

# Showing Efficacy in Treating Rare Pediatric Tumors: Introduction to European Regulatory and Scientific Support Available to Investigators

# 2

Ralf Herold and Jordi Llinares

## Contents

<b>2.1</b>	<b>General Perspectives on Rare Malignant Diseases</b> .....	15
<b>2.2</b>	<b>Scientific-Regulatory Guidances</b> .....	17
2.2.1	Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005).....	17
2.2.2	ICH Topic E 11: Clinical Investigation of Medicinal Products in the Pediatric Population (CPMP/ICH/2711/99).....	18
2.2.3	Addendum on Pediatric Oncology (CPMP/EWP/569/02).....	20
2.2.4	Summary and Further Guidances.....	21
2.2.5	Further Guidances.....	22
<b>2.3</b>	<b>Orphan Medicine Designation</b> .....	22
2.3.1	Implications for Rare Tumors in Children.....	23
2.3.2	Rationale for Development.....	24
2.3.3	Significant Benefit.....	24
<b>2.4</b>	<b>Incentives</b> .....	25
<b>2.5</b>	<b>Opportunities for Scientific and Regulatory Interactions on Pediatric Oncology Developments</b> .....	27
<b>2.6</b>	<b>Collaborative and Organization Aspects of Conducting Trials in Small Populations</b> .....	28
<b>2.7</b>	<b>Lack of Efficacy</b> .....	29
<b>2.8</b>	<b>Conclusions and Outlook</b> .....	29
<b>2.9</b>	<b>Suggested Further Reading and Resources</b> .....	30
	<b>References</b> .....	30

R. Herold (✉)  
Pediatric Medicines, European Medicines Agency (EMA), Canary Wharf, London, UK  
e-mail: ralf.herold@ema.europa.eu

J. Llinares  
Orphan Medicines, European Medicines Agency (EMA), Canary Wharf, London, UK

## 2.1 General Perspectives on Rare Malignant Diseases

The demonstration of safety and efficacy of a medicinal product or a medical treatment in cancer raises vastly different problems. In frequent cancer types, for example, lung carcinoma or breast carcinoma, such a demonstration is usually feasible within a short period of time, in a relatively large number of patients, although medicines' effect sizes are often modest and cure is seldom achieved despite multimodal treatment schemes.

In contrast, rare cancers discussed in this book generally create a dilemma on how to balance the small size of the patient populations with the strength of evidence that can be achieved and produced reliably. Additionally, rare tumors represent long-standing and unmet therapeutic needs, as no treatment schemes are established for many of them and, at best, only monotherapies are available.

This dilemma and the scientific challenges associated with the treatment of rare tumors have received special attention in Europe's pharmaceutical legislation and its application:

- Several European scientific guidelines are available: in oncology, on hematological malignancies, on pediatric oncology, on pediatric medicines, on small populations, and on adaptive design trials, in addition to the International Conference for Harmonization (ICH) guidance. The guidances are primarily aimed at pharmaceutical development, but can be useful to all clinical research using medicines. The paradigm is that the type of evidence that can change medical practice should be same to support the demonstration of efficacy and safety of a medicine, and

vice versa. The guidances generally apply, irrespective of whether research is performed in pediatric or adult patients, but increasingly, the guidances produced include specific pediatric recommendations.

- In order to encourage the application of the European scientific guidances for the development of medicines, several incentives have been introduced in Europe.
- Two different types of marketing authorization were created, which can be used in situations where not all data normally included have been submitted. The conditional marketing authorization can be granted where some evidence for a positive benefit–risk balance already exists and further supportive data will be made available in the near future. The marketing authorization under exceptional circumstances can be granted where further supportive data cannot be generated because, for example, the population affected is too small to provide robust data. The two types of marketing authorizations cannot be combined for the same product. In fact, the conditional marketing authorization is changed into a regular authorization, as soon as the remaining data have been submitted. The conditional marketing authorization and the marketing authorization under exceptional circumstances are both potentially applicable to pediatric medicines. Where an authorization already existed, any additional pediatric indication becomes part of that authorization, rather than being authorized separately. Scientifically sound development generally should provide data that permit to place a new anticancer medicine into medical practice, but this is not a strict regulatory criterion for marketing authorization.

The following principal design features are often discussed for clinical trials intended to generate efficacy and safety evidence in rare tumors:

- *Patient population and inclusion criteria:* Pediatric oncology studies may include patients from different lines of treatment, having largely different previous cumulative exposures to anticancer medicines. A balance should be sought between including a sufficient number of children to obtain conclusive data in subsets from early therapeutic settings that are well-recognized in medical practice and including patients from various lines of treatment or palliative therapeutic settings. This may also be applicable to dose-finding studies, in which differences in tolerability may or may not be related to

previous treatment exposures (Smith et al. 1998; Raphaël et al. 2010).

- *Efficacy endpoints:* Experience with efficacy endpoints, including time to event and response endpoints, exists since long in pediatric oncology trials. The time to event endpoints are generally applicable also to rare tumors, but the clinical importance of response may be less known in rare tumors. The progression-free survival (PFS) can be an appropriate primary efficacy endpoint in rare tumors, as tumor progression may indicate a clinically relevant symptomatic progress. For new medicines such as those with targeted or cytostatic effects, the PFS endpoint may represent a different meaning than for known cytotoxic compounds, as there may be differences in the components of PFS such as in treatment-related toxicities and deaths as well as in indicators of progression. In order to understand such differences, details of toxicities and of the treatment course after progression should be well documented. The specific guideline on PFS as primary endpoint in confirmatory trials covers further aspects including the importance of assessment schedules and the intention-to-treat principle toward censoring.<sup>1</sup>
- *Controlled or uncontrolled?* A dilemma is created by the well-rehearsed statement, “If the evidence is strong enough, then a randomized controlled trial is not needed.” Before a trial, the size and strength of the treatment effect cannot be judged. This statement then is rarely helpful when testing a medicine with a novel mechanism of action for a rare tumor, and even less so when the tumor biology is dissimilar in adult and pediatric patients. Historical (external) controls are often considered as a substitute for internal controls, but suffer from heterogeneity (e.g., molecular diagnosis, risk allocation, treatment) particularly in rare tumors. This may make comparisons statistically unreliable, with a significant risk that the study becomes inconclusive. Medical practice evolves continually in terms of methods of diagnosis and standards of antitumor and of supportive care, with the consequence that historical controls have not received what is the best available standard of care. The standard of care normally serves as control in clinical trials, on top of

<sup>1</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2009/12/WC500017749.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500017749.pdf)

which new medicines can be tested. If there is genuine uncertainty as to whether the standard of care is actually effective, then the best investigator's choice could be used as active comparator. Differences between trials, and between trial participants and non-participating patients, are known as trial effect. The trial effect diminishes any usefulness of external controls, although a trial effect may be less relevant for adult (Peppercorn et al. 2004), pediatric (Koschmann et al. 2010), or true population-based cancer trials. In the oncology literature, there is an ongoing debate of the usefulness of uncontrolled studies. The debate also concerns pediatric trials of infrequent malignant diseases, which are particularly criticized for their poor value in estimating a treatment effect (e.g., see Ratain 2010).

The following section presents scientific-regulatory guidelines addressing the principal design questions.

