AKAD
Wissenschaftliche
Hochschule Lahr

Diskussionspapier Nr. 31

Regulation (EC) No 1901/2006 and 1902/2006: Development of Pharmaceuticals for the Pediatric Population The Pediatric Investigation Plan (PIP)

Marguérite M. Mensonides-Harsema
mit einem Geleitwort von Andreas Otte

September 2010

Diskussionspapiere der WHL Wissenschaftliche Hochschule Lahr

http://www.akad.de/WHL-Diskussionspapiere.191.0.html

Verfasser:
Marguérite M. Mensonides-Harsema*
mit einem Geleitwort von Andreas Otte**

Herausgeber:
WHL Wissenschaftliche Hochschule Lahr
Hohbergweg 15–17
D-77933 Lahr

Phone +49-(0)7821-9238-50
Fax +49-(0)7821-9238-63

www.whl-lahr.de

* Dr. Marguérite M. Mensonides-Harsema ist promovierte Pharmazeutin und arbeitete lange als wissenschaftliche Mitarbeiterin in der präklinischen Forschung bei AstraZeneca in Schweden. Zur Zeit absolviert sie den Masterstudiengang Clinical Research Management an der WHL Wissenschaftliche Hochschule Lahr.

** Prof. Dr. med. Andreas Otte ist Facharzt für Nuklearmedizin, Honorarprofessor am Lehrstuhl für Volkswirtschaftslehre/Versicherungs- und Gesundheitsökonomik (Lehrstuhlinhaber: Prof. Dr. Tristan Nguyen) und Studiengangsleiter für den Teil Clinical Research des Masterstudiengangs Clinical Research Management der
WHL Wissenschaftliche Hochschule Lahr Hohbergweg 15-17, 77933 Lahr/Schwarzwald
Tel.: +49 7821/9238-69, Fax: +49 7821/9238-63
Mail: andreas.otte@whl-lahr.de.

Regulation (EC) No 1901/2006 and 1902/2006:
Development of Pharmaceuticals for the Pediatric Population
The Pediatric Investigation Plan (PIP)

Dr. Marguérite M. Mensonides-Harsema

TABLE OF CONTENTS

1. PREFACE

To the WHL Diskussionspapier from Marguerite Mensonides-Harsema:

Development of pharmaceuticals for the pediatric population

Today's international standardization in clinical research resulting in the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines is the result of a long historical development. Over many hundreds of years, pharmaceuticals have been developed, and they were developed without any regulatory framework.

Even until the early 1900s drugs could be sold and bought like any other consumer good. By this, many unsafe drugs were brought to market, which often led to serious drug-related events or even deaths.[1] Lethal medicines ''Grandma's Secret'', ''Kopp's Baby's Friend'', and ''Nurses' and Mothers' Treasure'' contained high amounts of morphine which even in small doses were lethal to children. These medicines were sold to families by physicians and pharmacies. The ingredients and quantities were not labelled on the bottle. Parents and general practitioners were led to believe that such medicines would cure their children; instead, the medicines were poisonous. Furthermore, some medicines contained morphine and chloroform (e.g., ''Dr. King's Consumption Cure'', ''Dr. Bull's Cough Syrup''). While some children recovered from their addictions, many suffered through life with addiction.

In 1906, the U.S. Pure Food and Drugs Act stopped this situation. However, it should take many more years up to standardized and international guidelines: the ICH GCP guidelines which describe how to conduct clinical studies for the development of new pharmaceuticals in adults, were published 90 years later in 1996. For the special situation of developing pharmaceuticals in the pediatric population, it took 10 more years to set up the obligatory European Regulation (EC) No 1901/2006 and 1902/2006: Development of Pharmaceuticals for the Pediatric Population, the so-called Pediatric Investigation Plan (PIP), which is the topic of the following working paper.

---

[1] Otte A, Maier-Lenz H, Dierckx RA. Good Clinical Practice (GCP): Historical background and key aspects. Nucl Med Comm 2005; 26: 563-574.

This working paper was set up as a “Seminararbeit” for the clinical research section of the master of science studies in clinical research management, a joint venture of the WHL Graduate School of Business and Economics, Lahr, and the Albert-Ludwigs-University Freiburg.

We would be happy if this paper reaches attention in the interested readership.

Prof. Dr. Andreas Otte
Studiengangsleiter des Masterstudiengangs Clinical Research Management

Lahr, September 2010

2. ABSTRACT

In 2006, the European Commission published Regulation EC 1901/2006. The objective of this legislation is to encourage the development of both in- and off-patent drugs that are suitable for the treatment of children. The final goal being the development of medication for children that is guaranteed to be as safe, effective and of high quality as the medication that has received market authorization for use in the adult population. This is done through a set of incentives (prolonged or renewed patent protection) and deterrents (refusal of market authorization).

This discussion paper portrays the history of Regulation EC 1901/2006 and the different constituents of this paediatric regulation. The article lays special focus on the paediatric investigation plan. The final part of the manuscript concentrates on the differences and similarities between paediatric legislation in the USA and in the EU. It is anticipated that these laws will curb the pharmaceutical industry into the inclusion of children/adolescents in their R&D schemes, both for their innovative as for generic drugs.

3. LIST OF ACRONYMS

AT	=	anti thrombin
CHMP	=	Committee for Medicinal Products for Human Use
cq	=	casus quo
EbM	=	Evidence-based Medicine
EC	=	European Commission
EFTA	=	European Free Trade Association
e.g.	=	exempli gratia
EMEA	=	European Medicines Agency
et al	=	et alii
EU	=	European Union
EudraCT	=	EU Community database for clinical trials
EudraPharm	=	European Union Drug Regulating Authorities Pharmaceutical Database
FDA	=	Food and Drug Administration

ICH	=	International Conference of Helsinki
i.e.	=	it est
IL	=	interleukin
LMWH	=	low molecular weight heparin
MA	=	market authorization
MAA	=	Marketing Authorization Application
MoA	=	mechanism/mode of action
NcWG	=	Nonclinical Working Group
NDA	=	New Drug Application
NIH	=	National Institute of Health
PD	=	parmacodynamic
PIP	=	Pediatric Investigation Plan
PK	=	pharmacokinetic
PMEAG	=	Expert Advisory Group on Pediatric Medicines
POC	=	Proof of Concept
PREA	=	Pediatric Research Equity Act
PUMA	=	Pediatric Use Marketing Authorization
PUVA	=	psoralen and ultraviolet-A
ROI	=	return on investment
SAWP	=	Scientific Advice Working Party of the EMEA
sc	=	subcutaneous
SmPC	=	Summary of Product Characteristics
SPC	=	supplementary protection certificate
UFH	=	unfractionated heparin
US	=	United States (of America)
USA	=	United States of America
VKA	=	vitamin K antagonists (VKA)
vs	=	versus
VTE	=	venous thromboembolism

4. LIST OF TABLES AND FIGURES

4.1 LIST OF TABLES

4.2 LIST OF FIGURES

4.3 PHOTO ON COVER

Taken from the oral presentation given by Dr. D. Murphy (director of the Office of Pediatric Therapeutics, FDA), titled: Europe & USA: Interactions on Pediatric Clinical Trials. 2008.

5. INTRODUCTION

BACKGROUND Before any medicine is given market authorization (MA) in the European Union (EU) by the European Medicines Agency (EMEA) and the local authorities of the different EU member states, the pharmaceutical product has undergone extensive testing - including pre-clinical tests and clinical trials - to ensure that it is safe, of high quality and effective. The results of all these (pre-) clinical studies will be carefully scrutinized and evaluated by the Committee for Medicinal Products for Human Use (CHMP).[2] Shockingly, a study in the early 2000's showed a situation in the EU in pediatric care that was as follows: 20% of all prescriptions were for children, 72% of these medicines provided to children were never tested in children and in intensive care less than 20% of the medicines used had been evaluated in a pediatric clinical trial. At this time point, only 7% of the clinical trials had been in children.[3, 4] It is well known among the pediatric profession that the off-label use of medication in children is widespread. In the EU, the pediatric population (0-18 years) represents about 75 million people (20% of the total population) ranging in age from preterm and term newborn infants to toddlers to children to adolescents.[5, 6] However.-.as over 70% of the medicines used in children have not been studied in this age group - the absence of suitable authorized medicinal products to treat conditions in children is an issue that has been of concern for quite some time now. Pharmaceutical companies have been reluctant to invest in the development of specific treatments or in adapting existing medicines to meet the needs of the pediatric population, mainly because the market is small and therefore of lower commercial interest. Another important reason is that studies can be difficult, long and expensive. And in addition, developing a suitable formulation which can provide an exact dose - for example a syrup - may be technically difficult and expensive on an industrial scale. This often leaves no alternative to the prescriber than to use 'off-label' and unauthorized products, without the necessary EbM information to guide prescribing and without a valid assessment of the risks versus the benefits.

Children are not miniature versions of adults, but a vulnerable group with developmental,

---

2 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/04/WC500089445.pdf.

3 Bickerstaff, R. Pediatric Workshop EFPIA 2003.

4 Le Cam, Y. Medicines for children: better, more and faster. Regulatory Rapport. May 2005: p8.

5 EMEA© Presentation: Overview of the new pediatric regulation; EUDRACT Pediatrics Overview PIP.

6 EMEA© Frequently asked questions on regulatory aspects of Regulation (EC) No 1901/2006 (Pediatric Regulation) amended by Regulation (EC) No 1902/2006; Doc. Ref. EMEA/520085/.

physiological and psychological differences from adults, which makes age- and development-related research particularly important. Specific clinical trials in pediatric populations are normally required, due to age-related differences in the drug handling or drug effects which may lead to different dosing requirements to achieve efficacy or to avoid adverse effects.[7,8,9]

The risks of administrating drugs and formulations that have been developed for adults to children are apparent:

- Overdosing, leading to an increase in adverse and/or toxic effects;
- Under-dosing, leading to ineffective treatments;
- Absence and/or delay in the development of appropriate formulations for the pediatric population, which will lead to a delayed access for this population to innovative drugs and treatments.

At the turn of the century, pediatric studies conducted in response to US legislation led to 34 labels containing new pediatric information for established medicines (1998 – 2002).[10] In 12 cases the new labels included important new dosing/PK or safety information which had an impact on the safe and effective use of the medicine in the pediatric population.2 Without such specific studies in the pediatric population this important information would not have been available. In addition, there are numerous practical problems of administration of 'adult' formulations. For example, children might have difficulties swallowing tablets. Or, more significantly, physicians cq pharmacists may make calculation errors when using adult formulations and weight adjustments to obtain pediatric dosages. Although there may be ethical concerns about conducting trials in the pediatric population, this has to be balanced by the ethical concerns about giving medicines to a population in which they have not been tested.[11, 12] This is why the EU in 2006 passed

---

7 Guideline on conduct of pharmacovigilance for medicines used by the pediatric population, EMEA, Aug 2005; http://www.emea.int.pdfs/human/phvwp/23591005en.pdf.

