA/FDA Common issues requested for discussion by the respective agency (EMA/PDCO and FDA/PeRC) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs])

- https://www.fda.gov/media/147197/download

Regulatory **agency alignment on paediatric development plans is especially critical given the demand for international clinical trial collaboration necessitated by small study populations in rare diseases** such as childhood cancer

Cluster calls provide an opportunity for regulatory agencies to engage in high-level scientific discussions of paediatric development plans of new drugs and inform regulatory decision making of each agency

- Attention to global product development requires consideration of additional regulatory agencies outside of the U.S. and EU

Describes key issues which are commonly requested by the respective regulatory agency to be further discussed by the sponsor

- Addressing these issues upfront will permit focused discussions during cluster calls, allowing for coordination of global development plans

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Good to Know! EMA and FDA Cluster Calls – Position Paper

- **EMA Position for PIPs and FDA Position for iPSP cover:**
  - Administrative and Product Information
    - Overall development of the medicinal product
    - Waiver discussions
  - Proposed paediatric plan
    - Non-clinical studies / Juvenile tox studies
  - Quality Development
  - Paediatric Clinical Development
  - Timelines/Deferral

Waiver Discussions:

EMA position for PIP applications

- The **default position by the PDCO is that no age specific waiver is accepted**, unless sufficient justifications are presented in support of one of the three existing waiver grounds for a lower age cut off.
- The approach taken by the PDCO is that **if the disease does occur even in very young patients with an acknowledged unmet medical need and/or if one can extrapolate based on disease similarity and there are no specific safety concerns, there should be no need for a lower waiver cut off age**, particularly if no minimum number of patients to be recruited are specified for the lowest age subset.

FDA position for iPSP applications

- **Planned waivers for drug products that are the subject of supplemental applications can be considered if the indication does not or only rarely occur in children making studies impossible or highly impracticable** or if the drug poses significant toxicity concerns or is unlikely to be used in children.
- **Plans for age specific waiver requests can be justified on the basis of excess toxicity concerns related to age or unavailability of an age-appropriate formulation where the sponsor has demonstrated due diligence**.

Common Pitfalls

Common Pitfalls *(include but not limited to…)*

- **Regulation Differences**
- **Where to start the Strategy Development**
- **Clinical Study Design**
  - Feasibility
  - Extrapolation
  - Endpoints
  - Standard-of-Care
- **Age Groups**
- **Age-Appropriate Formulation(s)**
- **Timing of Decision Making**

Where and When to Start the Strategy Development?

- **Keep pediatrics in mind from the beginning of development**
- Based on the adult program: *which **therapeutic benefit** could this drug have, based on including*
  - MOA
  - Disease progression
  - Role in a complex therapeutic regimen (including underlying conditions)
- Which are the **relevant pediatric populations/ages**?
- Would the pediatric **condition be identical to adult** appearance or are there differences?
- What are the **realistic approaches** to collect data, specifically feasibility and timelines?
- Could **extrapolation** from other indications or age ranges to be considered?

Targeted Condition

- **Current method(s)** of diagnosis, prevention or treatment
- **Similarities and differences**
  - of symptoms between populations
  - effect of the investigational product on the disease/condition
  - significance of therapeutic benefit
  - fulfillment of therapeutic need
- **Prevalence** and **Incidence**

Precedence

A good baseline but, the "devil is in the details" (*which you may not be privy to*)

- **Where to find**
  - **EMA**
    - EPAR
    - Summary of Product Characteristics (SmPC)
    - PIP opinions
  - **FDA**
    - Approval Letter – Shows PMC/PMR for agreed upon PSP studies both nonclinical and clinical
    - Review Summaries
  - **Clinical Trials Registries**
    - Clinicaltrials.gov
    - clinicaltrialsregister.eu (and other country/regional trial sites) / Clinical Trial Information System 'CTIS')
  - **Press releases**, and more
- **Context is key**
- **Landscape changes –** *don't assume, stay current!*

EMA Precedent – PIP Decision

Date/ Medical Product	Opinion/Decision on PIP	Rationale	Precedent Use Pitfalls
Date: 17/6/2021 **Opdivo, nivolumab, P/0280/2020** • Treatment of all conditions in the category of malignant neoplasms (except central nervous system neoplasms, haematopoietic and lymphoid tissue neoplasms other than Hodgkin lymphoma)	W: decision granting a waiver in all age groups **for all conditions or indications**	The specific medicinal product **does not represent a significant therapeutic benefit over existing treatments for paediatric patients**	• Assuming the indication for your product in development would "automatically" be considered the same (*this is a product specific waiver, not a class waiver*) • Not confirming current existing treatments