---

## 2.2 Scientific-Regulatory Guidances

The European Medicines Agency, as well as other regulatory agencies worldwide, and the International Conference of Harmonization (ICH) regularly issue guidance setting out the scientific rationale for regulatory requirements and recommendations on how to develop medicines, including how to design, conduct, and analyze clinical trials. The guidances are based on the experience gathered with successful and, maybe more importantly, with unsuccessful medicine developments.

The European Medicines Agency develops guidance on the basis of the applicable pharmaceutical legislations, and invites all stakeholders to comment during a public consultation phase. Guidances are made publicly available,<sup>2</sup> including guidance on evaluation of applications for Paediatric Investigation Plans (PIPs).<sup>3</sup> The scientific-regulatory guidances for development of medicines represent an overarching European view, independent of countries and health care systems, which each may have issued local treatment guidelines.

---

<sup>2</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000085.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac0580027549](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac0580027549)

<sup>3</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000293.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91#section3](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91#section3)

There are several ICH guidances which apply in particular to anticancer medicinal products, such as E6 (R1) "Guideline for Good Clinical Practice," E11 "Clinical Investigation of Medicinal Products in the Pediatric Population," E8 "General Considerations for Clinical Trials," E9 "Statistical Principles for Clinical Trials," E10 "Choice of Control Group in Clinical Trials," and E4 "Dose Response Information to Support Drug Registration." However, only the ICHS9 guideline is specific to the "Nonclinical evaluation for anticancer pharmaceuticals."

The ICHE3 guidance on the "Structure and Content of Clinical Study Reports" is of particular relevance to academic investigators collaborating with pharmaceutical companies, as it describes how to present the data that are submitted in applications for marketing authorization.

Three scientific-regulatory guidelines have been selected for the next sections. The aim is not to interpret the guidances, but rather to present the most relevant aspects, with the hope of encouraging a full reading of the documents and their application to pediatric oncology to improve the process of finding the best possible approaches and designs to investigate anticancer medicines in children.

### 2.2.1 Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)<sup>4</sup>

This guideline was created in an effort to summarize how the most convincing evidence could be generated by trials performed in a clinical setting where only a small number of patients and potential trial participants are available. The guideline came into effect in 2007 and it not limited to a specific therapeutic area. There is no similar guidance in other regions; therefore, pharmaceutical companies may have limited experience of this guideline, if pediatric oncology trials were only conducted in the USA.

The key principle is that a prospective plan should be set out to develop a medicine. The plan should cover the design, as well as the individual and combined analyses of all studies. The medicine's effects should be explained as much as possible by the study data.

---

<sup>4</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003615.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf)

Wherever possible, the plan should include collecting non-clinical data, e.g., by studying disease-specific models, dose-response relationships, and tumor dependency. The plan should aim to maximize the information from clinical trials, by prolonged follow-up, by maintaining participants in the trial even after discontinuation of the study medicine, and by balancing the trial-related burden to reduce patient dropout. Additionally, there should be attempts to explain the variability of the medicine's effect by characterizing the factors that introduce uncertainty, such as molecular target changes and associated pharmacodynamic differences, or insufficiently explored relationships of dose and treatment schedules with response. A further cause of variability observed in pediatric patients could be the dose (in-) accuracy, if an age-appropriate formulation that permits precise dosing was not used in the trial.

Some designs of clinical trials discussed in the guideline may be useful in pediatric oncology, namely those using response-adaptive methods, sequential designs, or Bayesian approaches (for design and analysis). All aim to maximize the statistical efficiency of the design. However, the guideline states that for measuring the treatment effect, a randomized controlled study with low statistical power may be preferable to uncontrolled studies.

The guideline also makes recommendations on the choice of endpoints, and how data from different sources could be collected to support a surrogate endpoint.

Excerpts of the guideline are provided in Table 2.1.

One of the main messages of the guideline is to avoid looking at pediatric oncology, in particular investigator-initiated trials in isolation. Instead, clinical trials in adult patients, the full set of non-clinical studies, and region-wide patient registries should be set out in advance in the development plan. The plan could focus on more than one medicine, to be used in sequence or in combination, or from which the best one is to be selected, and the plan should include approaches that are centered around the malignant pediatric disease.

Discussions of the plan in regulatory interactions are encouraged, as explained below, especially when alternative designs are considered, or randomized controlled trials are considered not feasible and only case series (external controls) or anecdotal case reports are available. Questions to regulatory authorities should focus for example on the choice of surrogate endpoint, any lack of randomization, or lack of control group. Although there is no defined format for such plan, the

structure of Paediatric Investigation Plans<sup>5</sup> could be used, and developed if necessary.

The guideline on clinical trials in small populations does not mention extrapolation of efficacy. However, extrapolation could be used in a plan including well-designed studies in one population, to support the extension of efficacy results to a different target population. This may be justified if for example the target population is perhaps more vulnerable or particularly small. It is still necessary to study pharmacokinetics and safety in an uncontrolled design. Using extrapolation of efficacy is relevant for pediatric medicine development and will be discussed for the next pediatric guideline.

## 2.2.2 ICH Topic E 11: Clinical Investigation of Medicinal Products in the Pediatric Population (CPMP/ICH/2711/99)<sup>6</sup>

Two principally different situations can be envisaged when considering the development of a medicine for use by the pediatric population. Both are addressed in the E11 guideline, which came into operation already in 2001 in the regions of the ICH (Europe, United States, and Japan).

- Firstly, the condition exists in adult and pediatric populations. This should trigger considering whether efficacy in pediatric populations can be extrapolated from adult or other relevant populations. The guideline presents several criteria for deciding if extrapolation is a valid option, and it indicates how to carry out extrapolation. While extrapolation does not generate data, which on their own allow to evaluate the benefit–risk relationship, this approach may allow to reduce the number of trial participants and therefore to protect them from the clinical trial burden. Extrapolation is encouraged whenever scientifically sound and justified.
- Secondly, the condition only exists in the pediatric population without a similar disease in adults. In this case, the guideline defines the safety and non-clinical

<sup>5</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b91)

<sup>6</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002926.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf)