8 EMEA Reflection paper: formulations of choice for the pediatric population. EMEA/CHMP/PEG/194810/2005.

9 CHMP Draft Guideline on the role of pharmacokinetics in the development of medicinal products in the pediatric population. EMEA/CHMP/EWP/147013/2004. February 2005.

10 http://www.fda.gov/cder/pediatric/peddrugsfinal.htm.

11 Isitt, V. Legal and ethical problems peculiar to pediatric clinical trials. Part 1: Legal issues. The Regulatory Review, June 2002 Volume 5 Issue 4; 12-16.

a new regulation on pediatric medicines (EC 1901/2006), which became effective the 26th of January 2007, to stimulate the development of better medication for children.[13, 14]

The objectives of the European Pediatric Regulation are:

- Increase the quality of research in medicines for children (Evidence-based Medicine, EbM)
- Promote the development and authorization of pharmaceuticals appropriate for the pediatric populations
- Improve the information on medications (labeling) used in the treatment of children.

These objectives are to be achieved without conducting unnecessary studies in children and without delaying the development and market entry of new medications for adults, through a system of requirements ('Stick') and incentives ('Carrot').

From 27 July 2008 if a company submitting a Marketing Authorization Application (MAA) in Europe does not have an approved Pediatric Investigation Plan (PIP) in place, the MA for their new drug will be automatically rejected, leading to huge losses of time, sales and thus return on investment (ROI). This consequently will benefit competitors and, of course, anger the share-holders. Companies may also suffer the humiliation of being "named and shamed" on the EMEA website. A PIP is legally binding and must outline how the company proposes to test the medicine in order to benefit child health and wellbeing. However if there is no known indication for use in children the company may apply for a waiver which must be approved before MAA submission. This is complex because the disease that the drug treats in adults may not be found in children (e.g. Alzheimer's) but the same drug may benefit children in other ways (e.g. pediatric brain injury). Table 2 lists examples for indications that are eligible for partial waivers for certain specific age subsets.[15] If it is not safe to test medicines in children before MA (due to lack of experience in the adult patient population) or if adult trials are still on-going, the company can apply

---

[12] EU Directive 2001/20/EC: Implementation of GCP in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities, 2001, L121/34-44.

[13] Regulation (EC) No 1901/2006 on medicinal products for paediatric use (amending Regulation 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004).

[14] Regulation (EC) No 1902/2006 on medicinal products for paediatric use (amending Regulation (EC) No 1901/2006.

[15] Severin, T. The EU PIP – a Step in Pediatric Drug Development. Oral Presentation, Bonn (D), 2009.

for a deferral which again must be approved before MAA submission.[16]

Table 1: *Examples of partial waivers for particular indications for specific age subsets. (Adopted from T. Severin, 2009)*

Example	Neonates	Infants	Children	Adolescents
Cardiovascular Diseases	W/W?	P	P	P
Infectious Diseases	W/W?	P	P	P

W = waiver; P = PIP

REQUIREMENTS IN OTHER COUNTRIES COMPARED TO THE EUROPEAN UNION In Australia, MAs may be denied or delayed if pediatric clinical data that are deemed appropriate are not included. In India, if a new drug is intended to treat both adults and pediatric patients, the pediatric population should be included in the clinical trials from an early point onwards. If pediatric data are not included then this needs to be justified in detail. In Canada and China, registration of a drug for pediatric use follows the normal procedure. In China, clinical trials in children are even discouraged, unless the drug-use is limited to the pediatric population.[17] In the USA, the Pediatric Rule was issued by the FDA in 1998 (and suspended in 2002). Since 2003, the Pediatric Research Equity Act (PREA) for patented, new pharmaceutical products has been in place. This act is being complemented by the Pediatric Exclusivity Provision for off-patent pharmaceuticals, as an incentive to perform pediatric clinical studies for these medications and develop formulations suitable for the pediatric population.[18]

The European counterpart of this provision is the Pediatric Use Marketing Authorization (PUMA), a regulation that has been in place since 26th July 2007.[19] Through these regulations, a supplementary protection certificate (SPC) i.e. an extension of a patent under a specific, different, set of rights may also be obtained (See Table 1 for a comparison

---

16 EMEA© Questions and answers on the preparation of applications for a PIP and/or waiver. Doc Ref: EMEA/346673/2009.

17 Sam, T. Regulatory requirements for the development of medicinal products for pediatric use. Presentation at WHO/FIP-sponsored workshop in Capetown (SA), April 2007.

18 Pediatric Research Equity Act of 2003 (http://www.fda.gov.cder.pediatric/index.htm).

19 EMEA© Revised priority list for studies into off-patent paediatric medicinal products. Doc. Ref. EMA/480235/2010.

between the USA and EU regulations).

Table 2: *Comparison of pediatric drug regulation USA vs EU (Adapted from T.Sam, 2007)*

	USA	**Europe**
Legislation	Pediatric Research Equity Act (PREA) 2003	Pediatric Regulation EC 1901/2006
Requirements	Pediatric Advisory Committee issues written requests for NDAs; a pediatric waiver or investigational plan must be submitted	Pediatric Committee (PDCO) will review a Peadiatric Investigational Plan (PIP)
Off-patent products	No legislation*	Off-patent products Pediatric Use Marketing Authorisation (PUMA) giving 10 years data protection
Incentive	6-month period of additional SPC during which generic competitors cannot be marketed	6-month period of additional SPC during which generic competitors cannot be marketed

* The Best Pharmaceuticals for Children Act provides a mechanism for public funding (via the NIH) of pediatric studies of certain drugs if the manufacturers of those drugs decline to conduct the requested studies

Originally, the SPCs were introduced to compensate for the long time needed to obtain regulatory approval of medical products and it only comes into force after the corresponding general patent has expired.[20] Normally, an SPC has a maximum life time of 5 years, which can be extended with an extra 6 months when the SPC relates to pharmaceuticals for which data have been collected through clinical trials conducted in accordance with an agreed PIP.[21]

6. PEDIATRIC COMMITTEE

The main pillars of the Pediatric Regulations EC 1901/2006 and EC 1902/2006 - with its aim to better the pharmaceuticals available for the pediatric population - are

---

[20] Council Regulation (EEC) No 1768/9 : Creation of a supplementary protection certificate for medicinal products.

[21] EMEA© Frequently asked questions on regulatory aspects of Regulations (EC) No 1901/2006 and Regulation (EC) No 1902/2006. Doc. Ref. EMEA/520085/ 2006 (Version 2.0).

(1) The Pediatric Committee (PDCO; Chapter 5);
(2) The Pediatric Investigation Plan (PIP; Chapter 6);
(3) Incentives and Rewards (SPCs; Chapter 7), as well as
(4) Database of pediatric clinical studies to be build onto the EU Community database for clinical trials (EudraCT), in which to include the protocols and results of current and (un)published previous pediatric clinical trials (http://www.eudra.org/emea.html), and
(5) Database of pediatric-'MAs' to be build onto the European Union Drug Regulating Authorities Pharmaceutical Database (EudraPharm), which is the database of medicinal products authorized in the EU that includes the information contained in the Summary of Product Characteristics (SmPC), the patient- or user package leaflet and the information shown on the labeling.[22]

The EudraPharm database (EU Regulation 726/2004) is accessible to the general public and the information thus made available is worded in an appropriate and comprehensible manner. A general drawback of this database, however, is that it only contains details of products that were licensed using the centralized procedure. At the entry into force date of the pediatric regulation EC 1901/2006 – the 26th January 2007 - the pharmaceutical industry was provided with free-of-charge, scientific advice about the new regulation and the requested PIP from the scientific board of the EMEA. After 6 months, in July 2007, the PDCO was established and the first of the required PIPs could be filed. At this date, the Pediatric Use Marketing Authorization (PUMA) provisions also became effective. The PUMA was a new type of MA for products that are developed exclusively for therapeutic indications which are relevant for the use in the pediatric population, or subsets thereof, with, if necessary, an age-appropriate formulation.[23, 24, 25, 26] This MA is only granted for medicinal products for human use that are not protected by an SPC cq patent. In other words, a PUMA of an authorized product is only possible after expiry of the relevant data protection. A PUMA application should include new pediatric data in compliance with an EMEA-adopted PIP.

---

[22] EMEA© Presentation of the EMEA Pediatric Team for Scientific Advice, Pediatrics and Orphan Drugs Sector: The Pediatric Regulation (2007).

[23] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000124.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e9e.

[24] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004749.pdf.

[25] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004754.pdf.

[26] EMEA© Revised priority list for studies into off-patent paediatric medicinal products Doc. Ref. EMA/480235/2010.

PUMA applications are submitted on a voluntary basis. As part of the incentives for development of pediatric medicines, PUMA applications have automatic access to the centralized procedure. Pharmaceuticals that are PUMA authorized through the centralized procedure will benefit from data -, market - and labeling exclusivity. From July 2008, pharmaceutical companies have been obliged to submit results of studies according to an adopted PIP, or, if appropriate, an accepted deferral or waiver, at the time of their submission of the MAA for their new pharmaceutical.

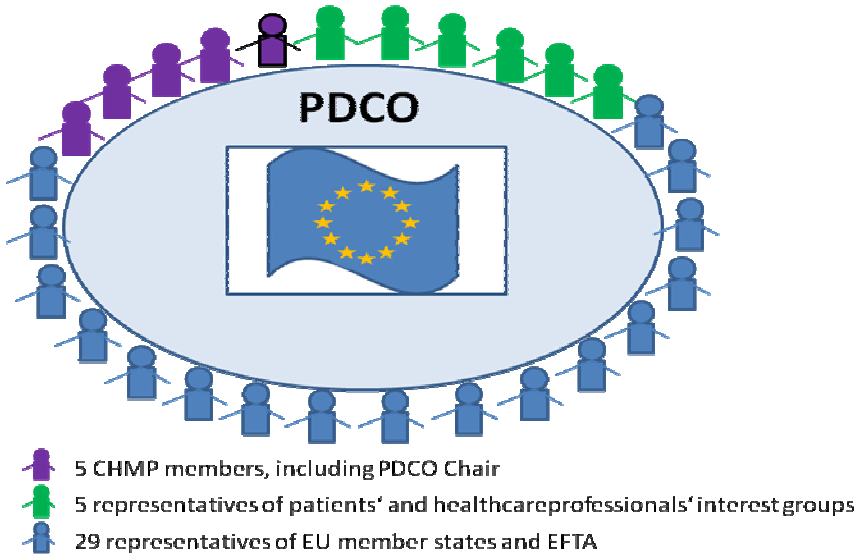

Figure 1: *Sketch illustrating the organization of the Pediatric Committee. (Adapted from P. Karoly, 2008)*

Two years from the entry into force of the new pediatric regulation (26th January 2009), the pharmaceutical industry were also required to submit the results of pediatric studies according to an adopted PIP upon the submission of a MAA for new indications, new routes of administration and/or new pharmaceutical formulations, unless the EMEA had granted a waiver cq deferral.[27]

The Pediatric Committee The PDCO consists of pediatricians, physicians, pharmacists and a few pre-clinical professionals. These 'competent authorities' are nominated by the EU member states (25 representatives), by the members of the European Free Trade Association (EFTA) - of which the members are Norway, Iceland, Switzerland and Liechtenstein - and by patients' and health care professionals' interest groups (5

[27] EMEA© Presentation of the EMEA Pediatric Team for Scientific Advice, Pediatrics and Orphan Drugs Sector: The Pediatric Regulation (2007).

representatives).

