Regulatory Toxicology and Pharmacology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

The evolution of juvenile animal testing for small and large molecules

Paul Baldrick [1]

Nonclinical Regulatory Strategy, Covance Laboratories Ltd., Otley Road, Harrogate, HG3 1PY North Yorkshire, United Kingdom

ARTICLE INFO

Article history:
Received 15 July 2013
Available online xxxx

Keywords:
Juvenile animal testing
Paediatric investigation plan
PIP
Regulatory agencies
Paediatric clinical trials

ABSTRACT

Recent formalised regulatory requirements for ensuring safe use if new drugs in children has increased the requirement, when considered relevant, to perform juvenile animal testing before commencing paediatric clinical trials. A key goal of this work is to identify or examine for a developmental or toxicity finding not seen in other toxicology testing. With our current knowledge, this paper examines what types of testing are occurring, what novel findings are being seen and their relevance in the safety evaluation process. Furthermore, trends for now and the future in the type of juvenile animal testing will be described including a need for more focused study designs and more published data on modern cross-species postnatal development.

1. Introduction

Although testing of candidate drugs in juvenile animals to support paediatric clinical trials and/or identify/examine a developmental or toxicity finding not seen in adult animals is not new, the process of evaluating whether such testing is needed or not for all new medicinal products, whether a chemically synthesised (“small molecule”) or a biological (“large molecule”) material, has become formalised in recent years. Briefly, in the European Union, a “Paediatric Investigation Plan” (PIP) needs to be submitted early in the new drug’s development to the European Medicines Agency (EMA) to describe any clinical testing in the paediatric population or to provide justification for a waiver/deferral from such studies (EMA, 2013a). The PIP also needs to describe any proposed juvenile animal work or robust scientific rationale why such testing is not considered necessary. In the USA, paediatric development also needs to be discussed with the Food and Drug Administration (FDA), with provision of a “Pediatric Safety Plan” (PSP) (FDA, 2013). Again, information on proposed or waivered juvenile animal work needs to be included. Information on nonclinical testing considerations in juvenile animals, albeit at a fairly high level, is covered in 3 regulatory guidelines from the USA in 2006, Europe in 2008 and recently, Japan in 2012 (EMEA, 2008; FDA, 2006; JMHLW, 2012). Further limited information is available from the International Conference on Harmonisation (ICH) Question and Answer guidance (ICH, 2013).

A few years ago it was pointed out that as a result of the changes in regulatory thinking the number of juvenile animal studies to support paediatric drug development has greatly increased (Baldrick, 2010). Key questions at this time were if these increased numbers of studies were (1) identifying any novel findings to assist safety assessment in the paediatric population and (2) whether studies were moving from a standard toxicology study design to mirror the adult animal testing situation or, to a more case-by-case design related to a specific safety signal. This paper will examine both these aspects as well as looking at trends for now and the future in the type of testing to be performed.

2. Juvenile animal study frequency

In Europe, regulatory opinions and decisions on PIPs, including whether or not juvenile animal work is needed, is readily available to interested parties (EMA, 2013b). Table 1 provides a summary of juvenile animal studies for a range of drugs that were deemed necessary to support paediatric drug development in Europe over the last few years from published PIP decisions (March 2008 to June 2013). It should be pointed out that it is not known how many of these studies were suggested by the regulators vs applicant companies themselves. However, collective responsibility is indicated from information in a review of 97 approved or ongoing PIPs in the period November 2008 to May 2010, for which juvenile animal studies were proposed by the applicant pharmaceutical company in 33% of cases and required by the European regulators in 26% of cases (it is not specified in the publication but is presumed that the remaining 41% of cases had no juvenile animal testing proposed or requested) (Carleer and Karres, 2011). The information in Table 1 shows that 148 PIP decisions had juvenile animal work requested to support a paediatric age range of from birth to less than 18 years of age. Of these requests, 101 specifically mentioned use of the juvenile rat (68%), while a further 21 decisions did not

[1] Visiting Chair (Regulatory Toxicology) of the Lincoln School of Pharmacy, University of Lincoln, United Kingdom.
E-mail address: paul.baldrick@covance.com

0273-2300/$ - see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.yrtph.2013.07.009

Table 1
PIP applications with juvenile animal studies.