Clinical Study Design - Feasibility

- **Determine:**
  - Number of Patients (and diversity/inclusion of patients)
  - Location of Patients
  - Pediatric specific endpoint (including PROs)
  - Need/benefit and acceptability to patients, parents, and/or caregivers
  - Technical limitations (e.g., blood volume, transportation/study location)

- **Consider engaging patient advocacy group(s)**

Clinical Study Design - Extrapolation

Effective dosing in many cases cannot be extrapolated:

- Obtain pharmacokinetic (adults and/or older pediatric sub-group) data to support dose selection
- Safety must be monitored in these studies
- Studies performed in patients with condition of interest

Modeling and simulation may be useful (e.g., popPK, physiologically based PK, sparse PK sampling strategy to evaluate exposure)

Safety data are needed in the target age range, mostly not possible to extrapolate:

- Safety data are needed to evaluate the safety of all proposed doses to be used in pediatric patients
- Safety database should be large enough and of long enough duration to detect common and potentially infrequent but not necessarily rare adverse events
- Existing data (e.g., published, registry, etc.) may be used as supportive data

Clinical Study Design - Endpoints

- Is the endpoint **feasible** in relevant groups/subgroups of children?
- Is the endpoint **validated** in children?
- Does the endpoint **capture the complexity** of the disease?
- Needs to describe something **relevant to the patient**
- Has **a patient reported outcome** (PRO) been developed? Is it validated?
  - Caregiver/parent or health-care-provided, are other options
- Could a **biomarker** be appropriate?
- Is safety the primary outcome?

Endpoint can be symptomatic or disease modifying *(both might be acceptable as benefit and might be relevant to the patient and/or the physician)*

A few examples:

- *Lowering body temperature might be perceivable to the patient, but does not necessarily treat the underlying infection, an anti-pyretic is not an anti-infective.*
- *An analgesic often does not treat the underlying cause for the pain*
- *An outcome like tumour marker level or an MRI outcome might not be evident to the patients, but is a clinically relevant outcome*

Clinical Study Design - Standard-of-Care

- **SoC often is often a moving target (*due to new treatments, scientific research…*)**

- **Differences in medical practice, treatments approved in EU and US**
  - In different subgroups
  - Historical or observational control data
  - In rare diseases, often no established SoC

- **Added v. replaced SoC treatment paradigms**

Age Groups

- **ICH age ranges (not obligatory)**
- **Heterogenous SoC in age groups**
  - Not considering subgroups
    - Not all children (ages) are alike
  - Over-considering subgroups (unable to complete trial)
- **Stepdown (age-staggered)**
  - Data in adults first, followed by adolescents – not always the best solution
  - Consider including adolescents in your adult clinical trial

Age-Appropriate Formulation(s)

- **A pediatric appropriate formulation should not contain any excipients that might be harmful to children**
  - This is handled much stricter than other industries (food), parabens, ethanol, dyes should be avoided
  - Sugar content, flavor masking
- **Adaptation of tablet sizes or utilization of other dosage forms, like liquids, granules, pellets**
- **Compatibility testing with food, milk/juice, nasogastric/feeding tubing**
- **Verification of acceptability (taste, texture, consistency), often will be part of the clinical program**
- Timing and age group considerations
  - Consider benefit of ped formulation to adult populations

Timing of Decision Making

Aspects

- **Commercial plan** (consider international footprint and Targeted Product Profile (TPP), also Company Core Data Sheet (CCDS) *aka core labeling*
- **Regulatory requirements and differences** in countries/regions
- **The scientific principle**, that a drug development program will follow a sequential approach, where studies have to be informed by prior data

Case Studies

Case Studies #1 - DMD (Duchenne Muscular Dystrophy)

Several products are already approved

- Eteplirsen approved in US (only exon 51 skipping), but failed to establish a clinical benefit, refused approval in EU
- Ataluren (Translarna) is approved in the EU
- Golodirsen (Vyondys 53) was approved in the US (only exon 53 skipping)
- Viltolarsen (Viltepso) was approved in the US (only exon 53 skipping)
- Casimersen approved in the US (only exon 45 skipping)

Efficacy in terms of clinical benefit is limited

Other medicinal products (mostly off label) & treatments are used and SOC

- Corticosteroids lead to short-term improvement but no maintained effect, adverse events!
- β_2 agonists increase muscle strength, but do not modify disease progression
- Muscle training can partly reduce symptoms, maintain muscle strength, flexibility, and function.
- orthopedic appliances (such as braces and wheelchairs) may improve mobility and the ability for self-care
- respiratory support in advanced cases needed.
- cardiac problems may require a pacemaker