Five further members of the PDCO are nominated by the Committee for Medicinal Products for Human Use (CHMP) cq its Expert Advisory Group on Pediatric Medicines (PMEAG). The chair of the PDCO is delivered and alternated between the representatives of the CHMP.[28] The PDCO meets 13 times per year.[29] The main role and responsibilities of the PDCO is to assess the content of PIPs and adopt opinions on them in accordance with Regulations (EC) 1901/2006 and 1902/2006, including the assessment of applications for a full or partial waiver and assessment of applications for deferrals.

Other tasks of the PDCO include:

- Assessing data generated in accordance with agreed PIPs and adopting opinions on the quality, safety or efficacy of any medicine for use in the pediatric population (at the request of the CHMP or a competent authority),
- Advising EU member states on the content and format of data to be collected for a survey on all existing uses of medicinal products in the pediatric population,
- Advising and supporting the EMEA on the creation and maintaining of a European network of persons and bodies with specific expertise in the performance of studies in the pediatric population,
- Providing advice on any question relating to pediatric medicines, at the request of the EMEA Executive Director or the European Commission (EC),
- Establishing and regularly updating an inventory of pediatric medicinal product needs,
- Advising the EMEA and the EC on the communication of arrangements available for conducting research into pediatric medicines.

The PDCO is not responsible for MAAs of medicinal products for pediatric use. This responsibility remains fully within the remit of the CHMP, in accordance with Regulation EC No 726/2004. The CHMP, or any other competent authority, may request the PDCO to prepare an opinion on the quality, safety and efficacy of a medicinal product for use in the pediatric population if these data have been generated in accordance with the adopted PIP.
In December 2008, Dr Carleer, an EMEA expert in pre-clinical safety and the Belgian

---

[28] PDCO members: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000007jsp& murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e9f.

[29] PDCO meeting reports: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/ document_listing_000192.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028eab.

alternate of the PDCO, established the Nonclinical Working Group (NcWG). The NcWG consists of 12 core, non/pre-clinical-expert members all belonging to the EMEA scientific committees and include members from the Scientific Advice Working Party (SAWP), the PDCO and EMEA coordinators. Additional non-clinical experts are invited to join on a case by case basis and the outcome. The main role of the NcWG is to help to solve some of the inconsistency previously seen with regard to the pre-clinical section of PIPs and to balance the underrepresented pre-clinical expertise in the PDCO, with special focus on additional pre-clinical studies requiring in vivo testing in juvenile animals. In Figure 2, the suggested approach to the use of juvenile animal studies for a PIP has been outlined.[30, 31]

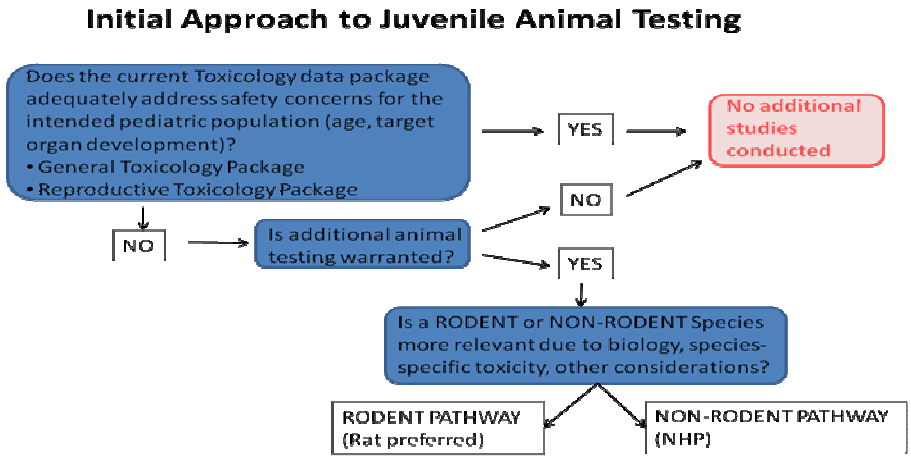

Figure 2: *Approach to additional in vivo studies to complete the PIP with juvenile animal models prior to clinical studies in pediatric subpopulations (Adapted from T. Coogan, 2009).*

In Figure 3, the timelines for the consultations between the pharmaceutical industry and the PDCO have been sketched. Normally, the first time of contact is after finalization of the Phase I clinical trials. At this point in time a PIP Letter of Intent needs to be sent to the PDCO. The letter of intent is submitted two months prior to the first PIP application (Summery Report).

After validation of the summery report, the PIP procedure starts and several meetings will be scheduled to plan, discuss and adopt an appropriate PIP with a final compliance check at the time of MA. This procedure is sketched in Figure 4.

---

[30] Coogan, T. Pediatric Investigational Plans (PIPs) and Case Studies. BioSafeMeeting, October 2009.

[31] CPMP Draft Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for pediatric indications. Doc. Ref. EMEA/CPMP/SWP/169215/2005.

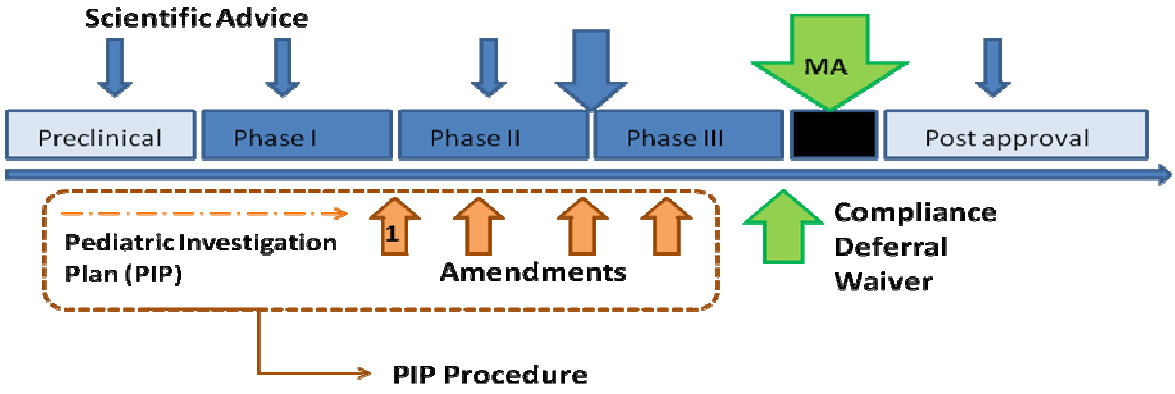

Figure 3: *Timelines for consultations of between the pharmaceutical industry and PDCO (Adapted from P. Karoly, 2008).*

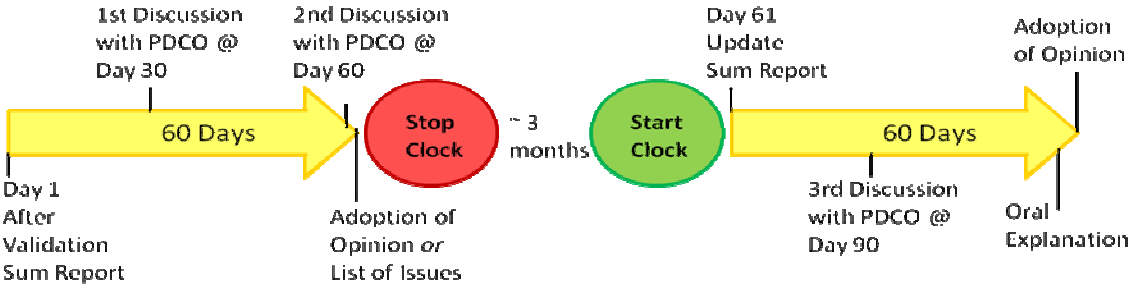

Figure 4: *Overview of the PIP Procedure (Adapted from P. Karoly, 2008).*

7. PEDIATRIC INVESTIGATION PLAN

Pediatric Investigation Plan (PIP)[32, 33, 34, 35, 36, 37, 38] The PIP is a research and development program, aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product may be authorized to treat a pediatric subpopulation. The principles of the PIP are that it

- Covers all the subsets of the pediatric population, and all the existing and new indications
- Covers all (new) routes of administrations and appropriate formulations,
- Focuses on trials that allow labeling medical products for the appropriate usage in all relevant pediatric subsets, and
- Contains all relevant information, *e.g*. (un)favorable, incomplete or discontinued safety, PK/PD or clinical trials and/or results from trials in other indications.

The key discussion points that impact the PIP are:

- The lowest age to be included in the clinical pediatric program
- The duration of treatment (*e.g*. acute vs. chronic),
- The identified toxicity in adult clinical program,
- The identified target organs in adult animal toxicity assessments,
- The previously identified developmental toxicity from the reproductive toxicology program,
- The route of administration,
- The unique formulation requirements with novel excipients,
- The PK and metabolism in adult animals and humans,

---

[32] Guideline on conduct of pharmacovigilance for medicines used by the pediatric population, EMEA, Aug 2005; http://www.emea.int.pdfs/human/phvwp/23591005en.pdf.

[33] EU Notice to Applicants. A guideline on summary of product characteristics. October 2005. (www.pharmacos.eudra.org/F2/eudralex/ vol-2/C/SPCGuidRev1-Oct2005.pdf.

[34] EMEA Working Group on Quality Review of Documents. Addressing the pediatric or incapacitated patient in the package leaflet. 2000.

[35] EMEA Reflection paper: formulations of choice for the pediatric population. (Doc. Ref. EMEA/CHMP/ PEG/194810/2005).

[36] EMEA Reflection paper: formulations of choice for the pediatric population. (Doc. Ref. EMEA/CHMP/ PEG/194810/2005).

[37] EMEA concept paper on the development of a committee for proprietary medicinal products (CPMP) points to consider document on the evaluation of the pharmacokinetics of medicinal products in the pediatric population (Doc. Ref. EMEA/18939/03).

[38] EMEA Discussion papers on the impact of renal immaturity (Doc. Ref. CPMP/PEG/35132/03), liver immaturity (Doc. Ref. EMEA/CHMP/PEG/194605/2005) and/or lung and heart immaturity (Doc. Ref. EMEA/CHMP/114218/2006) when investigating medicinal products intended for neonatal and pediatric use.

- The species selection supporting overall development (*e.g.* rat and dog) and species specific toxicity.