**Table 2.1** Highlights of the Guideline on clinical trials in small populations

Subtopic	Guidance text
Choice of control groups	Ideally, we wish to obtain an unbiased estimate of the effect of the treatment being investigated compared to placebo or to another active compound and, for this reason, every effort should be made to randomize patients from the beginning of the therapeutic testing phase. The goal of obtaining an unbiased estimate of the size of effect is true in studies in small populations as well as large trials for common diseases.
Use of placebo	In cases where there is no existing treatment, even in life-threatening diseases, the use of placebo as a comparator should be considered. Where a placebo control may not be possible, an appropriate control group may be “best standard of care.” When other treatments are available, then an active comparator could be used as control group. However, if the active comparator does not have its own good evidence base, then superiority to that comparator will usually be necessary.
Statistical analysis and result presentation	In almost all cases, confidence intervals of estimates of the treatment effect are much more informative than <i>P</i> -values.
Intervention-response relationship	The credibility of study results may be enhanced if a dose-response relationship is seen or in cases where a chain of events can be identified (for example, drug exposure to target occupancy, to pharmacodynamic measures, to clinical outcome). Cases where no such clear chain of events exists are much less convincing and will increase the data requirements regarding robustness and persuasiveness of study results.
Development plan for studies	In very rare disorders, it is important that every patient participating in a study contributes as much information as possible to make a benefit–risk assessment possible. Therefore, the well-planned use of the best available techniques to obtain and analyze information is crucial. This applies throughout the study process from pharmacokinetic and pharmacodynamic modeling to handling and analyses of biopsy material.
Disease models and non-clinical data	Detailed knowledge of the pathophysiology of the disease and the pharmacology of the drug will facilitate the design of efficient clinical studies and will help determine the amount of clinical data required. For rare diseases, preclinical pharmacodynamic studies can be of importance if there exist adequate animal models and may be informative for the design of clinical studies. Such studies may also give important information for dosing and/or route of administration and the investigation of these features in man can be focused.
Choice of endpoints	In other cases, the mode of action of the test treatment may not be well enough known to predict which of several possible outcomes will be affected. In such circumstances, the usual approach of pre-specifying the primary endpoint may be too conservative and more knowledge may be gained from collecting all sensible/possible endpoints and then presenting all the data in the final study report.
Surrogate endpoints	In the context of rare disorders for a given clinical endpoint or validated surrogate endpoint, recruitment of a sufficient number of patients would be difficult or demonstration of this endpoint would take an unreasonable length of time. Then use of other surrogate markers as substitutes for a clinical endpoint may be considered. The term “surrogate endpoint” should only be used for biomarkers, which have been validated. However, selection of a surrogate marker as study endpoint requires it to be reasonably likely – based on epidemiologic, pathophysiologic, or other evidence – to predict benefit. Prediction in itself may not be sufficient to establish efficacy. Considerations should include: <ul style="list-style-type: none"> <li>• How closely changes in the surrogate endpoint are causally linked to changes in a clinical endpoint or symptom.</li> <li>• How much risk is associated with the therapy</li> <li>• What other therapies (if any) are available for the same condition</li> </ul> Demonstrating that a surrogate endpoint adequately reflects the true clinical endpoint is difficult. Epidemiological data and data from patient registers may provide some help.
Ethical considerations	The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results, the latter being the most important. In situations where obtaining controlled evidence on the efficacy and safety of a new treatment is not possible, the regulatory assessment may accept different approaches if they ensure that the patients’ interests are protected.
Surrogate endpoints	Surrogate endpoints may be acceptable but need to be fully justified. Their relation to clinical efficacy must be clear so that the balance of risks and benefits can be evaluated.
Patient registers	Patient registers may supply important information on the natural course of disease and may help in the assessment of effectiveness and safety. Furthermore, such registers can be used as a source for historical controls. Registers used in this way should contain high-quality data; GCP inspection might be anticipated.

data that should be available before pediatric trials. A number of malignant diseases may occur principally but not exclusively in children, such as neuroblastoma and medulloblastoma. In contrast, rhabdomyosarcoma is more complex, as evolving biological characterization allows to subdivide soft tissue sarcomas, among which a number of subtypes may occur in adults. A first joint pediatric-adult symposium on drug development was held recently following the scientific debate on the most appropriate separation of adult and pediatric soft tissue sarcomas.

The guideline refers to the similarity of adult and pediatric conditions as a basis for the recommendations as to when pediatric clinical trials should be initiated relative to adult trials. However, it is not clear how to define and judge similarity. Some characteristics to compare pediatric and adult populations are listed in the addendum on pediatric oncology (presented below). The timing of initiation should take into account if there are available and/or authorized treatments for children. Accordingly, in a condition that occurs in children and adults and is life-threatening with no or limited treatments, pediatric trial(s) should start as early as after the “assessment of initial safety data” and “reasonable evidence of potential benefit” from adult studies. Even when a condition affects predominantly or exclusively the pediatric population, as is the case for the majority of pediatric malignant diseases, pediatric trials should commence once initial safety and tolerability data have been obtained, usually in adults. The guideline also states that results of pediatric trials should be part of the initial marketing authorization application.

The guideline recommendations can be implemented according to the European pediatric legislation, Regulation (EC) No 1901/2006, which requires a submission of a development plan as early as after the pharmacokinetic studies in adults, so when adult development is progressing to exploratory therapeutic studies.

The guideline’s considerations on extrapolation of efficacy were recently incorporated into a tool box for dynamic decision making and the optimization of pediatric clinical trials (Manolis and Pons 2009). For example, modeling and simulation can help to judge similarity of conditions in adults and children and to investigate factors that influence intervention-response relationships in adults and children. The inclusion in Paediatric Investigation Plans (PIPs) of such techniques was investigated (Manolis et al. 2011). Pharmaceutical companies have extensive experience in advanced biometrical

and statistical methods to optimize drug development studies, while experience with such methods for pediatric clinical trials may be limited. Out of 210 agreed PIPs, 47 made reference to modeling and simulation. As an example of such approaches in rare pediatric tumors, the PIP for imatinib requires both the “development and validation of an integrated physiology-based pharmacokinetic (PBPK) or population pharmacokinetics model” and a “measure to extrapolate efficacy to the pediatric population” for the treatment of Kit (CD 117)-positive gastrointestinal stromal tumors and dermatofibrosarcoma protuberans (EMA Web site ref EMEA/759693/2009, P/243/2009). The results of these studies will be the basis for the assessment of imatinib efficacy and safety.

The guideline also includes specific considerations on ethics, safety, and other critical issues in conducting trials in children. More detailed recommendations on ethics of pediatric clinical trials have been published (Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use 2008). These recommendations discuss, in particular, the decreasing ethical need for placebo when evidence in favor of an effective treatment increases. These recommendations apply to pediatric oncology, even though the academic community already makes efforts to account for the patients’ best interests and to safeguard patients from low quality studies.

Timely initiation of pediatric trials is also addressed in the following guidance, which is specific of pediatric oncology, covers early pediatric trials, such as dose-finding and initial exploratory therapeutic trials, but not how to demonstrate efficacy in specific pediatric malignant diseases.

### 2.2.3 Addendum on Pediatric Oncology (CPMP/EWP/569/02)<sup>7</sup>

This addendum is one of several addenda to the note for guidance on evaluation of anticancer medicinal products in man. It came into operation in 2004 and complements the ICH E11 guideline and a general anticancer guideline. It was drafted with the help of experts from the pediatric oncology community, who

<sup>7</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500003969.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003969.pdf)

had earlier on published detailed recommendations on inclusion criteria and how dose-limiting toxicities should be defined (Smith et al. 1998). The addendum requires careful selection of medicines for pediatric trials, based on “extensive testing of new agents in predictive model systems of pediatric tumors at an early stage of preclinical development.” This should be carried out by sponsors, irrespective of the target of the development among adult malignancies.

The addendum discusses early dose-finding and therapeutic exploratory clinical trials in children, making recommendations for pediatric-specific aspects of trial designs: For example, the starting dose should be sufficiently high so that pediatric patients can expect some therapeutic effect. Furthermore, intra-patient dose-escalation should be considered when the maximum tolerated dose is not established and toxicity is not a limitation. This may apply to targeted and cytostatic medicines in contrast to cytotoxic medicines, which show maximum tolerated, normalized doses that are almost identical in pediatric and adult dose-finding studies (Lee et al. 2005).

The addendum also addresses how anticancer medicines could be authorized for pediatric patients. A use approved in adults should be extended to the same cancer in children, after consideration of potential differences such as genotypic and phenotypic features, non-clinical activity, human pharmacokinetic and/or pharmacodynamic data on tumor markers, and the available and/or used therapeutic options. The addendum emphasizes the need for a sufficient number of patients studied, with a sufficient number of samples to determine the medicine’s pharmacokinetic profile in all the relevant age groups of children.

However, the addendum does not address efficacy trials on rare tumors, although it acknowledges the rarity of the majority of pediatric malignancies.

