EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/PDCO - General considerations on waiving requirements for pediatric investigations of same in class products

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Overview

Regulatory background

Challenges

Current approach and practical considerations

Conclusions

Background – EU Paediatric Regulation

Objectives:

- Improve the health of children:
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
- Achieve the above:
  - As **timely** as possible
  - Without unnecessary studies in children
  - Without delaying authorization for adults

Pillars:

- EMA and its Paediatric Committee (PDCO)
- Paediatric Investigation Plan (PIP)
- A system of **obligations** and **rewards**

Paediatric Investigation Plan (PIP)

Research and development programme framed around concept of **condition**

Quality
Pre-clinical
Clinical
} Marketing Authorisation

Tools like **deferrals, modifications** and **waivers** in place, intended to ensuring:

- timely evidence generation

while allowing:

- (re) focus of development efforts based on emerging evidence and potential changing needs over time

Challenges

Rarity of paediatric cancers may make it challenging to complete a paediatric development program in a setting with multiple same in class products.

- How to foster development approaches globally, able to best and timely address high unmet medical needs based on robust evidence.

- How to identify the most promising agents for timely initiation of (full) development in most appropriate target population based on mechanism of action, without discarding valuable candidates prematurely based on limited data, but to ensure data generation to support development(s) for most promising product(s).

Current regulatory strategy

- Creating a framework, involving all stakeholders and using all available regulatory tools, to take into account for progress of science, such that scientific evidence generation leads to evolving insights and prompts modifications of hypotheses and expectations.

- Optimal development efforts based on scientific data may lead to same in class products being initially subjected to equal obligations.

Current regulatory strategy

- While several PIPs could be agreed for same in class products, there is no expectation that all agreed PIPs will necessarily start at the same time or be all completed, let alone that all products will reach the market.

  - This takes into consideration the known high attrition rate at various stages of development and to increase chances of getting ‘at least one’ medicine authorised (and reimbursed).

Regulatory strategy – allowing for additional evidence generation as needed to support decision making

- Allowing for additional evidence generation as needed, to support decision making, (sometimes) involving repeated cycles of evidence considerations (as necessary) and revisited development efforts.

Regulatory strategy – allowing for additional evidence generation as needed to support (final) decision making

- Does not mean 'delaying' the agreement of regulatory development obligations until supporting evidence becomes available.

- To the contrary, it means to engage early (as per the Paediatric Regulation) in order to have predictability in terms of necessary (global) requirements and to ensure timely access for patients.

Practical considerations

Requests for product-specific waivers have to be based on one of the three existing legal grounds:

- disease or condition not existing in a specified age-subset
- likely lack of safety or efficacy
- lack of significant therapeutic benefit

If strong data are not available (yet), EMA/PDCO likely to take a full **waiver averse approach**, with sound evidence requested to be generated (eg by means of a focus on additional non clinical studies) to further support decision making on the ability to address unmet medical needs.

Practical considerations - likely lack of safety

For example:

- PI3K inhibitor for mature B cell malignancies [1]
- Hedgehog inhibitor for treatment of AML [2]
- Kinase inhibitor for treatment of benign soft tissue neoplasms [3]

1) https://www.ema.europa.eu/en/documents/pip-decision/p/0067/2020-ema-decision-18-march-2020-granting-product-specific-waiver-parsaclisib-emea-002696-pip01-19_en.pdf
2) https://www.ema.europa.eu/documents/pip-decision/p/0239/2018-ema-decision-15-august-2018-granting-product-specific-waiver-glasdegib-emea-002199-pip01-17_en.pdf
3) https://www.ema.europa.eu/documents/pip-decision/p/0044/2019-ema-decision-29-january-2019-granting-product-specific-waiver-pexidartinib-emea-001939-pip03-16_en.pdf

Practical considerations - likely lack of efficacy

For example:

