Quality and clinical supply considerations of Paediatric Investigation Plans for IV preparations – A case study with the FP7 CloSed project

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Abstract

A Paediatric Investigation Plan (PIP) is a development plan that aims to ensure that sufficient data are obtained through studies in paediatrics to support the generation of marketing authorisation of medicines for children. This paper highlights some practical considerations and challenges with respect to PIP submissions and paediatric clinical trials during the pharmaceutical development phase, using the FP7-funded Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit (CloSed) project as a case study. Examples discussed include challenges and considerations regarding formulation development, blinding and randomisation, product labelling and shipment and clinical trial requirements versus requirements for marketing authorisation. A significant quantity of information is required for PIP submissions and it is hoped that future applicants may benefit from an insight into some critical considerations and challenges faced in the CloSed project.

Key words

Paediatric Investigation Plan, paediatrics, clinical trials, formulation, clonidine

1 Introduction

Children under the age of 15 represent 16% of the total European population (Eurostat, 2015; Population Reference Bureau, 2013). However, a survey published in 2010 by the European Medicines Agency (EMA) found that 45-60% of all medicines given to children in the European Union (EU) were used off-label, especially in vulnerable groups such as neonates, patients with serious conditions and those in intensive care units (EMA, 2010). Off-label medicine usage refers to a medicine prescribed outside of its marketing authorisation. Reasons for the lack of availability and marketing authorisation for medicines for children include a scarcity of clinical trials in paediatric medicines, delays in the licensing of medicines for children, the absence of child-friendly formulations and a lack of commercial incentive (Ivanovska et al., 2013). In 2007, the EU introduced Regulation (EC) No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use as amended (Paediatric Regulation) to improve the health of children up to the age of 18 by supporting the development and accessibility of paediatric medicines and improving data available regarding their use. In doing so, the long-term goal was to achieve an integrated approach to the development of paediatric medicines within medicines development in general without unnecessary studies in children and without delaying marketing authorisations for medicines intended for use in adults. The Paediatric Regulation encourages pharmaceutical manufacturers to investigate drug development for the paediatric population by providing a Paediatric Investigation Plan (PIP) prior to marketing authorisation of new drugs. Incentives such as the extension of supplementary protection certificate (SPC) or a Paediatric Use Marketing Authorisation (PUMA) (for off-patent drugs) are provided if a previously agreed PIP is successfully completed. Whereas the Paediatric Regulation has been successful for new drugs, off-patent drugs are rarely studied. This is shown by the fact that only two PUMAs for off-patent drugs have been granted between 2008 and 2015 (EMA, 2015; Turner et al., 2014). In order to address this, the EMA developed a priority list of studies into off-patent paediatric medicines to serve as a platform for EU research funding.

The purpose of this paper is to highlight some considerations and challenges with respect to PIP submissions and the implementation of paediatric clinical trials during the pharmaceutical development phase, using the FP7-funded Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit (CloSed) project as a case study. A positive PIP opinion at the time of application was considered fundamental in supporting this funding proposal. At the time of PIP submission a significant amount of information is required, however the practical implementation of this plan may result in some challenges. Therefore, it is hoped that future applicants may benefit from an insight into some critical considerations and challenges faced in the CloSed project.

2 Clonidine and the CloSed project

The CloSed project is a five-year EU funded project (EudraCT: 2014-003582-24) that aims to generate data for a PUMA application in accordance with the Paediatric Regulation by developing an age-appropriate intravenous clonidine formulation and conducting a multicentre clinical trial of clonidine for the sedation of children aged 0-18 years in a Paediatric Intensive Care Unit (PICU) setting (see ClinicalTrials.gov, ref. NCT02509273). At the time of this publication, patient recruitment and data collection of the clinical trial was commencing. Although clonidine is used for sedation in many PICUs, it lacks authorisation for paediatric use. Clonidine was therefore included in the EMA Revised Priority List for Studies into Off-Patent Paediatric Medicinal Products July 2012 (EMA/98717/2012), which highlighted a need for paediatric data relating to pharmacokinetics, efficacy and safety and age-appropriate formulations for clonidine in the treatment of pain and sedation in PICUs (EMA, 2013). Prior to the funding application a PIP with a comprehensive development plan for clonidine was developed and agreed with EMA. The CloSed project has several concrete objectives, as outlined in **Table 1**. While these outcomes are specific to the CloSed project, they could be applied to any paediatric clinical trial. Further information on the CloSed project can be obtained from the official project website (http://www.closed-fp7.eu).