Case Studies #1 - DMD (continued)

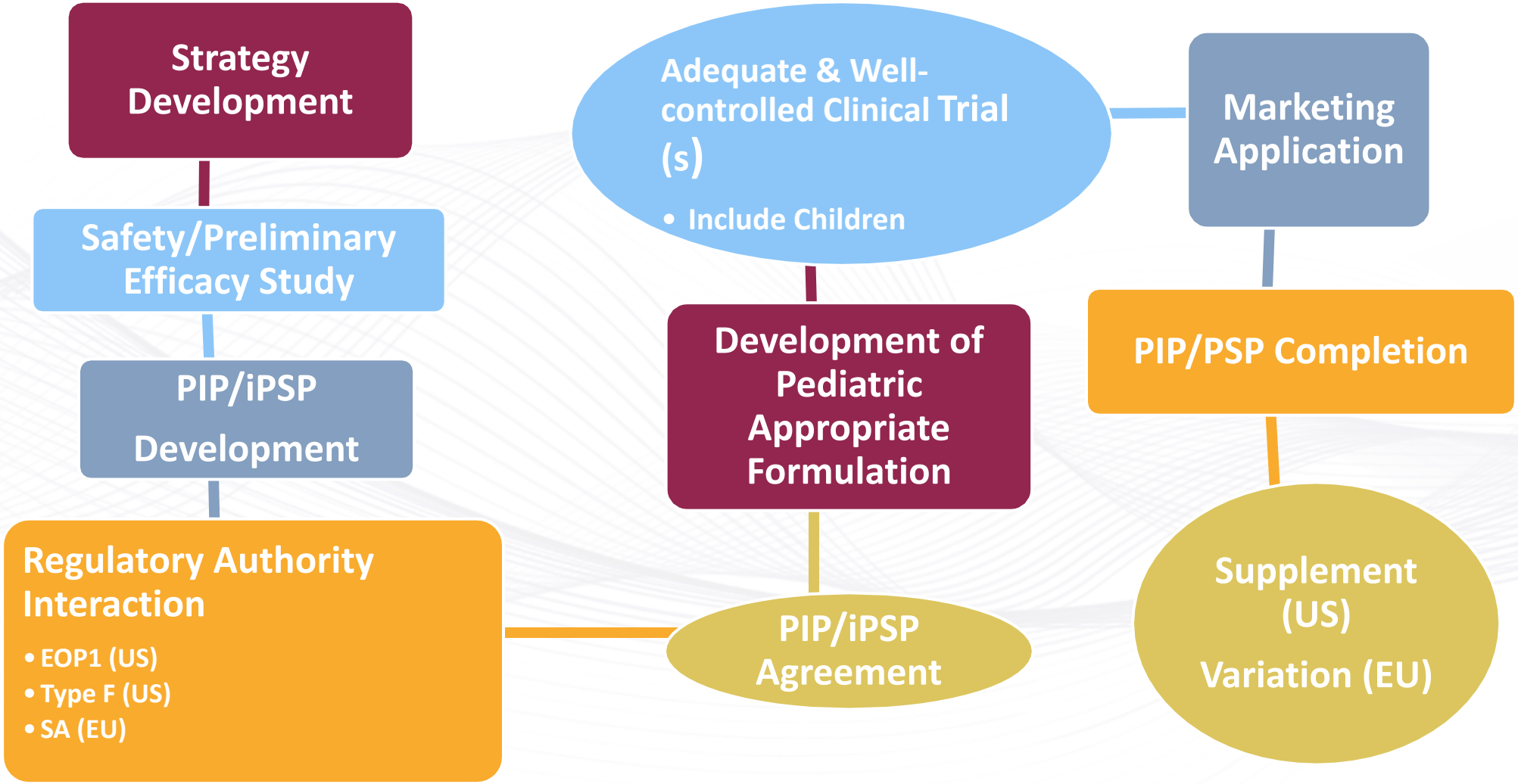
- In such a complex landscape it is difficult to define a study population that can have a benefit
- Need for a comparator to demonstrate a benefit over SOC
- Difficult to agree on a global strategy for investigation & commercialization (unmet needs, benefit over SOC,..)
- Difficulty to agree on a common endpoint (e.g. biomarker or clinical outcomes, what could be a feasible clinical outcome, also in small children
- Acceptability of outcomes like muscle biopsy in children
- How to balance symptomatic versus disease modifying (antisense, gene therapy)
- Long-Term outcomes

Case Study #2 - Orphan Disease & Relevant Molecular Target

- **Treatment of Acute Myeloid Leukemia**
  - Orphan Disease Precedent by FDA and EMA
  - Required pediatric evaluation under RACE ACT in the US