- Checkpoint inhibitors for solid tumours (excluding melanoma) [1]
- Products targeting BCMA for treatment of mature B cell malignancies [2]
- Bruton TK inhibitors for treatment of mature B cell malignancies [3]

1) https://www.ema.europa.eu/en/documents/pip-decision/p/0207/2019-ema-decision-12-june-2019-acceptance-modification-agreed-paediatric-investigation-plan_en.pdf
2) https://www.ema.europa.eu/en/medicines/human/paediatric-investigation-plans/emea-002369-pip01-18-m02
3) https://www.ema.europa.eu/en/documents/agenda/agenda-pdco-agenda-19-22-april-2022-meeting_en.pdf

Practical considerations - what might constitute significant therapeutic benefit

For example:

- related to the route of administration or availability of a suitable age-appropriate formulation
- improved activity over standard of care shown by either extrapolation of adult data (if biologically relevant) or relevant non-clinical data.
- better target organ penetration or the ability to overcome clinically relevant resistance.
- the ability of a product to be more suitable for combination developments, e.g. due to concomitant toxicities or evidence of less short-term or potential long-term toxicities as compared to other same in class products.

Practical considerations – general reflections

- Regulatory decision making on each individual product on its own merits, based on the robustness and rigor of the (available) contextualised submitted scientific evidence.

- As development progresses, using pre-specified decision points, based on the (accumulating) evidence, obligations may be modified, reduced and even lifted later.

- Importantly, emerging promising data should be used to further fill the gaps in the development program identified/outlined in the initially agreed higher level PIP.

Conclusions on general considerations by EMA/PDCO:

- 'waiver averse' approach, waiving PIP requirements early only based on sound scientific justifications – *see examples*.

- bringing development efforts together into one arena to allow for timely and (re) focused collaborative evidence generation according to (emerging) needs.

- a PIP is not an isolated regulatory requirement and not a protocol, but a plan that can be modified in light of emerging scientific evidence (eg full waiver at later stage) – *see examples*.

- early interactions with regulators is key.

Conclusion

- To guide developers, discussions on conceptual framework on considerations potentially able to support waiving regulatory requirements of same in class products, at the right time important and of benefit.

Acknowledgements:
Franca Ligas, Giovanni Lesa, Ralph Bax

PDCO colleagues
particularly Koen Norga, Siri Wang and Karen van Malderen

FDA colleagues
particularly Gregory Reaman

Any questions?

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EMA/PDCO Non-clinical considerations in decision-making related to waiving requirements for paediatric investigations

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Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
May 11, 2022

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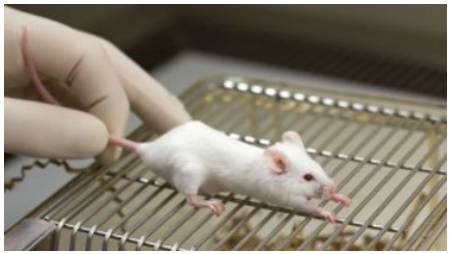
Introduction: Non-clinical data in oncology PIPs or waiver requests

- Pharmacodynamic data
  - Mode of action, anti-tumor activity in appropriate models, justification for combinations off-target effects
- Safety pharmacology
- Pharmacokinetics
- Repeat dose toxicity studies
  - Target organs, (ir)reversibility of the effects
- (Reproduction toxicology)
- (Genotoxicity)



PIP: Paediatric Investigation Plan

In humans as in other species, the major organ systems are not yet mature at birth and significant postnatal development occurs up to different ages