There are many challenges involved in developing and conducting a clinical trial, particularly in children and the CloSed project has been no exception. In the following

sections challenges and considerations regarding formulation development, blinding and randomisation, product labelling and shipment and clinical trial requirements versus PUMA requirements are discussed in detail.

Table 1 Summary of concrete outcomes expected from the CloSed project.

Development of an age-appropriate IV formulation of clonidine This will allow accurate dosing with minimum risk for errors.
Safety/efficacy data for clonidine in children Evidence-based data on the safety, efficacy and dosing recommendation for the use of clonidine for sedation of children in PICU.
Long-term neurodevelopmental outcomes An understanding of long-term outcomes following the sedative agents clonidine and midazolam in neonates will help in the assessment of risks and benefits for treatment.
Paediatric Use Marketing Authorisation (PUMA) Data will be used to apply for a PUMA for the age-appropriate IV clonidine formulation to facilitate the availability of a licensed product designed for use in PICUs.
European consensus guidelines International guidelines will be prepared based on the study results to address the lack of European guidelines and current low evidence to support treatment options. Clinical practice may be improved by the dissemination of results to a wide range of health professionals.
Extension of the availability of paediatric medicines to benefit children An estimated 120,000 critically ill children per year will benefit from a licensed clonidine product for sedation in PICUs and consensus guidelines for sedation.
Promotion of research in children CloSed Partners are encouraged to participate in clinical trials beyond CloSed and extend their knowledge and experience in conducting clinical research in the vulnerable paediatric population.
Innovation by strengthening links between academia and industry CloSed brings academic expertise together, using modern methods such as PK-PD modelling to define the best study design in an ethical manner. Assuming that the PUMA is granted, the developed formulation will be marketed, increasing the availability and providing synergism between scientific and market knowledge.

3.1 Formulation development

In the development of an age-appropriate formulation for paediatric patients including premature neonates right through to adolescents, selected strengths, volumes and excipients require careful consideration. In addition to the broad age range, dosing needs to be flexible in order to be adjusted based on individual patient requirements. The focus of the CloSed project is on the development of an age-appropriate parenteral clonidine formulation that may be used for the sedation of paediatric patients from premature neonates (>34 weeks gestation) right through to adolescents up to 18 years old. Currently, commercial IV clonidine formulations licensed for the treatment of hypertension in adults, such as Catapres® 150 mcg/mL (Boehringer Ingelheim, Berkshire, UK), are used for the sedation of children in PICU. This product is manufactured in 1 mL ampoules and anecdotal evidence indicates that up to 20 ampoules need to be opened and mixed to provide accurate dose-volume administration. The use of multiple ampoules is particularly prone to administration errors, inappropriate dosing and requires additional clinical or nursing time (WHO, 2007; Wong et al., 2009). It was important in the pharmaceutical development of the CloSed study that a minimal number of strengths were used to cover the entire age range in order for successful translation from investigational medicinal product (IMP) to final marketed product.

Before the formulation strengths can be selected, the dosing regimen must be established. Pharmacokinetic-pharmacodynamic (PK-PD) modelling was used in the CloSed study to determine the most appropriate starting and maintenance doses for critically ill children admitted to PICU. In addition, different dosing scenarios were considered to ensure that blinding could be maintained between the clonidine and midazolam arms. Although this was not part of the pharmaceutical development itself, it was a critical step in the determination of formulation strengths and excipients. In order to develop a formulation of appropriate strength(s), the dosing regimen requires careful consideration as this dictates both the concentration and volume to be administered to patients. In the CloSed study, midazolam was used as a comparator to clonidine and in order to maintain blinding, the dosing regimen for both IMPs needed to be the same. However, the elimination half-life of clonidine is long (9-17 hours) compared with that of midazolam (1-3 hours, increasing up to 12 hours in neonates) and this was an important consideration when developing a dosing regimen. A marketed product of midazolam is available at concentrations of 1mg/mL and

5mg/mL, which are appropriate for paediatric sedation (European Commission, 2014). However, it was not possible to maintain blinding by matching the dosing regimen and physical characteristics of the vials with clonidine using this product, so midazolam was also manufactured specifically for use as a comparator in this study.