#### 2.2.4 Summary and Further Guidances

Based on the three guidances presented in this chapter, three major approaches to establish efficacy in the treatment of rare tumors in children can be identified, although not the sole conclusions of the guidances. The guidances encourage to interact with scientists in regulatory authorities on the proposed development plans when alternative approaches to conventional efficacy trials may be considered.

- *Extrapolation of efficacy*: Extrapolation of efficacy as outlined in the preceding sections requires availability of adult data from well-designed and -conducted studies in a therapeutic setting that is relevant to the pediatric population. The necessary pediatric trials should focus on pharmacokinetics (PK), preferably using a PK model, and should document the tolerability, safety, and the acceptability of the formulation. Such a trial would normally collect any clinical activity and efficacy indicators, but would not need to be blinded, nor to include an internal control. The trial may be initiated before completion of the adult studies, depending on the strength of the biological rationale and the therapeutic exploratory studies in adults.
- *Bayesian approach based on quantitative assumptions*: This approach would not necessarily require pediatric trials to be powered for testing a superiority hypothesis (e.g., using a log-rank test), but outcome distributions would be combined with prior assumptions (e.g., on progression-free survival or on log-rank test values), and the inference would be the probability for the tested medicine to be beneficial or effective. Although Bayesian designs have rarely been used in submissions for marketing authorization at the European Medicines Agency so far, such approaches are welcome in Paediatric Investigation Plans, or in Scientific advice, as expressed in guidances described in this chapter. This approach has been suggested for rare tumors, on the basis of a theoretical example from pediatric oncology (Tan et al. 2003). In certain situations, a Bayesian approach is close to a prospective meta-analysis as particularly proposed for pediatric oncology (Valsecchi and Masera 1996). Bayesian approaches may be considered for controlled trials, but can also be implemented in single-arm trials (e.g., Thall et al. 1995) with the aim to inform therapeutic confirmatory trials. Bayesian methodology lends itself to a range of practical applications in clinical trials, their design and/or analysis, in early or late phases of development, and for large or small trials.
- *Small self-standing controlled study in relevant population, using multiple endpoints including pharmacodynamic and clinical outcomes*: In the long-standing scientific debate on the ethics of underpowered and thus potentially inconclusive trials, the two preceding sections may be the only justified approaches according to (Halpern et al. 2002). It is however

recognized that small *randomized* trials may be the “only way that any *unbiased* [emphasis added] measurements of effectiveness can be made.”<sup>3</sup> In purely pediatric malignant diseases (e.g., neuroblastoma), adult data would not be relevant or might not exist. The small controlled trial would unavoidably be unique as it could not be repeated for confirmation. However, the trial results could be supported by a chain of evidence linking a strong biological rationale (e.g., tumor dependency and knock-out or disease models), xenograft pharmacology studies, dose-response relationships, and available clinical activity/efficacy data, if applicable, from biologically related systems (e.g., overall survival improvement for a cancer histologically unrelated but responsive to similar pathway modulation). The chain of evidence is similar to the pharmacological audit trail proposed for anticancer medicines (Sarker and Workman 2007). To compensate for the small size of the controlled trial, in keeping with general recommendations, the trial could be strengthened by reducing bias, e.g., by blinding, by central review, by meticulous trial conduct, and by inclusion of a broad set of supportive endpoints. With a view to minimizing the number of participants in a clinical trial, it may be possible to assume a large treatment effect, if this is the minimum clinically relevant, realistic effect of a novel medicine worth detecting in a rare tumor with unmet needs. Alternatively, a trial could be discontinued on the basis of futility analyses if the desirable treatment effect cannot be achieved.

### 2.2.5 Further Guidances

Other European scientific guidelines cover general methodological issues that are relevant to pediatric oncology.

- Methodological Considerations for Using Progression-Free Survival (PFS) as Primary endpoints in confirmatory trials for registration (CHMP/EWP/27994/08)
- Confirmatory studies in Haematological Malignancies (EMA/CHMP/EWP/520088/08)
- Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design (CHMP/EWP/2459/02)
- Missing data in confirmatory clinical trials (CPMP/EWP/1776/99 Rev. 1)

- Conduct of Pharmacovigilance for medicines used by the pediatric population (EMA/CHMP/PhVWP/235910/2005-rev.1)
- Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3)
- Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study (CPMP/EWP/2330/99)

The guidances can be accessed at <http://www.ema.europa.eu> – Regulatory – Human medicines – Scientific guidelines.

## 2.3 Orphan Medicine Designation

Rare diseases, including the majority of pediatric malignancies, occur so infrequently that the development of medicines for these conditions would be negligible without incentives. The development of a number of incentives was necessary to stimulate the development and placing on the market of medicinal products for the treatment, prevention, and diagnosis of those conditions. These incentives and the criteria to accept the potential use in a defined condition are set up in the different orphan regulations that exist in the world – among others, in the USA since 1983,<sup>8</sup> in Japan since 1993 (Haffner et al. 2008), in Australia since 1997 and in the EU since 2000.<sup>9</sup>

In the European Union, an active substance to treat, prevent, or diagnose a rare condition is designated as an orphan medicinal product according to the following criteria:

- Prevalence of the condition of not more than 5 per 10,000 persons, and either
- Demonstration of insufficient return on investment, or,
- Absence of a satisfactory, authorized method(s) of diagnosis, prevention or treatment, or, if such method exists, a justified assumption that the product will be of significant benefit to those affected by the condition.

<sup>8</sup>Developing Products for Rare Diseases & Conditions. <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

<sup>9</sup>Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products. Official Journal of The European Communities. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>



**Table 2.2** European marketing authorizations of orphan designated medicines in oncology (February 2011)

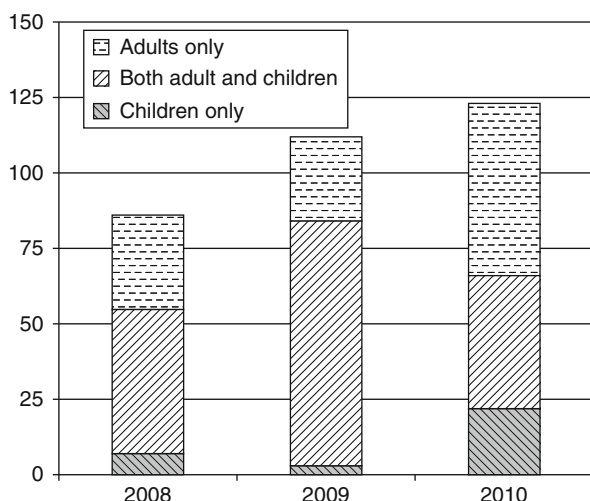
Product	Active substance	Condition/indication	Significant benefit shown at time of marketing authorization	Type of initial marketing authorization	Received Scientific Advice (Protocol Assistance)	Pediatric use (indication or dosing recommendation)
Glivec	Imatinib	Chronic myeloid leukemia	Yes	Exceptional circumstances	Yes	Yes
Trisenox	Arsenic trioxide	Acute promyelocytic leukemia	Yes	Exceptional circumstances	No	No
Busilvex	Busulfan	Hematopoietic progenitor cell transplantation	Yes	Normal	Yes	Yes
Onsenal	Celecoxib	Familial adenomatous polyposis	No	Exceptional circumstances	No	No
Litak	Cladribine	Hairy cell leukemia	Yes	Normal	No	No
Lysodren	Mitotane	Adrenal cortical carcinoma	Yes	Normal	No	Yes
Evoltra	Clofarabine	Acute lymphoblastic leukemia	Yes	Exceptional circumstances	No	Yes
Nexavar	Sorafenib	Advanced renal cell carcinoma	Yes	Normal	Yes	No
Sutent	Sunitinib	Gastrointestinal stromal tumor and metastatic renal cell carcinoma	Yes	Conditional	Yes	No
Sprycel	Dasatinib	Acute lymphoblastic leukemia and chronic myeloid leukemia	Yes	Normal	Yes	No
Atriance	Nelarabine	Acute lymphoblastic leukemia	Yes	Exceptional circumstances	No	Yes
Yondelis	Trabectedin	Soft tissue sarcoma	Yes	Exceptional circumstances	No	No
Tasigna	Nilotinib	Chronic myeloid leukemia	Yes	Normal	Yes	No
Torisel	Temsirolimus	Renal cell carcinoma	Yes	Normal	Yes	No
Ceplene	Histamine dihydrochloride	Acute myeloid leukemia	Yes	Exceptional circumstances	No	No
Mepact	Mifamurtide	Osteosarcoma	Yes	Normal	Yes	Yes
Vidaza	Azacitidine	Acute myeloid leukemia and myelodysplastic syndrome	Yes	Normal	No	No
Afinitor	Everolimus	Renal cell carcinoma	Yes	Normal	No	No