Although the pediatric assessment/PIP is required to be in place prior to MAA, it does not necessarily need to be completed prior to the authorization! The type of studies expected in a PIP include safety studies in the appropriate pediatric subsets (always), PK studies, PK/PD studies as well as clinical efficacy studies and suggested formulations appropriate for the relevant pediatric subgroups as well as several pre-clinical studies. EMEA's reflection paper on the need of special drug formulations for the pediatric subpopulations states that in general the formulations are to be as comfortable, painless and stress-less upon application as possible.
In particular this means for instance that oral formulations have to be suitable in size, taste, smell, texture and dosing-regime. The types of studies that need to be completed prior to the start of pediatric clinical trials are:

- Safety data from previous adult human exposure,
- Appropriate repeated dose toxicity studies, all reproduction studies and the standard battery of genotoxicity tests,
- Possibly juvenile animal studies, when appropriate (See Figure 2) as well as
- Carcinogenity testing if appropriate.

In accordance with the pediatric regulation, the European Commission (EC) has drawn up a document setting out the detailed arrangements for PIP applications as well as waiver or deferral requests, to cover:

(1) The format and content of applications for agreement or modification of PIPs and requests for waivers/deferrals,
(2) Operation of compliance check and
(3) Proposed criteria for assessing significant studies.

In addition, EMEA has published a procedural advice document on the EMEA pediatric webpage. The PIP application documents are setup in 5 sections (A-E) plus appendices (F):[39]

---

[39] Sam, T. Regulatory requirements fort he development of medicinal products for pediatric use. Oral

SectionA contains all the administrative and product information.
SectionB describes the overall development of the product, such as the similarities/differences of the disease/condition between populations (adult/pediatric), the anticipated similarities/differences in effect of the product on the disease/condition, the prevalence and incidence of the disease/condition in the pediatric population, the current methods of diagnosis, prevention or treatment in pediatric population and the significant therapeutic benefit cq the fulfillment of the therapeutic needs in the pediatric population.
SectionC describes how to apply for product-specific waivers.
SectionD is dedicated to strategic evaluations e.g. the overall proposed strategy, the strategy in relation to quality, (non-) clinical aspects, as well as the planned measures for the pediatric development - including an overall summary table of the non-clinical and clinical section, the outline of each of the planned or performed study and a synopsis of the protocol (non-clinical or clinical) - and the timeline of measures in the plan.
SectionE describes how to apply for a deferral.
SectionF is dedicated to appendices, lists of references, the investigator's brochure, expert opinions and scientific advice by competent authorities and the latest approved product information (for authorized products).

The PIPs have been introduced by the EC to help ensure that medicines for children are included in the mainstream drug development process in Europe, rather than as an optional extra. This means that children will benefit from more effective treatments and companies will be rewarded for the extra work and higher costs of pediatric drug development. The aim is not to test medicines on children at an earlier and earlier phase as this would neither be safe nor ethical. Rather it is to create a written, flexible dialogue between the EMEA, competent authorities (PDCO) and the pharmaceutical industry so that medicines that benefit children can be developed in tandem with – but not delay the time to market of the same new drug for adults. Overall the PIP's essence is a rationale for development of a pharmaceutical product suitable for the pediatric populations, including the known pharmacology of product, the non-clinical data for the product at the time of the MAA, the overall pediatric development plan, a proposal for age appropriate formulation, an outline of each trial suggested, the timelines, and at MAA, the binding decision and compliance check for the PIP of the pharmaceutical company that seeks the MA from the

---

Presentation at WHO/FIP-sponsored workshop in Capetown (SA), April 2007.

PDCO/CHMP.

The decision types taken by the PDCO/CHMP are:

P: decision agreeing on a PIP, with or without partial waiver(s) and or deferral(s)
W: decision granting a waiver in all age groups for all conditions/indications
PM: decision on the application for modification of an agreed PIP
RP: decision refers to a refusal on a proposed PIP
RW: decision refers to a refusal on a request for request on a waiver in all age groups.[40]

In the pre-clinical section, a justification for the non-clinical development strategy, e.g. a justification of the juvenile toxicity study designs (including species, age and duration of treatment) cq a justification of why juvenile studies are not warranted needs to be included (See Figure 2). A specification is given in this section of which studies (incl. juvenile in vivo studies) should be completed before dosing in children can be commenced, based upon actual and/or published (pre-)clinical data. Companies are encouraged to invest time to educate themselves and the 'general public' in issues concerning toxicology and biology. In the clinical-pharmacology sections, reflections need to be specified concerning (1) the need for proof of concept (POC) for the use of the pharmaceutical product in pediatric populations (for example using non-clinical in vitro and/or in vivo models) as well as (2) the need for PD-studies, e.g. to establish a dose relationship for a PD endpoint (including whether there is a reliable animal model to justify the selection of a specific species for potential juvenile animal studies) and (3) the need for safety pharmacology studies using non-clinical in vitro and/or in vivo models to investigate specific functions of the physiological system, (4) the need for specific PK studies selecting the most relevant species for potential juvenile animal studies (small molecule) and (5) the need for specific toxicity studies including tox-PK in juvenile animals as well as toxicity studies to address specific endpoints (e.g. neurotoxicity, immuno-toxicity or nephro-toxicity) at a particular developmental phase and additional local tolerance studies e.g. for topical application dosage forms. Templates for proposed pediatric study requests are available both at EMEA and FDA homepages.[41, 42]

---

[40] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d129.

[41] EMEA Form: Paediatric investigation plan application and request for waiver.pdf.

Of course, the clinical trial information provided at a clinical trial in a pediatric population should be easy to read and factual without being frightening. The European research guidance ICH E11 Reference 8 states that “All participants should be informed to the fullest extent possible…in language and terms they are able to understand”. Pharmaceutical companies and medical researchers testing pediatric medicines are therefore required to write information for children at a level appropriate for the reading age/ability of the population to be tested. It is very important that the information makes it clear that taking part is completely voluntary and that nobody will be angry with the child if it doesn’t want to take part. It can say “no” at any time before or during the research without having to give a reason.

It is an ethical "must" that children are happy to take part in the research. Information needs to be jargon free, factual and concise without being patronizing or frightening. Great care is needed in the translation of global pediatric trials’ information to avoid cross-cultural misunderstandings and recruitment failure! Since the European pediatric regulation came in force, a child's consent/assent to participate in research has especially become important.

Subsequently, if waivers are not granted and/or appropriate, the suggested pediatric clinical trials in the PIP need to address the following items:

(1) Type and objective of the proposed study,
(2) Indication(s) studied,
(3) Number of patients and specific age groups included in the study,
(4) Clinical endpoints, timing of assessments and entry criteria,
(5) Information about the pharmaceutical products used in the study, including information on the dosage forms, dosing regimens and route(s) of administration,
(6) Drug-specific safety concerns to be monitored or assessed,
(7) Statistical information, including power of study and statistical analyses of the data,
(8) Labeling that may result from the studies,
(9) Format of the report to be submitted to the authorities and, finally,
(10) Timeframe for the submitting of reports of the studies to the appropriate authorities.

---

[42] Template for a proposed pediatric study request is available at www.fda.gov/cder/pediatric/wr_template.htm.

Figures 3 and 4 (Chapter 5) illustrated the timelines and process of the PIP application. Scientific advice, including advice on pharmacovigilance and risk management systems is offered to the pharma-industry free of charge by the Scientific Advice Working Party (SAWP) in close cooperation with the PDCO; Prior to MA, the compliance with the agreed PIP will be tested and approved, and, where appropriate, a deferral or waiver will be granted. Waivers will be granted if the pharmaceutical products are unlikely to benefit children, or if clinical studies are impractical *cq* impossible in the specified pediatric populations, or if there is already existing evidence of ineffective *cq* unsafe use of the pharmaceutical product in children. These waivers are either disease or formulation specific (see also Table 1). A recent example of a granted waiver is the one asigned for Adalimumab (Humira®), a monoclonal antibody that inhibits TNFα and that has been developed by Abbott Laboratories Ltd.[43] Adalimumab is the third TNFα inhibitor, after infliximab and etanercept, to be approved.[44, 45, 46, 47]

The antibody is formulated as a solution for subcutaneous injection as an oral formulation would be destroyed by the digestive tract. Thus, administration of this drug will always be extremely stressful especially for the younger pediatric subsets. The inhibitor is intended for the treatment of Rheumatoid Arthritis (RA), Crohns' Disease (CD), Plaque Psoriasis (PP), Psoriatic Arthritis (PA), Enthesitis-related arthritis (EA) and Juvinile Idioparhic Arthritis. Adalimumab was approved in the USA by the FDA in 2008. The waiver was granted in accordance with Articles 13 and 18 of Regulation (EC) No 1901/2006 and applied to the indication RA in children from birth to less than 2 years on the grounds that the condition does not occur in the specified pediatric subsets, for Crohns', also on the ground that the condition does not occur in the specified pediatric subsets up to 6 years, for Psoriasis the waiver applied to children less than 4 years as the solution for subcutaneous injection is considered likely to be unsafe, for PA the waiver covered all pediatric subsets

---

[43] EMEA© P/102/2009 Decision on on the agreement of a PIP and on the granting of a waiver for adalimumab (Humira) (EMEA-000366-PIP01-08) in accordance with Regulation 1901/2006 of the European Parliament and of the Council as amended (Doc. Ref. EMEA/288840/2009).

[44] Scheinfeld, N. Adalimumab (HUMIRA): a review. J Drugs Dermatol. 2003; 2:375-7.

[45] Podolsky, D. K. Inflammatory bowel disease. New England Journal of Medicine 2002, 346 (6): 417–29.

[46] Croom, K.F. and McCormack, P.L. Adalimumab : in plaque psoriasis. Am J Clin Dermatol. 2009;10(1):43-50.

[47] Abbott publication: http://www2.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/ www/story/11-12-2001/ 0001613559&EDATE=.

up to 18 years on the grounds that this condition does not occur in any of the specified pediatric subsets, and finally for EA the waiver applied to the pediatric subsets up to 12 years, also on the grounds that this condition does not occur in children under 12 years. This means that Abbott only has to deliver a PIP for the conditions and age groups not covered in the waiver. In Chapter 8, two examples of a PIP for marketed drugs, a small molecule and a monoclonal antibody, are described in more detail. A deferral until a specified date after approval of the drug can be obtained only when studies in children will be more appropriate when more experience on use of a product in adults has been collected or when studies in children take longer than studies in adults. In addition, pediatric studies may be delayed when the development of a pediatric formulation is not complete.