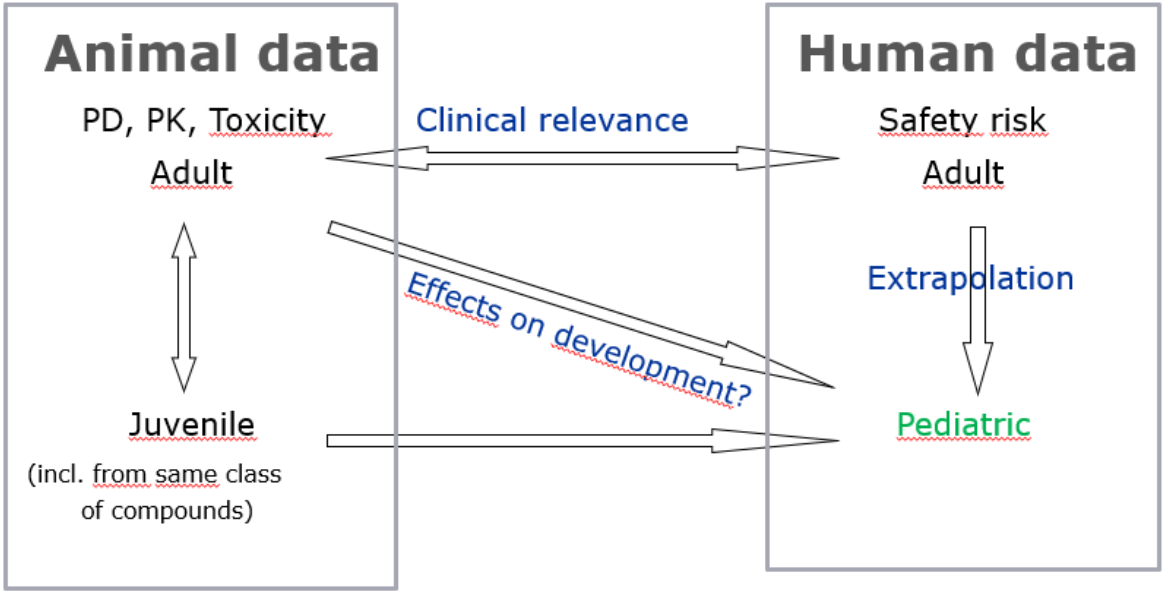
Table A1: age-dependent development of human organ systems

Milestones:	Birth		1st Solid Food	Weaning	Puberty	
Age Categories: / System:	Premature through full term birth	Neonate (Term Birth-27 days)	Infant/Toddler (28 days-23 months)	Child (2-11 years)	Adolescent (12-18 years)	Adult (> 18 years)
Cardiovascular	Critical neonatal physiologic transitions (pulmonary and vascular resistance, closure of fetal shunts)		Progressive increase in ion channels/conductance	Adaptive myocardial and vascular changes		
Endocrine	Fetal hormone production begins second trimester & structurally well developed at term Endocrine functions critical for growth/development			Adrenarche in late childhood	Pubertal sex hormone surge and maturation	
Eye	O_2-sensitive retinal angiogenesis	Morphologically well developed at term birth	Development of retina (fovea), lens, iris pigmentation complete by 1 year	Training of vision important between 1-4 years (focus and track at 1-4 months; color vision starts at 3 months)	Star sutures of lens form continuously during adolescence and into adulthood	
Gastrointestinal	Variable preterm suck/swallow reflex Critical functionality present in term neonates Acidification, transit, microbiome		Increased digestive functionality, and absorptive capacity with growth	Progressive adaptations in digestive function to accommodate shift in diet/complexity		
Hepatobiliary	Structurally well developed at term Important neonatal transitions in bile production and elimination		Important increases in metabolic and elimination capacity	Continued refinement of metabolic and elimination function and capacity		
Immune	Neonatal structural expansion of primary and secondary immune tissues		Progressive population of immune tissues and development of memory as a function of time and environment			
Integument	Cornification & vernix	Critical neonatal function (barrier, water, thermoregulation, sensation) High surface area relative to weight as compared to adults		Progressive surface acidification, local microbiome and immune function Pubertal hair growth, oil production		
Nervous	Neuronal subsets defined and active excitatory signaling initial myelination	Maximum neuron count and brain:body weight at term birth Myelin and glia present at term birth with continued refinement Postnatal neuronal apoptosis, synapse pruning, migration and circuit integration Metabolic functions, neurotransmitter and conduction systems mature at variable rates		Refinement of sensorimotor control and expanded capability for complex learning and memory function		CNS development continues into adulthood
Pulmonary	Critical liquid → air transition at birth Canalicular→saccular→alveolar structure Surfactant made preterm, secreted at term		Alveolization progresses	Increased alveolar surface area with growth to maximum aerobic function in adolescence		
Renal	Nephrogenesis not complete until term		Increases in renal function GFR precedes concentration	Tubular growth and refinement of function including erythropoietin and angiotensin axis		
Reproductive	Oocyte meiosis & testicular descent	Testes descended Postnatal HPG surge of sex hormones ('mini-puberty')	Quiescent period		Sertoli cell expansion Breast development Spermarche/Menarche	
Skeletal	Growth plate development	Growth plates present at term birth Critical period of rapid growth driven by growth hormone and thyroid hormone		Slower growth	Pubertal growth	Growth plate closure