Table 2.2 compiles the anticancer medicinal products designated as orphan, and the related regulatory information such as whether significant benefit was maintained at the time of marketing authorization, and which type of marketing authorization had been granted.

### 2.3.1 Implications for Rare Tumors in Children

The criteria on prevalence for orphan designation refer to the entire population of the European Union, without any reference to subgroups even if the disease manifests itself exclusively in a subgroup. Therefore, conditions affecting children can be designated as

orphan when they affect exclusively children or are part of diseases that also occur in adults. In cancer, the situations where the histological and clinical characteristics of the cancer are distinct in children are frequent, making rare cancers in children a natural target for orphan designation. As the prevalence that these orphan conditions must not exceed is based on a calculation with respect to the overall population, if the cancer occurs only in children, the resulting prevalence will be well below the threshold for designation. In any case, since the implementation of the orphan regulation, diseases affecting children have represented a considerable proportion of the total number of designations as shown in Fig. 2.1. This has been particularly notable in 2010 where 18% of the opinions adopted were for conditions affecting children exclusively. On



**Fig. 2.1** Orphan medicinal product designations in the EU for pediatric and/or adult conditions by year

average the conditions affecting children represented only about 10% over the last 3 years.

Oncology is consistently among designated conditions, the most frequent therapeutic area in respect of numbers of designations (about 30% of the opinions) and at the time of marketing authorization. The same holds true for conditions affecting children, where the relative contribution in oncology is 117 out of the total of 388 opinions (32%) on orphan designation. Among the conditions designated as orphan in pediatric oncology, the most frequent were neuroblastoma, Ewing sarcoma, and medulloblastoma.

### 2.3.2 Rationale for Development

To obtain orphan designation, the sponsor has to demonstrate that the active substance is of potential therapeutic use in the condition, what is referred to as biological plausibility. Additionally, when other products are authorized for the condition, the sponsor has to demonstrate the potential significant benefit of the medicine. The sponsor is required to provide justifications for these two criteria based on data, although this requirement has to be balanced with the principle that applications for designation can be submitted at any stage during the product development. The fine balance between these two requirements is developed in the “Recommendation on elements required to support the medical plausibility and the assumption of

significant benefit for an orphan designation” (EMA/COMP/15893/2009).

Usually, at the time of designation, little or no clinical experience is available. In this situation, the need to justify the biological plausibility of the product must be fulfilled mainly based on *in vitro* and *in vivo* non clinical models presented in the application for orphan designation. The model validity and the relevance of the results obtained will have to be discussed for the condition, and where appropriate, references should be made to other products developed for the same condition. If only *in vitro* evidence is available at the time of the application, the relevance of the findings should be discussed in the context of the proposed condition. The preclinical data provided by these experiments have to be discussed in full, even if preliminary results from first administration to humans are available.

To illustrate this situation, here is a recent example of orphan designation for the treatment of medulloblastoma. The candidate product is a peptide nucleic acid that inhibits MYCN transcription. The transcription of MYCN is associated with the development and progression of the disease, and this is widely accepted in the medical community as a tumor-driving process. Therefore, the medicine’s biological plausibility seems acceptable. Moreover, data from experimental models show that the product exerts its action through an anti-sense mechanism and stops transcription of MYCN. In addition to inhibition of protein expression, the data suggest that the product may induce inhibition of cell growth in MYCN-expressing medulloblastoma cell lines. Data corroborating the plausibility were seen in neuroblastoma. With all these data, the regulatory authorities were able to accept the medical plausibility for orphan designation, keeping in mind that the rationale for the development was justified and that the product deserved further development with the help of incentives from the orphan regulation. This case illustrates the balance between early development and sound and consistent biological data, which sends a strong signal of interest even though there is no guarantee of a successful development.

### 2.3.3 Significant Benefit

Significant benefit is a criterion for orphan medicine designation that is applied when – in the condition concerned by the application – there are products

authorized for the prevention, treatment, or diagnosis of the condition, whichever is the claimed use of the product. The concept of significant benefit implies an exercise of comparison with authorized treatments or otherwise established methods. As many sponsors apply for orphan designation at an early stage in development when comparative data are often not available, a critical review comparing authorized treatments and the proposed orphan medicinal product, and justifying the assumption of significant benefit should be provided. Importantly, the “review should be based not only on the limitations and risks of the authorized products but also on the benefit expected with the proposed product” according to the recommendation.<sup>10</sup>

There is another point in time when significant benefit is reviewed, which is at the time of marketing authorization. When the development of the product has progressed and allows for a benefit–risk assessment, the significant benefit criterion requires a demonstration and a higher level of evidence than earlier on, at the time of designation.

Significant benefit is defined as “a clinically relevant advantage or a major contribution to patient care” according to Article 3(2) of Regulation (EC) No 847/2000. This broad definition is sufficiently flexible for considering the specific aspects of the pediatric population and the benefit expected for them. In this context, features such as age-adapted formulations, formulations with potentially better compliance, have been specifically considered for the pediatric population, and have been accepted as a valid assumption of significant benefit. Another example is provided by the development of an anticancer drug in a disease where radiation therapy is the main therapeutic option. The medicine could bring significant benefit if the product avoids radiation therapy with its unwanted effects, and this prospect is superior to the potential risks of the medicine. With regards to providing an age-adapted formulation, this has been successfully used as justification for significant benefit when the existing product formulation(s) cannot address the therapeutic needs of the pediatric patients.

At the time of designation, the justification of significant benefit has to be supported by sound scientific arguments and a discussion based on data, either preliminary preclinical or clinical results.

So far, more than 60% of positive opinions adopted on orphan medicine designations were based on the assumption of significant benefit, with the remainder of designations based on absence of satisfactory, authorized method of diagnosis, prevention, or treatment.

---

## 2.4 Incentives

In the European Union, a number of incentives, financial and other, have been created for the development of medicines with the aim to improve public health in under-researched areas, and to strengthen the European research area. Indeed, incentives are available throughout the medicine development process (Table 2.3). Some of the incentives apply specifically to pediatric medicines; some incentives are available in European Member States (see “Inventory of rewards and incentives to support medicinal products for pediatric use”<sup>11</sup> published by the European commission based on information from Member States). This section describes incentives available at the European level.