The selection of excipients for each formulation was based on the marketed products Catapres® (clonidine, Boehringer Ingelheim, Berkshire, UK) and Hypnovel® (midazolam, Roche, Hertfordshire, UK). Both formulations were prepared in 0.9% v/v sodium chloride as the diluent (European Commission, 2014). The solubility of clonidine HCl in water is 77mg/mL at 20°C (O'Neil, 2013), whereas the solubility of midazolam decreases with increasing pH (10.3mg/mL at pH 3.4 compared to 0.24 mg/mL at pH 6.2). The final products were modified to pH 4.8-6.5 for clonidine HCl and pH 3.0-3.7 for midazolam, according to the stability profile of the drug substance (American Society of Health-System Pharmacists, 2015). No preservative was required, as a single-use product was desired.

Administration by continuous intravenous infusion allows for flexible dosing, but it is important to consider the minimal flow rate of infusion pumps. To this end, a preliminary audit was conducted to determine the pump capacity at each of the clinical sites involved in the study. The basic fluid requirement for a term baby is between 40 and 60 mL/kg/day plus urinary losses (BMJ Group, 2011). Neonates, particularly if fluid restricted, may tolerate only small volumes of medication to avoid fluid overload and allow sufficient room for fluid nutrition. In addition, in a paediatric intensive care setting it is common for several intravenous drugs to be required, which require dilution and flushing into the circulation. This could result in the child's fluid and sodium requirements being exceeded. According to the BNF for children, the sodium requirement in most healthy neonates is 3.0mmol/kg/day (BMJ Group, 2011), with UK guidelines recommending a maximum of 400mg (17.4mmol) sodium per day in children up to the age of 12 months (Scientific Advisory Committee on Nutrition, 2003). The maximum sodium intake for each formulation, calculated based on a patient requiring the maximum dose over 24 hours, was considered satisfactory as it was less than 30% of this recommended threshold.

After considering the above factors, three strengths were developed, each at a volume of 50mL. A 50mL volume was selected because even if a patient required the maximum dosage in 24 hours, one vial would be required unless the patient was over 47kg, where two vials may be required. The three strengths allowed infusion rates to remain greater than the minimal flow rate of the infusion pumps for all age groups at all clinical sites, whilst maintaining a low fluid volume to avoid fluid overload.

3.2 Blinding and randomisation

3.2.1 Blinding

The CloSed study, like many other clinical trials, is a double-blinded trial, so neither the principal investigator (and associated study site staff) nor the patient (and patient's family) are aware of the specific treatment allocation. PK-PD modelling played a large part in the ability to blind the reference and test product vials, by developing a matched dosing regimen. As previously discussed, the half-life of clonidine is much longer than of midazolam, so this had to be considered in order to maintain a blinded dosing regimen. To achieve this, an initial loading dose was proposed, followed by a maintenance infusion and additional loading doses if necessary at certain time points.

Although midazolam paediatric dosage forms are commercially available, bespoke reference product vials (containing midazolam) were developed to have the same appearance as the test product vials (containing clonidine) (Wan et al., 2013). A procedure has been developed so that the identity of individual study vials will remain unknown to the investigator, medical staff, and all subjects. All other individuals involved in the study (e.g. clinical study manager, medical experts and monitors) will also remain blinded.

3.2.2 Randomisation

Randomisation, like blinding, is fundamental to the integrity of a clinical trial. While it is easy to state in a funding application or even a study protocol that the study will be conducted in a randomised, double-blinded manner, the robust method in which this will be achieved in practice is often overlooked during the early phases of a trial (Wan et al., 2013). A centralised randomisation system is ideal for a study spanning multiple clinical sites, as randomisation occurs at the point of recruitment and as such, imbalances are minimised and it is easy to determine overall recruitment rates (Buyse,

2000). However, such a system is expensive and needs to be investigated and included into the initial budget in order to be feasible. A cheaper option for randomisation is the generation of random numbers by a third party using a permuted block design. This form of randomisation is completed at the point of shipment, and subject kits are selected in numerical order from each clinical site (subject one receives kit one, subject two receives kit two, and so on). Although this is a cheaper procedure, it can lead to significant wastage, especially when there are multiple formulation strengths depending on the body weight of the patient. If the IMP is expensive then the cost of wastage may outweigh the cost of setting up a centralised system. Due to the expense of using a centralised system compared to the relatively low production costs of the IMP, the CloSed project has achieved randomisation by the generation of random numbers by a third party. A comprehensive procedure has been developed to ensure that the integrity of the trial remains intact.