8. INCENTIVES AND REWARDS

For the pharmaceutical industry this regulation has brought tremendous opportunities and challenges and it is expected to have a profound effect on the entire drug development process. One of the challenges is to fulfill the objective to actually bring financial rewards to companies to offset the costs of the additional pediatric research.[48] Timing appears to be of key importance with regard to the presentation and discussion of the PIP with the PDCO and as part of the general strategy to develop a pharmaceutical product towards MA. At the end of Phase I, it is not at all certain that the compound in development will at the end of the clinical development program indeed be suitable for launching as a drug. At this early stage, adequate product specific data concerning safety and efficacy in adult humans are still lacking. Another concern for the pharmaceutical industry is the fact that the FDA authorities do not call for discussions of the pediatric plans until a much later stage in the development program, i.e. between Phase II and III.[49]

Fact is that both EU, including the EFTA-countries and the USA, upon submission of a MAAs cq NDAs (new drug applications) or line extensions (e.g. a MA for additional indications) require an adopted, compliance-checked PIP that either contains pediatric data, a deferral or a waiver for each of the defined pediatric population subsets. At this point, a

---

[48] Lamprill, J. Paediatric Regulation: Reasons to be Proactive: Scrip Drug Delivery 2006, p9-11.

[49] Pediatric Rule is codified at 21 CFR 314.55 and 601.27 with additional amendments to 21 CFR 201, 312, 314 and 601; the Pediatric Research Equity Act of 2003 can be accessed at http://www.fda.gov.cder.pediatric/index.htm.

pharmaceutical company needs to be careful to not commit itself to an unworkable PIP and/or protocols with unrealistic timelines. To date, the experience with PIPs, for small molecules especially, is substantial, while the experience with biopharmaceuticals is still relatively small. Initially, the EMEA tried to boost the development of existing medication into appropriate medication and/or formulations for the treatment of illnesses in the pediatric population, through the PUMA regulation. This voluntary regulation enables the pharmaceutical industry to obtain exclusive MA (i.e. data protection) for authorized, but off-patent/'off'-SPC medicines for a period of 10 years upon the submission of convincing clinical data and appropriate formulation in pediatric populations, in accordance to an agreed PIP. The PUMA part of the new pediatric regulation was the first to become effective. Today the EMEA demands a PIP for both new, in patent pharmaceuticals and for new indications, formulations or routes of administration of in patent drugs upon submission of an MAA by the pharmaceutical industry. Noncompliance with the pediatric regulation leads to rejection of the MAA. On the other hand, upon authorization in all EU member states and after inclusion of the pediatric study results in the SmPC - even when negative - the pharmaceutical company is eligible for a six months' patent extension (SPC) - the carrot or the stick approach. Companies that submit a PIP and conduct pediatric clinical trials in agreement to the adopted plan for off-patent, authorized drugs, also receive a 6 months SPC of exclusive labeling and marketing of this off-patent product in the pediatric population. Orphan-drugs, i.e. pharmaceutical products designated for commercially uninteresting diseases and/or patient groups, even benefit from two years extra market exclusivity in addition to the 10-year exclusivity awarded under the EU Orphan Regulation (EC) No 141/2000.

9. EXAMPLES OF PEDIATRIC INVESTIGATION PLANS

9.1 RIVAROXABAN; A SMALL MOLECULE

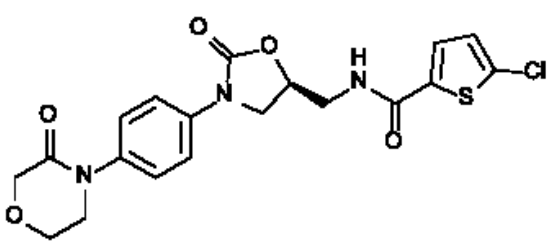

Figure 5. *Molecular structure of Rivaroxaban (BAY 59-7939, Xarelto®, C19H18Cl1N3O5S1, (S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-5-yl]methyl} thiophene-2-carboxamide,).*

Rivaroxaban(BAY 59-7939; Xeralto®)[50, 51, 52] Kakkar, A.K. et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008, 372 (9632): 31–39. was granted MA by the EU and Health Canada in September 2008 and in March 2009 by the FDA. The MA holder is Bayer Schering Pharma AG. In Europe, the CHMP decided that rivaroxaban's benefits were greater than its risks when used in the prevention of venous thromboembolism (VTE, the formation of clots in the veins) in adult patients undergoing elective hip or knee replacement surgery. [53, 54] Rivaroxaban is available as red, round tablets (10 mg) taken once daily with or without food. The medicine can only be obtained with a prescription and the treatment schedule should start 6 to 10 hours after surgery, provided that the patient is no longer bleeding from the site of surgery. Treatment should continue for 5 weeks in patients who have had hip replacement surgery, and for 2 weeks in patients who have had knee replacement surgery. Rivaroxaban was compared with enoxaparin (Lovenox®, marketed by Sanofi-Adventis, a low molecular weight heparin derived from intestinal mucosa from pigs) in three main studies, two in patients undergoing hip replacement surgery and one in patients undergoing knee replacement surgery.[55, 56, 57, 58, 59] The endpoint in all these studies was the efficacy in preventing blood

---

[50] Roehrig, S et al. Discovery of the novel antithrombotic agent 5-chloro-N-({(5S)-2-oxo-3- [4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene- 2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. J. Med. Chem. 2005, 48 (19): 5900–5908.

[51] Eriksson, B.I. et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006, 114 (22): 2374–2381.

[52] Turpie AG. New oral anticoagulants in atrial fibrillation. Eur. Heart J. 2008, 29 (2): 155–165.

[53] EMEA Rivaroxaban Information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124#non.

[54] European Medicines Agency (2008). CHP Assessment Report for Xarelto (Doc. Ref. EMEA/543519/2008).

[55] Eriksson, B.I. et. al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008, 358 (26): 2765–2775.

[56] Kakkar, A.K. et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008, 372 (9632): 31–39.

[57] Lassen, M.R. et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008, 358 (26): 2776–2786.

[58] Turpie, A. et al. Comparison of rivaroxaban – an oral, direct factor Xa inhibitor – and subcutaneous enoxaparin for thromboprophylaxis after total knee replacement (RECORD4: a phase 3 study). European

clotting (measured by looking at the number of patients who either had blood clots in the veins or in the lungs), and preventing death during the treatment period. Rivaroxaban was more effective in these clinical trials in preventing the formation of blood clots and/or death than enoxaparin. In the USA, an FDA advisory panel concluded that the RECORD trials demonstrated that rivaroxaban is non-inferior and possibly superior to subcutaneous enoxaparin 40 mg once daily. However, they also found an increased risk of bleeding with rivaroxaban and that the studies did not address the question of long-term (i.e. > 35 days) use. It was noted that one participant out of 6183 randomized to rivaroxaban died of liver toxicity.

The structure of rivaroxaban (Figure 2) is very similar to the structure of the antibiotic linezolid: both drugs are built around an oxazolidinone-derived core structure. Linezolid - marketed by Pfizer under the trade names Zyvox® (USA, UK and Australia) and Zyvoxid® (in Europe) – is a synthetic antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.[60] A member of the oxazolidinone class of drugs, linezolid is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA). Linezolid was discovered in the 1990s but first approved for use in 2000. It is the first commercially available oxazolidinone antibiotic, and to date the only marketed oxazolidinone, although others are in development.1 However, studies addressing possible mitochondrial toxicity (known complication of long-term linezolid use) or antimicrobial effects with rivaroxaban and its metabolites were low to negative. As rivaroxaban is only meant (and approved) for short-term use, the mitochondrial toxicity found in in vitro studies is not likely to be of clinical consequence. Rivaroxaban's mechanism of action (MoA) is the inhibition of both free Factor Xa and Factor Xa bound in the prothrombinase complex. It is a highly selective direct Factor Xa inhibitor with oral bioavailability and rapid onset of action. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not

---

Federation of National Associations of Orthopaedics and Traumatology Annual Meeting; May 29 – June 1, 2008; Nice, France, Abstract F85.

[59] Turpie, A.G. et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009, 373 (9676): 1673–1680.

[60] Pfizer ZYVOX® (linezolid) Label Information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016, 021131s013,021132s014lbl.pdf.

inhibit thrombin (activated Factor II), and no effects on platelets have been demonstrated. The most common side effects with rivaroxaban (seen in up to 10% of the patient population) are bleeding following an operation, nausea, anaemia (low red blood cell counts) and increased levels of some liver enzymes in the blood. Rivaroxaban is contra-indicated in people who may be hypersensitive (allergic) to rivaroxaban or any of the other ingredients, in patients who are bleeding or in patients who have a liver disease that is associated with an increased risk of bleeding and in women who are pregnant or breast-feeding. A number of anticoagulants inhibit the activity of Factor Xa. Unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux inhibit the activity of factor Xa indirectly by binding to circulating antithrombin (AT). However, these agents must be injected. Warfarin, phenprocoumon, and acenocoumarol are orally active vitamin K antagonists (VKA) which, also indirectly, decrease hepatic synthesis of a number of coagulation factors, including Factor Xa. In recent years, a new series of oral, direct acting inhibitors of Factor Xa have entered clinical development. These include rivaroxaban, and several not yet approved compounds (apixaban, betrixaban, LY517717, YM150, and DU-176b). Rivaroxaban has predictable PK across a wide spectrum of patients (age, gender, weight, race) and a flat dose response across an 8-fold dose range (5–40 mg). Clinical trial data have shown that it allows predictable anticoagulation with no need for dose adjustments and routine coagulation monitoring. However, these trials have excluded patients with liver disease and end-stage liver disease and use of rivaroxaban may be unsafe in these populations.

At the moment, rivaroxaban is being studied in phase III clinical trials for stroke prevention in non-valvular atrial fibrillation (ROCKET-AF), prevention of VTE in hospitalized medically ill patients (MAGELLAN), treatment and secondary prevention of VTE (EINSTEIN), and secondary prevention of major cardiovascular events in patients with acute coronary syndrome (ATLAS ACS TIMI 51).[61, 62, 63, 64, 65, 66] In the original

---

[61] Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation (ClinicalTrials.gov).

[62] MAGELLAN - Multicenter, Randomized, Parallel Group Efficacy Superiority Study in Hospitalized Medically Ill Patients Comparing Rivaroxaban with Enoxaparin (ClinicalTrials.gov).

[63] The Einstein-Extension Study: Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism (ClinicalTrials.gov).