- *Scientific Advice (Protocol Assistance, in case of an orphan designated medicine)*: The European Medicines Agency provides scientific advice on how to optimize the development for a future marketing authorization. This helps applicants to maximize the chances of their marketing authorization application being successful. Scientific advice is free for questions related to pediatric medicine development, and has reduced fees for orphan designated medicines. For micro, small and medium enterprises (SME), there is a substantial fee reduction for scientific advice.
- *Agreement of a Paediatric Investigation Plan (PIP) or a waiver*: A free procedure for any medicine defining whether a pediatric development is required through a PIP, or is waived. This procedure is mandatory before submission of marketing authorizations. It is provided by the Paediatric Committee (PDCO) of the European Medicines Agency, a scientific body comprising of pediatric experts appointed by member states, of representatives of the EMA’s Committee for Medicinal Product for Human Use (CHMP), and of health professionals and patient organization representatives appointed

---

<sup>10</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/07/WC500095341.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf)

<sup>11</sup>[http://ec.europa.eu/health/files/pediatrics/docs/inventory\\_on\\_pediatrics\\_07-2008\\_en.pdf](http://ec.europa.eu/health/files/pediatrics/docs/inventory_on_pediatrics_07-2008_en.pdf)

**Table 2.3** Support and incentives to the development of medicines for the treatment of rare tumors

Incentive	Provided by	Scope of incentive	Where to start
Fee reductions for European scientific advice and protocol assistance	European Medicines Agency	For any questions on the pediatric development of a medicine Includes regulatory consultation Free Pre-submission meetings and discussion meetings Possibility for parallel advice with US Food and Drug Administration	<a href="http://www.ema.europa.eu/">http://www.ema.europa.eu/</a> – Regulatory – Scientific advice and protocol assistance
Orphan medicine designation	EMA/European Commission	Protocol assistance, access to central marketing authorization procedure	<a href="http://www.ema.europa.eu/">http://www.ema.europa.eu/</a> – Regulatory – Orphan designation
SME registration	European Medicines Agency	For micro, small, and medium enterprises (SME) developing medicines, including for example academic spin-offs Regulatory advice throughout all interactions with the European Medicines Agency Special trainings and workshops on scientific topics	<a href="http://www.ema.europa.eu/">http://www.ema.europa.eu/</a> – Regulatory – SME office
Agreement of Paediatric Investigation Plan (PIP) or Waiver	Paediatric Committee (PDCO) of the European Medicines Agency	Mandatory, Decision on pediatric data required for marketing authorization	<a href="http://www.ema.europa.eu/">http://www.ema.europa.eu/</a> – Regulatory – Pediatric Medicines
Innovation Task Force (ITF)	European Medicines Agency	Informal information exchange, and scientific guidance early in development process through briefing meetings	<a href="http://www.ema.europa.eu/">http://www.ema.europa.eu/</a> – Regulatory – Innovation Task Force
Clinical research support	Member States		<sup>a</sup>
Framework programs	European Commission		<sup>b</sup>

<sup>a</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002926.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf)

<sup>b</sup>[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500003969.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003969.pdf)

by the European Commission. Currently, there are several pediatric oncologists in the PDCO, which has a broad coverage of pediatric therapeutic areas. The PDCO agree binding opinions on PIPs or Waivers; in case difficulties are encountered, modifications of PIPs can be requested.

- *When submitting for marketing authorization:* For orphan designated medicinal products, there is direct mandatory access to the centralized marketing authorization procedure to address efficiently European public health needs. New anticancer active substances including those for pediatric use also fall in the mandatory scope of the centralized marketing authorization procedure. New pediatric indications of nationally authorized anticancer medicines have access to the central procedure.
- *When the pediatric medicine development is completed according to a PIP:* Irrespective of whether the data allow authorization for pediatric use, or provide information reflected in the Product

Information (PI) recommending that a medicine should not be used in children because of safety or lack of efficacy concerns, a reward may be obtained. This reward may be a 6-month extension of the protection of the medicine's basic patent, or a 2-year extension of market exclusivity (in case of an orphan medicine), or 10-year data exclusivity (in case of a pediatric-only product).

- *When the orphan development is successful:* Orphan medicinal products will benefit from market exclusivity in all EU member states for 10 years after the granting of a marketing authorization. During that period, directly competitive similar products cannot be placed on the market for the same indication. It is not possible either to extend an existing authorization of a similar product for the same orphan indication. In addition, consortia and sponsors developing orphan or off-patent medicinal products may be eligible for grants from the EU and Member States' programs<sup>6</sup> and initiatives supporting research and development,

including calls for the European Commission framework program.<sup>12</sup>

In any case, academic investigators may be interested by scientific and regulatory exchange about development plans, as described in the following section.

## 2.5 Opportunities for Scientific and Regulatory Interactions on Pediatric Oncology Developments

A number of opportunities for exchange on scientific questions with the European regulatory network are available at the European Medicines Agency (EMA). The EMA may interact with academic investigators as well as pharmaceutical companies (see also Table 2.3 on available financial incentives for such interactions). The outcomes of such interactions will help to improve or confirm scientifically pediatric trials. The interactions will help to navigate the complex regulatory system and to share responsibility for discussing how to study and develop a medicine.

All interactions are kept confidential by the EMA, but investigators are free to share the outcome (e.g., Scientific advice letter, agreed Paediatric Investigation Plans). During the interaction, EMA will however use its accumulated scientific experience on medicine regulation, trial methodology, successful or failed trials, and related medicinal products. This experience is provided by European experts from various Member States and by the EMA scientific staff, with a view to ensuring that a single European position is developed and communicated.

- *Innovation task force (ITF)*: The ITF classifies innovative medicinal products, including emerging therapies and technologies, and clarifies the relevant regulatory pathways. A multidisciplinary discussion with the ITF can be requested.
- *Scientific advice (SA, called protocol assistance for orphan medicines)*: Questions from applicants drive the content of SA. The SA letter (outcome) provides the background considerations and specific answers to requested pharmaceutical quality, non-clinical and clinical questions as well as to significant benefit questions in the case of a protocol assistance. Members of the Paediatric Committee of the EMA

are usually involved in pediatric questions of the SA. The SA process aims to complete within 40 days, or 70 days if a discussion meeting is necessary. The SA letter is not binding on applicants. Details on the importance of scientific advice for successful medicine developments have recently been reported (Regnstrom et al. 2010).

- *Paediatric Investigation Plan (PIP)*: The PIP is a comprehensive view on a medicine development for children, and it includes the studies that are necessary to provide an age-appropriate formulation, non-clinical and clinical trials to conclude on a safe and efficacious pediatric use, including long-term follow-up. A PIP agreed by the EMA Paediatric Committee is binding on applicants, and compliance with the PIP is a requirement for a valid submission of an application for marketing authorization. All agreed PIPs are made public by the EMA on its website, after deletion of commercially confidential information.<sup>13</sup> For example, the design of the agreed studies can be scrutinized by the public.
- *Pediatric oncology task force*: This is an informal group composed of experts from the pediatric oncology scientific communities and of EMA scientists, which meets as needed to discuss general issues related to research into anticancer medicines in the pediatric population. It also serves as a contact point for members of the pediatric oncology community who want to bring issues to attention, such as difficulties attracting early dose-finding and safety trials.
- *Pre-submission meeting with SME office*: After successful registration as a SME, academic consortia could be supported in their interactions with the regulatory system.