+ Pharmacokinetic (PK) differences
+ Age-related pharmacodynamic (PD) responses

3 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s11-nonclinical-safety-testing-support-development-paediatric-pharmaceuticals-step-5_en.pdf

Assessment of product-specific waivers based on the grounds of lack of safety



To be conducted at the time of initial PIP submission, but reassessed if there are new safety signals in nonclinical or clinical studies, changes in drug product formulation and/or indications

CSF 1 receptor inhibitor

Treatment of symptomatic Tenosynovial Giant Cell Tumour (TGCT)

Full waiver; from birth to pre-pubertal children on the grounds of lack of safety

- Adverse effects observed in rodent studies
- Role of targeted receptor during paediatric development
- Existing standard of care (surgery)
- Full waiver for same in class CSF1R inhibitor (in different condition) based on safety concerns

https://www.ema.europa.eu/en/documents/agenda/agenda-pdco-agenda-18-21-january-2022-meeting_en.pdf

CSF: Colony-stimulating factor

Multi-Tyrosine kinase inhibitor (TKI)

Treatment of soft tissue sarcomas / Treatment of Ewing sarcoma

Waiver requested <12y for lack of safety, based on MoA and concerns known for other TKI inhibitors

Effects on developing organs expected based on MoA and off-target effects

Tyrosine kinases inhibited by different TKI and their potency varies

Waivers for some (but not all) same in class products in youngest age range (i.e. 6 months or 2 yrs) supported by lack of tolerability in juvenile animal toxicity studies

Outcome: **No waiver**, deferral. **Further non-clinical studies requested** to generate additional evidence supporting development OR waiver in 0 to <12y age range

https://www.ema.europa.eu/en/documents/agenda/agenda-pdco-agenda-22-25-february-2022-meeting_en.pdf

MoA: Mode of action

SMO/Hedgehog inhibitor

Treatment of AML in children **2 to <18 years**

Full waiver granted, on the grounds that the specific medicinal product is likely to be unsafe (in children from birth to closure of the epiphyses)

Based on pre-clinical irreversible adverse effects complemented with clinical data available for other SMO inhibitors

SMO: Smoothened

https://www.ema.europa.eu/documents/pip-decision/p/0239/2018-ema-decision-15-august-2018-granting-product-specific-waiver-glasdegib-emea-002199-pip01-17_en.pdf

RET-inhibitor

Initial PIP

Treatment of paediatric patients with RET-altered, locally advanced or metastatic, solid tumours or primary central nervous system (CNS) tumours.

Partial waiver for infants < 6 months for lack of significant therapeutic benefit

Several non-clinical toxicity studies planned

1 clinical study in patients 6mo to less than 18y

Modification

Staggered development <12y based on emerging non-clinical data indicating lack of tolerability at clinically relevant exposure levels

https://www.ema.europa.eu/en/medicines/human/summaries-opinion/retsevmo-0

https://www.ema.europa.eu/en/documents/pip-decision/p/0369/2019-ema-decision-8-november-2019-agreement-paediatric-investigation-plan-granting-deferral-granting_en.pdf

RET: Rearranged during transfection

NK1 receptor antagonist

Initial PIP

Prevention of chemotherapy-induced nausea and vomiting; from **6 months to <18y**

Modification

Full waiver for all subsets of the paediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product is likely to be unsafe.