[64] Einstein-DVT Evaluation: Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Deep-Vein Thrombosis (DVT) Without Symptomatic Pulmonary Embolism:

CHMP assessment report for rivaroxaban (Procedure no. EMEA/H/C/000944) there is no PIP. According to the European legislation valid at the time of the submission of an MAA (before July 2008), there was no requirement to submit a PIP. However, as Bayer Schering Pharma AG is seeking to extend its MA for other indications apart from the prevention of VTE in adult patients undergoing elective hip and knee replacement surgery, a PIP has been drafted, discussed with the PDCO and agreed upon (EMEA-000430-PIP01-08-M01). The current PIP version for rivaroxaban, that was accepted 2nd June 2010 (P/95/2010), includes several deferrals (adjusted timelines for pediatric clinical studies) and waivers. It addresses age-appropriate formulation (smaller film coated tablets for oral use in the different pediatric subsets), as well as the changes in measures and the timelines of the PIP. The condition considered is VTE. The (additional) adult indications proposed for rivaroxaban for the extended MA are (1) the prevention of VTE in hospitalized medically ill patients, (2) the prevention of stroke and non-central nervous system embolism in subjects with non-valvular atrial fibrillation, the prevention of VTE in adult patients undergoing elective hip and knee replacement surgery and (4) the prevention of atherothrombotic events in patients with a recent acute coronary syndrome. A waiver applies to all subsets of the pediatric population from birth to less than 18 years of age for age-appropriate formulation and film coated tablets for oral use and on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified pediatric subsets.[67]

The indications targeted in the PIP are the treatment and, secondary, the prevention of VTE in all pediatric subsets from birth to less than 18 years of age. For these clinical studies, the following formulations are developed: film coated tablets with 1.25 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg rivaroxaban for oral use. Table 3 describes the studies and clinical trials to be performed by Bayer Schering Pharma AG in more detail. The required date of completion of this program is October 2017.

(ClinicalTrials.gov).

65 Einstein-PE Evaluation: Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Pulmonary Embolism (PE) With Or Without Symptomatic Deep-Vein Thrombosis (ClinicalTrials.gov).

66 A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome (ClinicalTrials.gov).

67 EMEA PIP information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/ EMEA-000430-PIP01-08-M01/pip_000339.jsp&murl=menus/medicines/medicines.jsp&mid= WC0b01ac058001d129.

Table 3: *Studies and Pediatric Clinical Trials agreed to for Rivaroxaban*

Area	**# of Studies**	**Description**
Quality	1	Age appropriate formulation for oral use
Non-clinical	2	Non-Clinical Study **1**: Toxicologic study in juvenile rats with a treatment duration of 3 weeks Non-Clinical Study **2**: Toxicologic study in juvenile rats with a treatment duration of 13 weeks
Clinical	5	Clinical Study **1**: Relative bioavailability and food effect of age-appropriate formulation in healthy adults Clinical Study **2**: Safety, tolerability, PK, and PD study of rivaroxaban Clinical Study **3**: 4 week multinational, multicenter, open-label, active-controlled, randomized, multiple dose, prospective study to evaluate safety and PK/PD of rivaroxaban film coated tablets in pediatric subjects from 6 years to less than 18 years of age who have been pre-treated for at least two months with either LMWH and/or vitamin K antagonist for VTE Clinical Study **4**: 4 week multinational, multicenter, open-label, active-controlled, randomized, multiple dose, prospective study to evaluate safety and PK/PD of rivaroxaban age-appropriate formulation in pediatric subjects from 6 months to less than 6 years of age who have been pre-treated for at least two months with either LMWH and/or vitamin K antagonist for VTE. Clinical Study **5**: 3 months multinational, multicenter, open-label, active-controlled, randomized, multiple dose, prospective study to evaluate safety and efficacy of rivaroxaban age-appropriate formulation and film coated tablets in pediatric subjects from birth to less than 18 years of age who have acute VTE

9.2 USTEKINUMAB; A MONOCLONAL ANTIBODY

Ustekinumab (Stelera®, CNTO 1275) has been approved in Canada, Europe and the USA to treat moderate to severe plaque psoriasis in adult patients. The EMEA granted an MA to Janssen-Cilag International NV for ustekinumab for the treatment of moderate to severe plaque psoriasis in adults (a disease causing red, scaly patches on the skin) with the authorization date being 16/01/2009 (Ref. Doc. EMEA/CHMP/582270/2008). The MA is valid for five years, after which it may be renewed. Ustekinumab, is a human monoclonal antibody that is directed against interleukin 12 (IL-12) and interleukin 23 (IL-23), two naturally occurring cytokine proteins that regulate the immune system and immune-

mediated inflammatory disorders.[68, 69, 70, 71, 72, 73, 74] Ustekinumab is a solution for subcutaneous (sc) injection, it is available in a vial or in a prefilled syringe. Each vial or syringe contains either 45 or 90 mg ustekinumab. Ustekinumab is used in patients who failed to respond to or cannot use other systemic (whole-body) treatments for psoriasis, including ciclosporin, methotrexate and PUVA (a combination therapy of psoralen and ultraviolet-A light exposure).[75, 76, 77] The CHMP noted that, although ustekinumab has a new mode of action - blocking the activity of two messenger molecules (IL-12 and IL-23) rather than only one - the unexpected increases in problems affecting the heart and blood vessels and psychiatric problems such as depression that were seen in some studies and that might be related to ustekinumab were of high concern, and they decided to restrict the use of ustekinumab to patients in whom other treatments had failed or who could not receive them. The medicine can only be obtained with a prescription. The following dosing regimen of ustekinumab is being advised: a first injection of 45 mg, followed by a further injection 4 weeks later, and then an injection every 12 weeks. Treatment should be interrupted if there is no response after 28 weeks. Patients weighing over 100 kg should be given ustekinumab in 90-mg doses. Patients may be trained to inject ustekinumab themselves. The MoA of ustekinumab is as follows: the antibody attaches itself to the p40 subunit of cytokines IL-12 and IL-23. By blocking the activity of these two interleukins, ustekinumab reduces the activity of the immune system and the symptoms of the disease.

---

68 EMEA: http://www.emea.europa.eu/pdfs/human/opinion/Stelara_58227008en.pdf.

69 Reddy, M. et al. Modulation of CLA, IL-12R, CD40L, and IL-2Ralpha expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. Cell. Immunol. 2007, 247 (1): 1-11.

70 Leonardi, C.L. et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008, 371 (9625): 1665–1674.

71 Papp, K.A. et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008, 371 (9625): 1675–1684.

72 Griffiths, C. et al. Comparison of Ustekinumab and Etanercept for Moderate-to-Severe Psoriasis. N Engl J Med 2010, 362 (2): 118–128.

73 Cytokine tutorial published by the University of Arizona http://www.biology.arizona.edu/immonology/ tutorials/ immunology/main.html.

74 Weber, J. and Keam, S. BioDrugs 2009;23(1): 53-61.

75 Psoralen is a furo-coumarin (high UV absorbent small molecule) that is a natural product and is taken orally to sensitize the skin to the then applied UV-A radiation. Psoralen appears in parsley, celery and figs.

76 Long term use of UV-A light therapy has been associated with skin cancer; James, W.D. et al. Andrew's Diseases of the Skin: clinical dermatology. Sanders Elsevier 2006.

77 de Mol, N.J. Involvement of molecular singlet oxygen in the photosensitiying action of furocoumarins. Thesis, 1980 Leiden (NL).

In two Phase III trials for moderate to severe psoriasis (PHOENIX I and II; multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of ustekinumab in the treatment of subjects with moderate to severe plaque psoriasis), the longest lasting over 1.5 years at the time of submission for MAA, ustekinumab was found safe and effective.[78, 79, 80] Over half of the patients included in these studies had failed one or more other treatments for psoriasis or could not receive other treatments. Both studies looked at two doses of ustekinumab (45 and 90 mg). The main measure of effectiveness was the number of patients who 'responded' to treatment after 12 weeks, meaning that symptom scores improved by 75% or more. There was no difference in response rates between the two doses of ustekinumab in patients weighing below 100 kg. Patients weighing over 100 kg had a better response to the 90-mg dose. One of the Phase III clinical trials was still ongoing at the time of the medicine's assessment by the admission authorities and was scheduled to last for up to five years. A third Phase III trial, ACCEPT, compared the efficacy and safety of ustekinumab with etanercept (a protein based drug licensed to treat psoriasis) in the treatment of moderate to severe plaque psoriasis.[81, 82] This trial found a significantly higher clinical response with ustekinumab over the 12-week study period compared to high-dose etanercept. It also demonstrated the clinical benefit of ustekinumab among patients who failed to respond to etanercept. Other ongoing clinical trials include investigations for treatment of psoriatic arthritis (Phase III), multiple sclerosis (Phase II) and sarcoidosis (versus golimumab; Simponi).[83, 84] The most common side effects with ustekinumab (seen in more than 10% of the patients) are upper respiratory tract infection (colds) and nasopharyngitis (inflammation of the nose and throat). Ustekinumab is contra-indicated in people who may be hypersensitive (allergic) to ustekinumab or any of the other ingredients. It must not be used in patients who have an active infection and treatment should be interrupted in patients who develop a serious

---

78 A Study of the Safety and Efficacy of CNTO 1275 in Patients With Active Psoriatic Arthritis (ClinicalTrials.gov NCT00267956).

79 A Study of the Safety and Efficacy of Ustekinumab in Patients With Psoriatic Arthritis (ClinicalTrials.gov NCT01009086).

80 Johnson, L.L. Study: Drug for serious psoriasis tops competition Associated Press. 18 Sept 2008.

81 Etanercept is a fusionprotein marketed by Takeda Pharmaceuticals Ltd in Japan and by Wyeth/Amgen in the USA and the EU.

82 Peppel, K. et al. A tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein as a bivalent antagonist of TNF activity. J. Exp. Med. 1991, 174(6), 1483-1489.

83 A Safety and Efficacy Study of CNTO1275 in Patients With Multiple Sclerosis (ClinicalTrials.gov NCT00207727).

84 A Study to Evaluate the Safety and Effectiveness of Ustekinumab or Golimumab Administered Subcutaneously in Patients With Sarcoidosis (ClinicalTrials.gov NCT00955279).

infection. The CHMP assessment report for ustekinumab (Procedure no. EMEA/H/C/ 000958) also includes the submission of a PIP (EMEA-000311-PIP01-08).[85] Janssen-Cilag International NV provided an application for a PIP for ustekinumab, including deferrals and waivers for agreement to the EMEA on 25 June 2008. The procedure started end of July 2008. Supplementary information was provided by the applicant end of October 2008. The current version of the PIP was adopted in February 2009 (P/19/2009) and it includes several deferrals and waivers. The proposed indication for the use of ustekinumab in the pediatric population is chronic plaque psoriasis.

Table 4: *Studies and Pediatric Clinical Trials agreed to for Ustekinumab*

Area	**# of Studies**	**Description**
Quality		Not applicable
Non-clinical	4	Non-Clinical Study **1**: 1 month repeated-dose toxicology study with intravenous ustekinumab Non-Clinical Study **2**: 26 week (with 13 week interim sacrifice) repeated-dose toxicology study with subcutaneous ustekinumab in juvenile monkeys. Non-Clinical Study **3**: 18 day local tolerance and pharmacokinetic study with ustekinumab in juvenile monkeys. Non-Clinical Study **4**: combined embryo-foetal development/pre- and postnatal development study of ustekinumab in monkeys (gestation day 20, lactation day 33, exposure of neonates for 6 months).
Clinical	3	Clinical Study **1**: randomized, double-blind, placebo-controlled, multicentre trial to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of ustekinumab in children aged from 12 to less than 18 years with moderate to severe chronic plaque psoriasis. Clinical Study **2**: randomized, double-blind, placebo-controlled, multicentre trial to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of ustekinumab in children aged from 6 to less than 12 years with moderate to severe chronic plaque psoriasis. Clinical Study **3**: Setting up of a prospective cohort study/registry to assess long-term safety and long-term impact on growth and development.