Academic investigators can request scientific advice as well as propose a Paediatric Investigation Plan for a medicine. There is no requirement to be a marketing authorization applicant or holder (MAH), or to have an agreement with a MAH. Scientific advice letters and agreed Paediatric Investigation Plans can be then shared and discussed with pharmaceutical companies for the performance of trials.

<sup>13</sup>Oncology: [http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fpip\\_search.jsp&murl=menus%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d129&searchkwByEnter=false&alreadyLoaded=true&keyword=Enter+keywords&searchType=Invented+name&currentCategory=Oncology](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fpip_search.jsp&murl=menus%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d129&searchkwByEnter=false&alreadyLoaded=true&keyword=Enter+keywords&searchType=Invented+name&currentCategory=Oncology)

<sup>12</sup><http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.FP7CallsPage#Health>

Scientific advice is also offered by some national regulatory agencies. This may be of interest to anticipate a clinical trial application.

Any trial with a medicine is of interest to the regulators, because it can provide complementary data on the benefit–risk relationship in an authorized indication, or it can bring data on a potential use of the medicine. New indications may help regulators to address public health needs, which is a major objective of the EMA. Results from such trials and recommendations will then be included in the Product Information (PI) and reflected in the European Public Assessment Report.

For the benefit of all healthcare professionals, special provisions of the Pediatric Regulation (EC) No 1901/2006 were set out to make the PI as informative as possible, such as the submissions and publications of existing trials according to Articles 45 and 46 of the Pediatric Regulation. The recently updated Summary of Product Characteristics (Product Information) guideline<sup>14</sup> requires clear-cut pediatric information if pediatric trials are still awaited, have been waived, or if results allow to recommend the use or not of the medicine.

Obtaining SA may be particularly relevant for rare pediatric tumors, because standard treatment protocols or guidelines may not be available, in contrast to more frequent pediatric malignant diseases.

Other opportunities exist for public exchange of information. The EMA contributes to dialogue at (non-commercial) public scientific meetings, such as ECCO-ESMO, EORTC-AARC-NCI, ASCO, and SIOP meetings. EMA has organized joint meetings with EFPIA and DIA on topics such as adaptive designs, pediatric medicines, and pediatric oncology.

---

## 2.6 Collaborative and Organization Aspects of Conducting Trials in Small Populations

In addition to the scientific and methodological aspects, there are other aspects related to the organization and conduct of pediatric oncology trials, which are of importance from a regulatory perspective.

Clinical trials in pediatric oncology share the challenges and requirements of trials in other pediatric therapeutic areas. It may be informative to review the

paradigm changes and the methodological progresses in autoimmune diseases and neuromuscular diseases (NDM), for example. The TREAT-NMD network, which involves academic and patient representatives, is organized to collaborate with pharmaceutical companies. It organized with EMA an expert workshop on how to develop novel medicines for the treatment of Duchenne muscular dystrophy (Muntoni 2010).

In malignant diseases that peak in adolescence or young adulthood, conducting safety and efficacy trials open to both pediatric and adult populations should be considered. The pediatric oncology community has made renowned efforts over the last decades to establish pediatric-specific successful treatments. However, for specific research questions, such a combined approach may be reasonable and efficient to simplify and accelerate the setting up of a study and limit the number of trials. When pediatric patients can be included, needs to be carefully considered. If needed, the adult protocol can be opened to pediatric patients through an amendment that takes into account the safety data obtained from the study so far. Such approaches may specially apply to dose-finding and early therapeutic exploratory studies.

The global frequency of pediatric malignant diseases is low. Issues due to differences in standards of care will become more obvious when pharmaceutical companies conduct pediatric oncology trials outside the European and North American regions, e.g., in India and China. For some malignant diseases, e.g., brain tumors, there are even differences among European countries due to different health care systems. Moreover, the “quality control treatment titration studies” as defined by pediatric oncologists for a number of malignant diseases include only some but not all EU member states. Recently, European multinational studies for some pediatric malignant diseases have been set up comparing different treatments in different countries, with the aim to establish an international standard. A PIP aims to generate data that are useful to any children in Europe but may not have the same relevance in every Member State. Pediatric oncology trials in a PIP need to include the best available standard of care despite divergent scientific views and availabilities of treatment options, e.g., high-dose therapy.

When discussing Paediatric Investigation Plans with pharmaceutical companies, the Paediatric Committee would like to see academic communities involved, in

---

<sup>14</sup>[http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc\\_guide\\_line\\_rev2\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guide_line_rev2_en.pdf)

the treatment, setting up of registers, or clinical research, or as pediatric networks.

Before the start of trials with novel medicines or in a novel indication, agreements between academia and pharmaceutical companies are encouraged. Such trials are relevant to the refinement and understanding of the benefit–risk relationship of the medicine. Public access to the resulting information through regulatory assessment can be construed as an ethical duty, even more when investigator-initiated trials have received public funding. The consent form and other templates<sup>15</sup> of the US National Cancer Institute for sponsored trials in pediatric oncology explicitly mention that data will be shared with regulatory authorities, and templates for contracts and SOPs have been made freely available by platforms such as the TMF.<sup>16</sup>

## 2.7 Lack of Efficacy

Trial results are usually analyzed for any indicators of efficacy, but analyses should be open for the possibility that the data may indicate a lack of efficacy. In a rare condition, the treating physician may rely on low levels of evidence in favor of the efficacy of a treatment. However, if the treatment is ineffective, patients suffer from a loss of chance, and can be harmed, as toxicity will still occur, and increased by higher doses given when the activity (response) is unsatisfactory. Convincing evidence of lack of efficacy could come from large controlled studies, which are not available in rare tumors. For example, we propose that the following is considered in the case of rare tumors:

- Formulate and pre-specify assumptions on minimum treatment effect that is clinically relevant and desirable, or expected to change medical practice. The definition should be achieved by consensus of the community whose members will later take decisions for their patients.
- Ensure that clinical results are published and interpretations are clearly communicated and implemented in medical practice, e.g., in therapeutic guidelines. Conclusions should also specify whether the same medicine may be further tested, and if another medicine would be tested in subsequent trials.

- Absence of evidence of efficacy is not evidence of absence of efficacy for a medicine. A careful analysis should look into whether non-positive study results may be related to the design and conduct of a study, and if signs of activity of the medicine could be picked up. Any further use of such a medicine should take place in a controlled environment, that is, in a clinical trial. More evidence (positive or negative) would be built up and patients would be protected.

There are few examples where marketing authorizations granted conditionally have been revoked based on lack of efficacy shown in further studies (Richey et al. 2009). Regulatory agencies have seen negative efficacy studies of authorized anticancer medicines in a new therapeutic setting of the same malignant disease. Data from “negative” pediatric trials are included in the European Public Assessment Reports, even when the pediatric malignant diseases studied were not related to the authorized adult indications (e.g., Torisel (temsirolimus)).

## 2.8 Conclusions and Outlook

This chapter summarized some regulatory aspects relevant to pediatric trials, the opportunities to obtain scientific-regulatory advice, as well as incentives and support available to academic researchers, be they academic investigators or investigators in pharmaceutical company–sponsored projects on the development of anticancer medicines.