3.2.3 Preparation of patient kits

As with many paediatric dosing regimens, selection of the appropriate formulation strength (low, medium or high) for the CloSed study is dependent on the body weight of the subject. However, in order to gain a representative sample of participants from preterm neonates right through to 18 year olds, the study is stratified into three age subsets (< 28 days, 28 days to < 2 years and ≥2 years). To maintain blinding and randomisation by subset, patient kits are prepared that contain enough medication to last the seven-day maximum trial period. The patient kit for subset 1 contains the low and medium formulation strengths, whereas the patient kit for subset 2 contains the medium and high formulations. The patient kit for subset 3 contains 14 vials of the high strength formulation, in case the patient weighs over 47kg and requires more than one vial in 24 hours. The clinician is responsible for first selecting the subject kit based on the age of the participant and randomisation number, then selecting the correct strength from within the kit based on the body weight of the patient.

3.2.4 Shipment to clinical sites

International shipment to each clinical site is an expensive and time-consuming process. Each site is responsible for ordering enough subject kits to last approximately six months, so that no more than four shipments are required to each site over the two-year trial period. As midazolam is a controlled drug, both an import and export

licence are required, specifying the quantity of midazolam. As the study kits will be randomised and blinded at the point of shipment, it is assumed that all vials contain midazolam. Temperature-controlled shipment takes place once the import and export licences have been processed and regulatory approval acquired.

3.3 Labelling the investigational medicinal products

As multiple countries are involved in the CloSed study, labelling of the IMPs needed to include multiple languages. As recruitment numbers from each site were unknown, it was decided to print labels as a multi-language booklet. In this way, the English version was on the front page, but each local language could be found by peeling open the booklet. The printing of labels was contracted out and guidelines were obtained from the printing company in the early stages of label drafting. One point to consider was that only the front page could be printed with variable text, therefore, the translated labels needed to refer to this page for medication and randomisation numbers. Colours were used to differentiate between the three different formulation strengths, with the aim of minimising dispensing errors. The selected colours were blue, black and orange. Red and green were intentionally excluded from the labels due to the high number of individuals with red-green colour blindness.

Annex 13 (Articles 26-30) of the European Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use sets out clear guidelines regarding the labelling of IMPs for clinical trials. However, there are country-specific deviations for this and these also needed consideration (**Table 2**). For example, the details of Principal Investigator are a requirement in Sweden. Labels were drafted and approved by representatives from all countries involved in the clinical trial. Following approval, the label needed to be translated into each local language. Once the labels were translated and merged into a single master label copy, this document had to be signed by each of the translators as well as the trial co-ordinator. The cycle of drafting, translating and approving the labels was a lengthy process that required co-ordination between the IMP manufacturer, labelling company and representatives from each of the five clinical sites.

Table 2 Overview of IMP label requirements, based on the European Guidelines to Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use (Annex 13, Articles 26-30).

Packaging information	
• Study reference number	• Route of administration
• EudraCT Number	• Directions for use
• Pharmaceutical form	• Quantity of dosage units
• Subject number	• Retest date
• Vial/box number	• 'For clinical trial use only'
• Content of vial/box	• Storage instructions
• Name, address, and telephone number of sponsor	• Additional labelling according to local requirements
• Name, address, and telephone number of the Principal Investigator	• Other instructions/information

3.4 Paediatric use marketing authorisation requirements

The Paediatric Regulation was introduced to support the development and availability of paediatric medicine. It combines paediatric drug development requirements, or Paediatric Investigation Plans (PIPs), with incentives for the pharmaceutical industry to test medicines in children, such as the extension of SPC and generation of PUMA. Therefore, when conducting a paediatric clinical trial, a key goal should be to generate sufficient robust data to apply for a PUMA. This is important because even if, as in the CloSed study, the IMP manufacturer is different to the commercial manufacturer, the quality data generated needs to be sufficient not only for the clinical trial application and IMP Dossier (IMPD), but also for the PUMA. Although the production process may differ slightly between manufacturers and the IMP supplier may be different, meaning that not all quality data will be transferable, the generation of a robust set of usable data right from the early pharmaceutical development stage is an essential step towards a successful PUMA application.

4 Summary

The EMA has developed the Paediatric Regulation to improve the health of children by increasing high quality, ethical research into medicines for children. PIPs require careful planning and an awareness of how they will lead to a PUMA is paramount. However, PIP applications are often completed at an early stage, perhaps even before funding has been granted. A gap exists between the PIP application and the clinical trial phase and this is a particular challenge for publicly funded studies. Challenges

often arise in the clinical trial phase that were not foreseen in the PIP application. By sharing some of the considerations and challenges encountered during the pharmaceutical development phase of the CloSed project, it is hoped that future projects will benefit in generating successful PIPs that ultimately lead to an increase in PUMA applications and licensed paediatric indications for new drugs.

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