[85] EMEA pediatrics: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-000311-PIP01-8/pip_ 000170.jsp&mid=WC0b01ac058001d129&murl=menus/medicines/ medicines.jsp&jsenabled=true.

The waiver applies to preterm newborn infants, term newborn infants (from birth to less than 28 days), infants and toddlers (from 28 days to less than 24 months) and children (from 2 to less than 6 years) for subcutaneous use of solution, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. The PIP itself applies to pediatric clinical studies in children from 6 years to less than 18 years that suffer from moderate to severe chronic plaque psoriasis that cannot be adequately controlled with topical therapy and/or phototherapy. Table 4 describes the studies and clinical trials to be performed by Janssen-Cilag International NV in more detail. The required date of completion of these studies is December 2018.

10. SUMMARY AND CONCLUSIONS

Both from publications and from personal communications out of the pediatricians' praxis, it has become apparent to me that the palette of pharmaceutical products - with proven clinical safety and efficacy in the pediatric population- from which pediatricians and other physicians may choose when looking for medications to treat their pediatric patients with, is disappointingly limited. It is therefore not surprising that administrations, like the USA or the European Union seek for possibilities to curb the pharmaceutical industry into including the pediatric populations in their R&D programs for new pharmaceutical products. However, it is, rather unfortunate that the timelines and local requirements at both sides of the Atlantic Ocean are quite different, despite the fact that both administrations maintain that they build their regulations on the ICH E-11 guidelines. The ICH principles state that pediatric patients should be given medications that have been appropriately evaluated for their use in such populations, that the development of product information in these patients should be timely, that the well-being of pediatric patients that participate in a clinical trial should not be compromised and that the responsibility for the health of pediatric patients is one that is shared among regulatory authorities, health professionals, the pharmaceutical industry and society as a whole.

The differences in US and EC laws and regulations include

(1) The timing of the submission of the pediatric plans: at conclusion of phase I (EMEA) and between Phase II and III (FDA).

(2) The FDA only encourages validation of small molecules in the pediatric population; the EMEA requires a plan for validation of both small molecules and biologicals in the pediatric population.
(3) The FDA can ask for studies for indications that are particular for the pediatric population but that do not exist or are not approved for the adult population; this is not possible under the current regulations of the EU.
(4) In Europe, an MA can be refused if the pediatric program is not complied with; this is not possible under the current laws in the USA.
(5) The EMEA focuses on getting pediatric information as early as possible in the development process while the FDA traditionally focuses on gathering safety information in the pediatric population post-marketing. The FDA requires a review of post marketing adverse events and a public review of the data, even if the product does not have a pediatric indication (not approved nor labeled) in the pediatric population. In Europe, if the product does not have a pediatric indication, than a pediatric safety review is not obligatory.

Over the past years, the two regulatory authorities have started an intensive exchange of scientific and ethical information on pediatric development programs that are either ongoing or have been completed in either/both Europe and the US, with the ultimate goal of avoiding exposing children to unnecessary clinical trials, while, at the same time, optimizing the global pediatric developments.

On a monthly basis, through the secure EudraLink, information is exchanged concerning PIPs (EMEA), Written Requests (FDA), Waivers and Deferrals. EMEA's spreadsheets to the FDA include product name, active substance, formulation, approved conditions, proposed PIP indications or proposals for waivers cq deferrals for pediatric studies. On the occasion that expanded scientific discussion is required, the Summary Reports are forwarded to the FDA as well. The FDA spreadsheets to the EMEA include product name and active substance, as well as information from the Written Request, if applicable, the PREA application (including indication, types of studies, age groups studied, date studies are due), approved indications and the regulatory status (e.g. end-of-PhaseII meeting, pre-NDA meeting, pediatric studies ongoing and completed, waivers and/or deferrals). Scientific information exchanges between the two authorities include deliberations on the status of the ongoing pediatric studies (the type of studies, e.g. placebo vs. active or whether the active control is/is not the standard therapy), the results of the conducted pediatric clinical trials (including negative results), the age groups to be studied (e.g. the views of FDA and EMEA on what the lower age limit should be in for instance antihypertensive, cholesterol-lowering trials or topical anti-viral agent trials), the

indications to be studies (e.g. the FDA has the possibility to request trials for indications of interests and is not limited to indications that are (going to be) approved in adults, as is the case in Europe), the safety concerns and plans for long-term safety monitoring, the endpoints and trial designs, differences in dosing and dosing regimens, reasons for failure (e.g. the afterward discussion of the timing of the endpoint assessment and the impact of the high placebo response rate on the ability to demonstrate a treatment effect in a trial that looked at the treatment of migraine in adolescents), rationales for waivers and collaborations on conduct of pediatric trials with international sites.

These intensive discussions are of detrimental importance for the pediatric populations and for the chance of success of the actual development of EbM for children. The anticipation that in some years the safety-, quality- and efficacy-assurance of pharmaceutical products used in children will mirror the confidence we have today for these same products when used in adults is hopefully justified. It will be a grand day, when 'THAT STUDY' is published that states that of all medicines used in children, most have been evaluated in clinical trials and that this particular future 'THAT STUDY' has found that pediatricians and other specialists chose pediatric treatments on the basis of now available EbM rather than on the basis of personal positive experience so far or, worse, trial and error.[86]

Fact is that with the introduction of the EC Pediatric Regulations 1901/2006 and 1902/2006, the number of submitted pediatric investigation plans to the EMEA and the incentive for the pharmaceutical industry to develop their new drugs, including their true innovative ones, for the pediatric population as well has increased significantly. This conclusion may at least be drawn from the number of proposals for PIPs/waivers that was handed in during the first 18 months from the entering into force of the regulation: a staggering 356 applications.

---

[86] Murphy, D. Europe & USA: Interactions on Pediatric Clinical Trials. Oral Presentation 2008.

LITERATURE

MacKinlay, A. C., 1997, Event Studies in Economics and Finance. Journal of Economic Literature, Vol. 35, No. 1, pp. 13-39.

Abbott publication: http://www2.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/ 11-12-2001/0001613559&EDATE=.

Bickerstaff, B. Pediatric Workshop EFPIA 2003.

Council Regulation (EEC) No 1768/9: Creation of a supplementary protection certificate for medicinal products.

Coogan, T. Pediatric Investigational Plans (PIPs) and Case Studies. BioSafeMeeting, 2009.

Croom K.F. and McCormack P.L. Adalimumab : in plaque psoriasis. Am J Clin Dermatol. 2009, 10(1):43-50.

Eriksson, B.I. et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006, 114 (22): 2374–2381.

Eriksson, B.I. et. al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. The N Engl J Med 2008, 358 (26): 2765–2775.

Griffiths, C. et al. Comparison of Ustekinumab and Etanercept for Moderate-to-Severe Psoriasis. N Engl J Med 2010, 362 (2): 118–128.

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/04/WC500089445.pdf

http://www.fda.gov/cder/pediatric/peddrugsfinal.htm;

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000124jsp & murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e9e.

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004749.pdf.

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004754.pdf.

http://www.fda.gov/cder/pediatric/wr_template. htm (template for a proposed pediatric study request).

http://www.fda.gov.cder.pediatric/index.htm (Pediatric Rule is codified at 21 CFR 314.55 and 601.27 with additional amendments to 21 CFR 201, 312, 314 and 601; the Pediatric Research Equity Act of 2003).

http://www.biology.arizona.edu/immonology/tutorials/immunology/main.html (cytokine tutorial published by the University of Arizona).

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016, 021131s013,021132s014lbl.pdf (Pfizer ZYVOX® (linezolid) Label Information).

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&murl=menus/ medicines/medicines.jsp&mid=WC0b01ac058001d129.

Isitt, V. Legal and ethical problems peculiar to pediatric clinical trials. Part 1: Legal issues. The Regulatory Review, June 2002 Volume 5 Issue 4; 12-16.

Johnson, L.L. Study: Drug for serious psoriasis tops competition. Associated Press, 18 Sept 2008.

Kakkar, A.K. et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008, 372 (9632): 31–39.

Lamprill, J. Paediatric Regulation: Reasons to be Proactive: Scrip Drug Delivery 2006, p9-11.

Lassen, M.R. et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008, 358 (26): 2776–2786.

Le Cam, Y. Medicines for children: better, more and faster. Regulatory Rapport. May 2005: p8.

Leonardi, C.L. et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008, 371 (9625): 1665–1674.

Mol de, N.J. Involvement of molecular singlet oxygen in the photosensitiying action of furocoumarins. Thesis, Leiden, the Netherlands 1980.

Murphy, D. Europe & USA: Interactions on Pediatric Clinical Trials. Oral Presentation 2008.

Papp, K.A. et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008, 371 (9625): 1675–1684.

Peppel, K. et al. A tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein as a bivalent antagonist of TNF activity. J. Exp. Med. 1991, 174(6), 1483-1489

Podolsky, D. K. Inflammatory bowel disease. N Engl J Med 2002, 346 (6): 417–429.

Reddy, M. et al. Modulation of CLA, IL-12R, CD40L, and IL-2Ralpha expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. Cell. Immunol. 2007, 247 (1): 1-11.

Regulation (EC) No 1901/2006 on medicinal products for paediatric use (amending Regulation 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004).

Regulation (EC) No 1902/2006 on medicinal products for paediatric use (amending Regulation (EC) No 1901/2006.

Roehrig, S. et al. Discovery of the novel antithrombotic agent 5-chloro-N-({(5S)-2-oxo-3- [4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene- 2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. J. Med. Chem. 2005, 48 (19): 5900–5908.

Sam, T. Regulatory requirements for the development of medicinal products for pediatric use. Presentation at WHO/FIP-sponsored workshop in Capetown (SA), April 2007.

Scheinfeld, N. Adalimumab (HUMIRA): a review. J Drugs Dermatol. 2003, 2, 375-7.

Severin, T. The EU PIP – a Step in Pediatric Drug Development. Oral Presentation, Bonn (D), 2009.

Turpie , A.G. New oral anticoagulants in atrial fibrillation. Eur. Heart J. 2008, 29 (2): 155–65.

Turpie, A. et al. Comparison of rivaroxaban – an oral, direct factor Xa inhibitor – and subcutaneous enoxaparin for thromboprophylaxis after total knee replacement (RECORD4: a phase 3 study) European Federation of National Associations of Orthopaedics and Traumatology Annual Meeting; May 29 – June 1, 2008; Nice, France, Abstract F85.

Turpie, A.G. et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009, 373 (9676): 1673–80.

Weber J and Keam S. BioDrugs 2009, 23(1): 53-61.

EMEA PUBLICATIONS

EMEA© Presentation: Overview of the new pediatric regulation; EUDRACT Pediatrics Overview PIP.