- New non-clinical data indicating irreversible adverse findings to organs under development
- Availability of other NK1 receptor antagonists aprepitant & foserepitant with less severe tox profile

NK1: Neurokinin 1

https://www.ema.europa.eu/en/documents/pip-decision/p/0194/2020-ema-decision-15-may-2020-acceptance-modification-agreed-paediatric-investigation-plan_en.pdf

Conclusions

- Regulatory decision making on each individual product, based on the robustness and rigor of the available scientific evidence
  - Based upon available pharmacodynamic, pharmacokinetic, and toxicology data on the compound itself or from same class of compounds
  - Taken into account maturation of the organ/systems : literature or actual data (eg receptors ontogeny)
  - Understanding of the overall clinical development plan and clinical experience from same class products
- As clinical development progresses, adjustments to the plan can be made based on all the available data at that time
- The decision can be different for different applications of the same drug product depending on target population (incl age, indication, duration of treatment…)

Conclusions

- Use of data from compounds of the same class
  - Cautiousness when extrapolating results from one multi-TKI to a « similar » one.
  - Unexpected toxicities not related to primary pharmacology have occured

- Waiving PIP requirements early only based on sound scientific justifications – *see examples*
  - When serious safety concerns arise, waivers are usually requested for the youngest patient population where medical needs are
  - More efforts should be undertaken to understand the clinical relevance ie. when the reason for greater sensitivity or significant differences in toxicity is not understood, additional investigations guided by review of available ADME, safety and developmental biology knowledge can be useful for the interpretation of these differences

Acknowledgements:
Dominik Karres, Franca Ligas

PDCO and NcWP colleagues

Product quality and formulation considerations in decisions related to pediatric investigation of same in class agents

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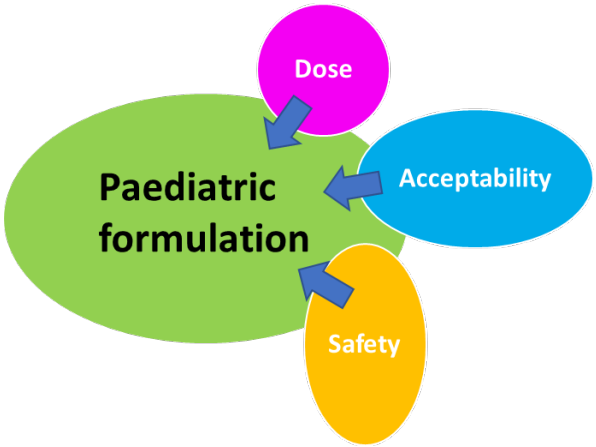
Basic formulation principles



- Formulation that
  - gives accurate **dose**
  - is **safe**
  - is **acceptable**

  ➢ ***for the full target age range***
  potentially in need of the product for the specific condition

- Requirement for appropriate formulations being the **default**

Prioritisation based on --

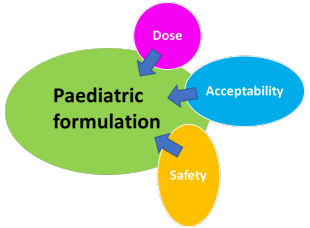
Route of administration?

Pros and cons driven mainly by condition/line/phase etc., but also other factors

- E.g.

Oral		Parenteral
Home treatment ☺	**Practicalities**	☹ Hospital treatment
Non invasive ☺	**Invasiveness**	☹ Invasive
Easier access? ☺	**Accessability of treatment**	☹ Can be limited?
Delay if paed formulation to be developed ☹	**Timely development**	☺ No delay if same formulation as adults
Depending on marketing strategy re paediatric formulation ☹	**Timely availability**	☺ No delay

Prioritisation based on --
Formulation characteristics?