The European Medicines Agency is building up experience in oncology (Pignatti et al. 2002), including pediatric oncology, although too few new anticancer medicines are available for children, in particular to treat rare tumors. As expressed in the European Medicines Agency Road Map on its contribution to science, medicines, and health,<sup>17</sup> the paradigms for authorization, information, and surveillance of medicines are evolving fast, and greater uncertainty on a medicine may be a trade-off for earlier availability (Eichler et al. 2008).

However, the development of new medicines requires the generation of as much as possible data, so to quantify and characterize what is known of the

<sup>15</sup><http://www.cancer.gov/clinicaltrials/education/simplification-of-informed-consent-docs/page3>

<sup>16</sup><http://www.tmf-ev.de/EnglishSite/ProductsServices.aspx>

<sup>17</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000292.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac05800293a4](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac05800293a4)

medicine's efficacy and safety and to reduce uncertainty as much as possible.

In keeping with this principle, trials in pediatric oncology cannot be seen in isolation, even when conducted by individual investigators, but as public contributions to build up evidence; trials should be designed with support from scientists at regulatory agencies. All such contributions, positive or negative, should be made available to the public and to agencies, for evaluation and eventually inclusion in Product Information. This would honor and respect each child patient participating in clinical research. This is an ethical imperative to make new medicines available to children with rare tumors.

## 2.9 Suggested Further Reading and Resources

- Introduction to the European regulatory system: User guide for micro, small and medium-sized enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in regulation (EC) No 726/2004. This guide is of particular relevance to SMEs, but provides a useful overview of the system. <http://www.ema.europa.eu> – Regulatory – Human Medicines – SME office – Guidance
- Scientific guidance of the European Medicines Agency, <http://www.ema.europa.eu> – Regulatory – Human medicines – Scientific guidelines – Clinical efficacy and safety – Antineoplastic and immunomodulating agents
- Recent scientific-regulatory presentations by the European Medicines Agency and its network, <http://www.ema.europa.eu> – Document library – Filter by document type: Presentations
- Scientific training resources on Rare Diseases Europe (Eurordis), <http://www.eurordis.org/training-resources>
- Reports on the European Medicines Agency's workshops with pediatric experts, <http://www.ema.europa.eu> – Regulatory – Human medicines – Paediatric medicine – Related information – Workshops
- Reports on scientific-regulatory workshops of the EMA SME office, <http://www.ema.europa.eu> – Regulatory – Human Medicines – SME office – Workshops
- Scientific evaluation guidance in EMA/PDCO summary reports on Paediatric Investigation Plans, [http://www.ema.europa.eu/docs/en\\_GB/](http://www.ema.europa.eu/docs/en_GB/)

[document\\_library/Templates\\_and\\_Form/2009/09/WC500003740.doc](http://www.ema.europa.eu/docs/en_GB/document_library/Templates_and_Form/2009/09/WC500003740.doc)

- Medicinal products for human use authorized by the European Commission, [http://ec.europa.eu/health/human-use/index\\_en.htm](http://ec.europa.eu/health/human-use/index_en.htm): European community medicine registers, News on pharmaceuticals and updates on Medicines for children
- EU Legislation (Eudralex) [http://ec.europa.eu/health/documents/eudralex/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/index_en.htm)

**Disclaimer** The views expressed in this chapter are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

## References

- Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (2008) Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. [http://ec.europa.eu/health/files/eudralex/vol-10/ethical\\_considerations\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf) (accessed 18 September 2011).
- Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A (2008) Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov* 7(10):818–826. doi:10.1038/nrd2664
- Haffner ME, Torrent-Farnell J, Maher PD (2008) Does orphan drug legislation really answer the needs of patients? *Lancet* 371(9629):2041–2044. doi:10.1016/S0140-6736(08)60873-9
- Halpern SD, Karlawish JHT, Berlin JA (2002) The continuing unethical conduct of underpowered clinical trials. *JAMA* 288(3):358–362
- Koschmann C, Thomson B, Hawkins DS (2010) No evidence of a trial effect in newly diagnosed pediatric acute lymphoblastic leukemia. *Arch Pediatr Adolesc Med* 164(3):214–217. doi:10.1001/archpediatrics.2009.282
- Lee DP, Skolnik JM, Adamson PC (2005) Pediatric phase I trials in oncology: an analysis of study conduct efficiency. *J Clin Oncol* 23(33):8431–8441. doi:10.1200/JCO.2005.02.1568
- Manolis E, Pons G (2009) Proposals for model based paediatric medicinal development within the current EU regulatory framework. *Br J Clin Pharmacol* 68(4):493–501. doi:10.1111/j.1365-2125.2009.03484.x
- Manolis E, Eldirdiry Osman T, Herold R, Koenig F, Tomasi P, Vamvakas S, Saint RA (2011) Role of modeling and simulation in pediatric investigation plans. *Paediatr Anaesth*. doi:10.1111/j.1460-9592.2011.03523.x. <http://www.ncbi.nlm.nih.gov/pubmed/21244569>
- Muntoni F (2010) The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy: report on a TREAT-NMD workshop hosted by the European Medicines Agency (EMA), on September 25th 2009. *Neuromuscul Disord* 20(5):355–362. doi:10.1016/j.nmd.2010.03.005



- Peppercorn JM, Weeks JC, Cook EF, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 363(9405):263–270. doi:10.1016/S0140-6736(03)15383-4
- Pignatti F, Aronsson B, Vamvakas S, Wade G, Papadouli I, Papaluca M, Moulon I, Le Courtois P (2002) Clinical trials for registration in the European Union: the EMEA 5-year experience in oncology. *Crit Rev Oncol Hematol* 42(2):123–135
- Raphaël M, le Deley M, Vassal G, Paoletti X (2010) Operating characteristics of two independent sample design in phase I trials in paediatric oncology. *Eur J Cancer*. doi:10.1016/j.ejca.2010.01.024, <http://www.ncbi.nlm.nih.gov/pubmed/20176476>
- Ratain M (2010) Bar the windows but open the door to randomization. *J Clin Oncol* 28(19):3104–3106. doi:10.1200/JCO.2010.29.3787
- Regnstrom J, König F, Aronsson B, Reimer T, Svendsen C, Tsigkos S, Flamion B, Eichler HG, Vamvakas S (2010) Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol* 66(1):39–48. doi:10.1007/s00228-009-0756-y
- Richey EA, Lyons A, Nebeker JR, Shankaran V, McKoy JM, Ha Luu T, Nonzee N et al (2009) Accelerated approval of cancer drugs: improved access to therapeutic breakthroughs or early release of unsafe and ineffective drugs? *J Clin Oncol* 27(26):4398–4405. doi:10.1200/JCO.2008.21.1961
- Sarker D, Workman P (2007) Pharmacodynamic biomarkers for molecular cancer therapeutics. *Adv Cancer Res* 96:213–268. doi:S0065-230X(06)96008-4
- Smith M, Bernstein M, Bleyer WA, Borsi JD, Ho P, Lewis IJ, Pearson A et al (1998) Conduct of phase I trials in children with cancer. *J Clin Oncol* 16(3):966–978
- Tan SB, Dear KBG, Bruzzi P, Machin D (2003) Strategy for randomised clinical trials in rare cancers. *BMJ* 327(7405):47–49. doi:10.1136/bmj.327.7405.47
- Thall PF, Simon RM, Estey EH (1995) Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med* 14(4):357–379
- Valsecchi MG, Masera G (1996) A new challenge in clinical research in childhood ALL: the prospective meta-analysis strategy for intergroup collaboration. *Ann Oncol* 7(10):1005–1008