EMEA© Frequently asked questions on regulatory aspects of Regulation (EC) No 1901/2006 (Pediatric Regulation) amended by Regulation (EC) No 1902/2006; Doc. Ref. EMEA/520085/2006 (Version 2.0).

EMEA© CHMP Draft Guideline on the role of pharmacokinetics in the development of medicinal products in the pediatric population. EMEA/CHMP/EWP/147013/2004.

EMEA© CPMP Draft Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for pediatric indications. Doc. Ref. EMEA/CPMP/SWP/169215/2005.

EMEA© Reflection paper: formulations of choice for the pediatric population. Doc. Ref. EMEA/CHMP/PEG/194810/2005.

EU Directive 2001/20/EC: Implementation of GCP in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities,

EMEA© Questions and answers on the preparation of applications for a PIP and/or waiver. Doc Ref: EMEA/346673/2009.

EMEA© Revised priority list for studies into off-patent paediatric medicinal products. Doc. Ref. EMEA/480235/2010.

EMEA© Presentation of the EMEA Pediatric Team for Scientific Advice, Pediatrics and Orphan Drugs Sector: The Pediatric Regulation (2007).

EU Notice to Applicants. A guideline on summary of product characteristics. October 2005. (www.pharmacos.eudra.org/F2/eudralex/ vol-2/C/SPCGuidRev1-Oct2005.pdf.

EMEA© Working Group on Quality Review of Documents. Addressing the pediatric or incapacitated patient in the package leaflet. 2000.

EMEA concept paper on the development of a committee for proprietary medicinal products (CPMP) points to consider document on the evaluation of the pharmacokinetics of medicinal products in the pediatric population (Doc. Ref. EMEA/18939/03).

EMEA© Discussion papers on the impact of renal immaturity (Doc. Ref. CPMP/PEG/35132/03) when investigating medicinal products intended for neonatal and pediatric use.

EMEA© Discussion papers on the impact of liver immaturity (Doc. Ref. EMEA/CHMP/PEG/194605/2005) when investigating medicinal products intended for neonatal and pediatric use.

EMEA© Discussion papers on the impact of lung and heart immaturity (Doc. Ref. EMEA/CHMP/114218/2006) when investigating medicinal products intended for neonatal and pediatric use.

EMEA© Form: Paediatric investigation plan application and request for waiver.pdf

EMEA© P/102/2009 Decision on the agreement of a PIP and on the granting of a waiver for adalimumab (Humira) (EMEA-000366-PIP01-08) in accordance with Regulation 1901/2006 of the European Parliament and of the Council as amended (Doc. Ref. EMEA/288840/2009).

EMEA Rivaroxaban Information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124#non.

EMEA© Guideline on conduct of pharmacovigilance for medicines used by the pediatric population, Aug 2005; http://www.emea.int.pdfs/human/phvwp/23591005en.pdf.

European Medicines Agency (2008). CHP Assessment Report for Xarelto (Doc. Ref. EMEA/543519/2008).

EMEA PIP information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-000430-PIP01-08-M01/pip_000339.jsp&murl=menus/medicines/medicines.jsp&mid= WC0b01ac058001d129.

EMEA: http://www.emea.europa.eu/pdfs/human/opinion/Stelara_58227008en.pdf.

EMEA© PDCO members: http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000007jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e9f.

EMEA© PDCO meeting reports: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/ document_listing_000192.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028eab.

EMEA pediatrics: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/pips/EMEA-000311-PIP01-8/pip_000170.jsp&mid=WC0b01ac058001d129&murl=menus/medicines/medicines.jsp&jsenabled=true.

CLINICAL TRIALS

Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation (ClinicalTrials.gov).

MAGELLAN - Multicenter, Randomized, Parallel Group Efficacy Superiority Study in Hospitalized Medically Ill Patients Comparing Rivaroxaban with Enoxaparin (ClinicalTrials.gov).

The Einstein-Extension Study: Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism (ClinicalTrials.gov).

Einstein-DVT Evaluation: Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Deep-Vein Thrombosis (DVT) Without Symptomatic Pulmonary Embolism: (ClinicalTrials.gov).

Einstein-PE Evaluation: Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Pulmonary Embolism (PE) With Or Without Symptomatic Deep-Vein Thrombosis (ClinicalTrials.gov).

A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome (ClinicalTrials.gov).

A Study of the Safety and Efficacy of CNTO 1275 in Patients With Active Psoriatic Arthritis (ClinicalTrials.gov NCT00267956).

A Study of the Safety and Efficacy of Ustekinumab in Patients With Psoriatic Arthritis (ClinicalTrials.gov NCT01009086).

A Safety and Efficacy Study of CNTO1275 in Patients With Multiple Sclerosis (ClinicalTrials.gov NCT00207727).

A Study to Evaluate the Safety and Effectiveness of Ustekinumab or Golimumab Administered Subcutaneously in Patients With Sarcoidosis (ClinicalTrials.gov NCT00955279).

Diskussionspapiere der WHL Wissenschaftliche Hochschule Lahr

1 Dirk Sauerland: *Medizinische Dienstleistungen und Qualitätswettbewerb*, 2004.

2 Günther Seeber, Sabine Boerner, Helmut Keller und Peter Beinborn: *Strategien selbstorganisierten Lernens bei berufstätigen Studierenden. Ausgewählte Ergebnisse einer empirischen Untersuchung*, 2004.

3 Dirk Sauerland: *Strategien zur Sicherung und Verbesserung der Qualität in der medizinischen Versorgung – GKV und PKV im Vergleich*, 2005.

4 Ansgar Wübker: *Beurteilung der Qualität eines Gesundheitssystems – Die Entwicklung und Prüfung eines Bewertungsrahmens am Beispiel des Krankheitsbildes der koronaren Herzkrankheit*, 2005.

5 Dirk Sauerland: *Gesundheitsreformgesetze und ihre Auswirkungen auf Ausgaben und Beitragssätze der Gesetzlichen Krankenversicherung*, 2005.

6 Dirk Sauerland: *Künftige Herausforderungen der Langzeitpflege in Deutschland: Ordnungspolitische Anmerkungen*, 2006.

7 Günther Seeber: *Ökonomische Bildung in der Schule – Notwendigkeit und Handlungsbedarfe*, 2006.

8 Robert J. Zaugg: *Fallstudien als Forschungsdesign der Betriebswirtschaftslehre – Anleitung zur Erarbeitung von Fallstudien,* 2006.

9 Robert J. Zaugg: *Work-Life Balance. Ansatzpunkte für den Ausgleich zwischen Erwerbs- und Privatleben aus individueller, organisationaler und gesellschaftlicher Sicht*, 2006.

10 Björn A. Kuchinke, Ansgar Wübker: *Defizite öffentlicher Krankenhäuser in Deutschland: Empirische Befunde 1998 – 2004,* 2007.

11 Dirk Sauerland, Björn A. Kuchinke, Ansgar Wübker: *Warten gesetzlich Versicherte länger? Zum Einfluss des Versichertenstatus auf den Zugang zu medizinischen Leistungen im stationären Sektor*, 2008.

12 Mirko Heinke, Jürgen Keil, Marc Lengle, Michael Schneider, Jana Wendt: *Mobilisierung interner Ratings*, 2007 im Rahmen des Postbank Finance Award 2006/2007.

13 Clemens Böcher, Jörg Eisele, Dominik Hartmann-Springorum, Sebastian Hirsch, Heimo Tübel: *Asymmetrische Informationsverteilung im Kapitalmarkt – Wie und wann interne und externe Ratings zur Problemlösung beitragen können*, 2007, Wettbewerbsbeitrag im Rahmen des Postbank Finance Award 2006/2007.

14 Christoph Schwierz, Ansgar Wübker: *Regionale Leistungsunterschiede im deutschen Gesundheitswesen – Ausmaße und Ursachen für die Diagnosegruppe der ischämischen Herzkrankheiten*, 2008.

15 Ansgar Wübker, Dirk Sauerland, Achim Wübker: *Wie Qualitätsinformationen die Krankenhauswahl beeinflussen – eine empirische Untersuchung*, 2008.

16 Günther Seeber, Bernd Remmele: *Does Economic Competence Indicate the Individual Level of Agreement with Market Economy?, 2008.*

17 Bernd Remmele, Günther Seeber: *Exams To Go – Open Learning Motivation Through Accreditation, 2008.*

18 Tristan Nguyen, Wolfgang Bach: Prinzipienbasierte *Aufsicht am Beispiel des Proportionalitätgrundsatzes von Solvency II*, 2009.

19 Tristan Nguyen, Natalie Djodat*: Empirical Evidence of Corporate Governance Disclosure in Brazil, China, India, Korea and Russia*, 2009.

20 Robert D. Molinari: *Der Richtlinienentwurf zum neuen Solvabilitätssystem für die Versicherungsbranche – Ein Zwischenfazit*, 2009.

21 Tristan Nguyen: *Versicherbarkeit von Katastrophenrisiken und staatliche Risikoübernahme*, 2009.

22 Andreas Otte: *Funktionelles Neuroimaging beim HWS-Schleudertrauma,* 2009.

23 Konrad Wink, Andreas Otte: *Die Bedeutung der klinischen Forschung an kardiovaskulären Erkrankungen für die Gesundheitsforschung*, 2009.

24 Tristan Nguyen, Philipp Molinari: *Fair Value-Bewertung von Versicherungsverträgen im Spannungsfeld zwischen Relevanz und Verlässlichkeit,* 2009.

25 Stephan Schöning, *Zur Bedeutung regionaler Marktstrukturen im Kreditwesen für Bankkreditfinanzierungen von (kleinen) KMU in Deutschland,* 2009.

26 Marian Pollmann, Stephan Schöning: *Modifikation der 1. Säule von Basel II: Zusätzliche Anforderungen im Bereich der Marktrisiken,* 2010.

27 Tristan Nguyen, Robert Danilo Molinari: *Solvency II – Considering Risk Dependencies,* 2010.

28 Gerhard Wörtche, Tristan Nguyen: *How did different Investment Strategies perform when applied to an International Portfolio?,* 2010.

29 Gerhard Wörtche and Tristan Nguyen: *M&A Transactions by Private Equity and Hedge-Fundes – Some Empirical Evidence for Financial Regulation*, 2010.

30 Tristan Nguyen und Jonathan Ben Shlomo: *Hat ein Reverse Mortgage mit Wohn-Riester eine Zukunft in Deutschland?*, 2010.

31 Marguérite M. Mensonides-Harsema (mit einem Geleitwort von Andreas Otte): *Regulation (EC) No 1901/2006 and 1902/2006, Development of Pharmaceuticals for the Pediatric Population, The Pediatric Investigation Plan (PIP)*, 2010.

Abrufbar unter:
http://www.akad.de/WHL-Diskussionspapiere.191.0.html

AKAD
Wissenschaftliche
Hochschule Lahr