Drug (PIP number)*	Indication [therapeutic area]	Paediatric age from	Juvenile animal study
Paliperidone (P/13/2008)	Schizophrenia [Psychiatry]	12 years	7 week juvenile rat toxicity study (day 24–72)
Interleukin-1 beta Mab (P/27/2008)	Inflammatory disease [Immunology]	4 weeks	Juvenile toxicity study in mice
Caspofungin (P/30/2008)	Fungal infections [Infectious diseases]	Birth	Efficacy and PK study in juvenile rodent model + 5 week toxicity study in juvenile monkeys
Dalbavancin (P/31/2008)	Infections [Infectious diseases]	Birth	Range-finding and main juvenile rat toxicity studies
Taranabant (P/39/2008)	Obesity [Endocrinology]	6 years	Juvenile rat toxicity study
Tapentadol hydrochloride (P/48/2008)	Acute pain [Pain]	Birth	Juvenile rat toxicity study
Eplivanserin hemifumarate (P/69/2008)	Insomnia [Psychiatry]	2 years	Range-finding and main juvenile rat studies
Retigabine (P/77/2008)	Epilepsy [Neurology]	Birth	Juvenile (12 week) rat toxicity study
Catridecacog (P/90/2008)	Factor XIII deficiency [Haematology]	Birth	Single dose PK study in juvenile vs mature monkeys
Aprepitant (P/97/2008)	Nausea and vomiting [Oncology]	6 months	Range-finding and main juvenile rat toxicity studies
Belatacept (P/99/2008)	Renal transplantation [Immunology]	2 years	13 week toxicity study + 3 month immunotoxicity study, both in juvenile rats
Vicriviroc maleate (P/104/2008)	Viral infection [Infectious diseases]	Birth	Juvenile rat toxicity study
$TGp1PTH_{1-34}$ (P/110/2008)	Bone cysts [Endocrinology]	4 years	Toxicity study in juvenile sheep model
Telbivudine (P/111/2008)	Hepatitis B [Gastroenterology]	2 years	Range-finding (20 days) and main (10 weeks) juvenile rat toxicity study
Pyrrole-dione derivative (P/112/2008)	Psoriasis [Endocrinology]	6 years	Juvenile rat toxicity study
Alipogene tiparvovec (P/119/2008)	Hyperchylo-micronaemia [Cardiovascular diseases]	2 years	Three studies in juvenile/immature mice (pharmacology, pilot biodistribution + toxicity and biodistribution)
Voclosporin (P/126/2008)	Uveitis [Ophthalmoscopy]	2 years	Juvenile animal toxicity study
Casopitant (P/6/2009)	Nausea and vomiting [Oncology]	6 months	Prelim toxicity, pre-weaning toxicity and 28 day toxicity study in juvenile rats
Apixaban (P/8/2009)	Thrombosis [Cardiovascular diseases]	Birth	Range-findings (day 4–21) and main (day 4–90) studies in juvenile rats
Ceftobiprole medocaril sodium (P/9/2009)	Infections [Infectious diseases]	Birth	Juvenile studies in rats (2)
Grass pollen allergy vaccine (P/18/2009)	Pollen allergies [Pneumology]	5 years	7 week study in juvenile rat
Ustekinumab (P/19/2009)	Psoriasis [Dermatology]	6 years	1 + 26 week study + 18 day local tolerance and PK study, all in juvenile monkeys
Plerixafor (P/27/2009)	Myelo-suppression treatment [Oncology]	1 year	Juvenile animal toxicity study
Carboxamide derivative (P/30/2009)	Cystic fibrosis [Pneumology]	Birth	Juvenile animal toxicity study (later updated to juvenile rat toxicity + TK study – P/0155/2012)
Nilotinab (P/60/2009)	Gastrointestinal tumour [Oncology]	Birth	Oral gavage juvenile development study in rats
R04858696 (rh h Mab) (P/70/2009)	Tumour [Oncology]	2 years	Juvenile toxicity study
House dust mite extract (P/72/2009)	Allergic rhinitis/asthma [Pneumology]	5 years	Juvenile toxicity study