- Adult formulation **not suitable** for paed population
  - Acceptability, safety, appropriate dosing
  - → ***Generally not acceptable justification***
- Age appropriate formulation potentially **not feasible**
  - Technical challenges (taste masking, enteric coating, prolonged release approach, avoiding excipients with safety concerns etc.)
  - → ***Generally too early for such justification***
  - → *Later stage decision, if at all*
- Adult formulation particularly useful/relevant for children
  - Prolonged release, long acting substances, convenient administration, simplified treatment regimens/duration
  - → ***Discuss limiting/deleting deferral***

Rarely (initial) **waiver based on formulation aspects, - degree of deferral to be discussed**

Prioritisation based on --

Unmet need for formulation as such?

e.g.

Combination products (Fixed Dose Combination, FDC)

- Ex: Two intravenous substances, combined in one FDC
  - Already existing products for each components individually.
    PIPs for each components individually, also involving (this) combination treatment
  - Added value of the combination product?
  - *Not 'early stage' decision*
- Ex: Two oral substances, combined in one FDC
  - Only one of the components available as existing product
  - Waiver proposed < 6years,
    "unable to swallow tablets, development of age appropriate formulation unfeasible and resuspension impractical"
  - Concl: Waiver < 3months, age appropriate formulation proposed (oral solid formulation or granules/powder for oral liquid, + alt. strategies to enable the adult form until then)

‘Evolutionary approach’ - also for formulations

- Hard capsules, two strengths (size 2/18mm, size 0/21.7mm) for adults + adolescents 12y+
  - The hard capsules should be swallowed whole and must not be opened or dissolved since the contents of the capsule are very bitter
  - Paed dosing not yet fully clear
- At early stage / initial paediatric investigation plan (PIP):
  - A ‘placeholder PIP measure’:
    Age appropriate solid dosage form
  - The details of the age-appropriate form (including the formulation, excipients and type of palatability and acceptability studies to be conducted) to be agreed by PDCO before study initiation
- At later modification:
  - Details and specifics included
  - ‘Coated granules’, acceptability measures, nasogastric tube strategy etc.
- Evidence based & data driven

Conclusion

- **Rarely** (initial) **waiver based on (route,) formulation or quality aspects**
- Later modifications possible if/when data emerge (technical, unmet need+)

- **Early** consideration re strategies on age appropriate formulations is crucial
  - Timely progress of paed studies
  - Optimising clinical trial outcome (e.g. dose, compliance)
  - Timely authorisation also for the youngest

Acknowledgements:

Dominik Karres, Franca Ligas, Brian Aylward, PDCO colleagues

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Thank you for your attention

Norwegian Medicines Agency

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INVENTING FOR LIFE

An Industry Perspective on Waiving Requirements for Pediatric Investigations of Same in Class Products

Scott J. Diede, MD, PhD

Executive Director
Global Clinical Development
Merck Research Laboratories

Financial Disclosures

- I am an employee and shareholder of Merck & Co., Inc.

Outline

- RACE for Children Act
- Case study: Anti-PD-(L)1 inhibitors
- Challenges and opportunities
- Summary

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" when the subject of an initial NDA/BLA
- Focus on **accelerating** appropriate initial pediatric evaluations **early** in development timeline
- Legislation has stimulated extensive conversations and work in pediatric cancer
- Challenges on implementation still being resolved

RACE for Children Act

Consideration for granting of waivers

- If known (e.g., from studies conducted in adult humans or animals) or strongly suspected (e.g., based on target biology) serious toxicity of a drug precludes its use in all or one or more pediatric age groups
- If there are known (e.g., from studies conducted in adult humans or animals) or strongly suspected (e.g., based on target biology) severe developmental toxicities which may present an unreasonable risk to pediatric patients of a particular maturational stage
- When a sponsor is not able to develop an appropriate pediatric formulation for an age group

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act, Guidance for Industry, May 2021.