- **Consider**
  - Clinical Study Design Feasibility
  - Standard of Care/Comparator
  - Age-Appropriate Formulation Necessity

Case Study #2 - Timing Scenario



A Special Note About Pediatrics and Oncology

Building on the RACE Act…

- **Pediatric Oncology Product Development Early Advice Meeting (Type F)**
  - Sponsors planning to submit original applications for a new active ingredient on or after August 18, 2020 (RACE Act) may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program, Medical Officers with Board certification in pediatric oncology, and select members of the Oncology Subcommittee of the Pediatric Review Committee (PeRC) (although not in their official PeRC capacity) through the appropriate review division or office, to seek advice on the development of the iPSP
  - **Timing/Documentation aligned with Type A Meeting**
- **Relevant FDA Guidance**
  - FDARA Implementation Guidance for Industry on Pediatric Studies of Molecularly Targeted Oncology Drugs (May 2021)
  - Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (July 2020)
- **US FDA May Invite European Regulators To Observe 'Type F' Meetings With Sponsors** (July 2021)
  - FDA will start asking sponsors when they receive a request for a Type F meeting if they would be open to having representatives from the **EMA attend as observers**
    - *Not intended as joint advice*
  - In an effort to coordinate review and decisions on iPSPs and Pediatric Investigation Plans (PIPs) required in the EU, **the FDA and EMA's Paediatric Committee (PDCO) have conducted 17 pediatric cluster calls on 20 oncology products from August 2019 to April 2021**

Case Study #3 – Strategic Challenges

- **Background: 18 June 2021, *the EC has approved Aubagio (teriflunomide) as a first-line treatment for paediatric* relapsing-remitting multiple sclerosis (RRMS) *patients aged 10 to 17 years old.*** Aubagio was first approved in the EU in 2013 for treating adult patients with RRMS. The EC approval for the pediatric indication provides an additional year of marketing protection in the EU https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio

- ***This approval comes after the FDA issued the company a complete response letter for the same patient population on 11 June 2021***
  - The FDA deemed the data submitted were not sufficient to obtain approval of an indication in the pediatric population at this time. **The FDA updated the Aubagio label to include safety data from the pediatric clinical trial program.** The indicated use of Aubagio in patients 18 years and older remains unchanged
  - https://www.sanofi.com/en/media-room/press-releases/2021/2021-06-11-07-00-00-2245628

https://clinicaltrials.gov/ct2/show/NCT02201108?term=terikids&draw=2&rank=1

Case Study #3 – Strategic Challenges

The EC approval is based on the Phase 3 TERIKIDS clinical trial, evaluating the safety and efficacy of Aubagio in paediatric patients with relapsing forms of MS.

- *The study consisted of a screening period of up to four weeks followed by a double-blind treatment period, with up to 96 weeks of randomisation. The study participants either received Aubagio, at a dose equivalent to 7mg in adults during the first eight weeks followed by 14mg, or a placebo.*
- *Data from this study showed that Aubagio cut the risk of MS relapses by 34% in the first 96 weeks of treatment and prolonged the median time to first confirmed relapse to 75.3 weeks compared with 39.1 weeks for placebo – although this difference was not statistically significant.*
- *Aubagio was also found to reduce the risk of high disease activity by 43% versus placebo, significantly prolonging the media time until the first indications of disease activity – 72.1 weeks for Aubagio versus 37.0 weeks for placebo.*
- ***Key secondary endpoints** showed that Aubagio significantly reduced the number of new or enlarging MRI lesions in children, with a relative risk reduction of 75% for T1 lesions and 55% for T2 lesions.*

https://clinicaltrials.gov/ct2/show/NCT02201108?term=terikids&draw=2&rank=1

Case Study #3 – Strategic Challenges

- **Don’t assume approval in EU will result in an approval in the US (or, vice versa)**

- **Importance of hierarchy the secondary endpoint(s)**
  - Predefined subsets
  - Clinical relevance (rather than statistically significant)
    - *Understand the disease!* Consider also what’s important to the patient (benefit), in addition to relevance to the clinician

Conclusion and Q&A

Conclusions for Pediatric Development: Increasing Success and Overcoming Obstacles

Common Pitfalls *(include…)*

- Regulation Differences
- Where to Start the Strategy Development
- Clinical Study Design
  - Feasibility
  - Extrapolation
  - Endpoints
  - Standard-of-Care
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- Age-Appropriate Formulation(s)
- Timing of Decision Making

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Q&A for Pediatric Development: Increasing Success and Overcoming Obstacles