Benzoic acid derivative (P/83/2009)	Muscular dystrophy [Pneumology]	6 months	Juvenile toxicity study (+range-finder)
Rolofylline (P/87/2009)	Heart failure [Cardiovascular diseases]	Birth	Juvenile toxicity study in rats (+range-finder)
Alogliptin benzoate (P/93/20090	Type-2 diabetes [Endocrinology]	10 years	Juvenile toxicity study in rats + juvenile toxicity study in male rats for effect on repro organs
Avalox (Moxifloxacin HCl) (P/96/2009)	Pneumonia/sinusitis/bronchitis/skin infections/inflammatory disease/ infection [Infectious diseases]	3 months	Juvenile toxicity study in rats
Abatacept (P/100/2009)	Arthritis [Immunology]	6 years	13 week juvenile toxicity study in rats + 3 month immunotoxicity study in juvenile rats
Azilsartan medoxomil (P/105/2009)	Hypertension [Cardiovascular diseases]	6 months	Range-finding and toxicity study in juvenile rats
Carisbamate (P/108/2009)	Epilepsy [Neurology]	1 month	2 week range finding and 39 day toxicity study in juvenile rats + 2 week range finding study in juvenile dogs
Brivaracetam (P/126/2009)	Epilepsy [Neurology]	1 month	9 week + 30 day recovery in juvenile rats, 9 month + 2 month recovery in juvenile dog and brain weight evaluation in juvenile vs adult rat
Telavancin (P/127/2009)	Skin and soft tissue infections/ pneumonia [Infectious diseases]	Birth	6 week juvenile toxicity study in rats + 7 day TK study in juvenile rats
Fosaprepitant dimeglumine (P/137/2009)	Nausea and vomiting [Oncology]	6 months	Range-finding and toxicity study in juvenile rats
Denosumab (P/148/2009)	Bone loss + metastases/arthritis [Oncology]	4 years	Study (long bone geometry) in juvenile (normal and transgenic) rats + study (tooth eruption/bone parameters) in juvenile (normal) rats
Cinacalcet hydrochloride (P/167/2009)	Parathyroid carcinoma/hyper-parathyroidism [Uro-nephrology]	Birth	Single dose, escalating PK + 2 week toxicity study + 6 month oral toxicity study, all in juvenile dogs
Benzo derivative (P/177/2009)	Hypertension [Cardiovascular diseases]	Birth	Range-finding and toxicity study in juvenile rats
Benzylamide derivative (Dolutegravir) (P/178/2009)	Human immunodeficiency virus-1 infection [Infectious diseases]	Birth	Juvenile toxicity study in rats
Ticagrelor 9P/199/2009)	Thromboembolic events [Cardiovascular diseases]	Birth	Lung function + range-finding and toxicity study in suckling rats + toxicity study in weaning rats
Fluticasone furoate/triphenlyacetic acid (P/202/2009)	Asthma [Pneumology]	5 years	Repeat dose toxicity study (+TK) in juvenile dogs
Icatibant acetate (P/222/2009)	Hereditary angioedema [Immunology]	2 years	Local tolerance (subcutaneous route) + 7 week toxicity study (with fertility assessment before and after recovery), both in juvenile rats
Rivaroxaban (P/223/2009)	Venous thromboembolism [Cardiovascular diseases]	Birth	3 week + 13 week toxicity studies in juvenile rats
Ambrisentam (P/224/2009)	Pulmonary hypertension	1 year	2 week range-finding and 8 week oral toxicity (+TK) study (with a

Please cite this article in press as: Baldrick, P. The evolution of juvenile animal testing for small and large molecules. Regul. Toxicol. Pharmacol. (2013), http://dx.doi.org/10.1016/j.yrtph.2013.07.009