RACE for Children Act

Consideration for granting of waivers

- For studies of subsequently developed (i.e., later-generation) products with the identical mechanism of action when ongoing, competing studies in the pediatric population are being or have been conducted and when there is no convincing evidence that the new active ingredient would provide a superior pharmacologic, toxicity, or activity profile when compared to products with the same molecular mechanism of action already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation
- When a drug or drugs with the same mechanism of action directed at the same molecular target expressed in the same cancer(s) in children has/have failed to demonstrate evidence of activity

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act, Guidance for Industry, May 2021.

RACE for Children Act

- One challenge is how we prioritize studies of several similar targeted therapies in the same pediatric population.
  - There is a limited number of pediatric patients and there should be a reasonable expectation of direct benefit for the patient
- Mechanism to help Sponsors clarify initial Pediatric Study Plan (iPSP) requirements with Agency
  - Early Advice Meetings (Type F)
  - Scheduled and held within 30 days of request

Case Study: Anti-PD-(L)1 inhibitors

- The use of immune checkpoint inhibitors, such as anti-PD-1 (programmed cell death-1) or anti-PD-L1 (programmed cell death-1 ligand 1) blocking antibodies, has led to improved outcomes in a wide variety of adult cancers
- Three pediatric Phase I/II studies studying atezolizumab, nivolumab, or pembrolizumab were initiated within 9 months of each other in 2015
- Data from approximately 250 patients were discussed at a meeting in September 2018 jointly organized by ACCELERATE and the European Medicines Agency (EMA)

ACCELERATE Paediatric Strategy Forums

- Created to evaluate science, facilitate dialogue and provide an opportunity for constructive interactions on specific topics requiring open discussion on development of medicines in the best interests of children and adolescents with cancer
- Multistakeholder
  - patients/patient advocates
  - clinicians
  - academics
  - biotechnology/pharmaceutical companies
  - regulators

ACCELERATE Paediatric Strategy Forums

Key conclusions of the Paediatric Strategy Forum

- High rate of activity of monotherapy checkpoint inhibitors, including complete responses, were observed in Hodgkin lymphoma and hypermutant tumors
- Very limited activity of checkpoint inhibitors as single agents in other pediatric tumors (overall response rate ~2.8% with Hodgkin lymphoma excluded)

Pearson ADJ, et al. European Journal of Cancer 2020;127:52–66.

ACCELERATE Paediatric Strategy Forums

Key conclusions of the Paediatric Strategy Forum

- There is no benefit to children to be included in new monotherapy trials of other checkpoint inhibitors with the *same* mechanism of action unless there is more scientific knowledge
- Academic-industry consensus on the scientific merits of a proposal before submission of a pediatric investigation plan would be of great benefit to regulators

Pearson ADJ, et al. European Journal of Cancer 2020;127:52–66.

Challenges / Opportunities

- How should multiple same in class products be developed simultaneously?
  - How many different therapeutics should initiate pediatric trials?
- Global collaboration is essential for pediatric drug development
  - Limited number of relapsed/refractory pediatric patients requires trials to have a global footprint
- How best to coordinate between different health regulatory agencies?
  - Ideally granting of waivers would be consistent across agencies
  - Sponsors should consider simultaneous submissions of iPSP and Pediatric Investigation Plan (PIP)
  - Planning and early interactions are key

Challenges / Opportunities

- Mechanisms to facilitate coordinated, global approaches to pediatric development
  - Pediatric Cluster Teleconferences
  - Common Commentary Process
  - Formal Parallel Scientific Advice
  - International multi-stakeholder meetings

Summary

- Global trials are essential to be able to find rare patients and answer scientific questions in an efficient manner
- Obtain multistakeholder input
- Early communication with regulatory agencies is key and Sponsors should take advantage of the variety of mechanisms that are available
- Strategy and resultant regulatory requirements should be driven by the science