Towards the development of a paediatric biopharmaceutics classification system: Results of a survey of experts

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DOI:
10.1016/j.ijpharm.2016.06.115

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PII: S0378-5173(16)30605-6
DOI: http://dx.doi.org/doi:10.1016/j.ijpharm.2016.06.115
Reference: IJP 15872

To appear in: *International Journal of Pharmaceutics*

Received date: 3-3-2016
Revised date: 23-6-2016
Accepted date: 24-6-2016

Please cite this article as: Batchelor, Hannah, Ernest, Terry, Flanagan, Talia, Klein, Sandra, Turner, Roy, Fotaki, Nikoletta, Storey, David, Towards the development of a paediatric biopharmaceutics classification system: Results of a survey of experts.International Journal of Pharmaceutics http://dx.doi.org/10.1016/j.ijpharm.2016.06.115

Title: Towards the development of a paediatric biopharmaceutics classification system: Results of a survey of experts

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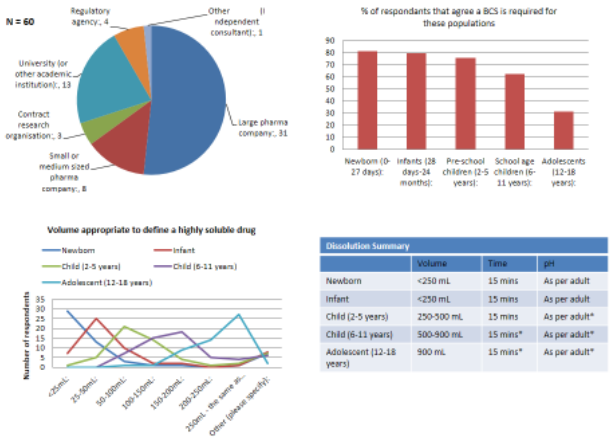
Graphical abstract



Dissolution Summary			
	Volume	Time	pH
Newborn	<250 mL	15 mins	As per adult
Infant	<250 mL	15 mins	As per adult
Child (2-5 years)	250-500 mL	15 mins	As per adult*
Child (6-11 years)	500-900 mL	15 mins*	As per adult*
Adolescent (12-18 years)	900 mL	15 mins*	As per adult*

Abstract

The aim of this research survey was to understand current global thinking around the need for and development of a paediatric biopharmaceutics classification system (pBCS) to be used for the development of paediatric medicines and regulatory purposes (e.g. Biowaivers).

A literature review highlighted the paucity of data in this area and therefore a survey was developed to better understand this topic to identify areas of common thinking and highlight future research needs.

Global experts in paediatric biopharmaceutics were identified from existing networks and public forums. An online survey was developed and circulated broadly to maximise participation. Sixty individuals (including academics, health care professionals, pharmaceutical industry scientists and regulators) completed the survey, bringing together their views on the need for a pBCS.

The results highlighted that the area of greatest concern was the definition of BCS II and IV drugs within this population and additional research is required to generate evidence to underpin this issue. In questions relating to permeability and dissolution consensus was generally reached within the expert population suggesting that little additional research is required to define suitable criteria.

More than 90% of those experts who participated agreed that a pBCS would be useful for paediatric populations with a greater need identified for the younger populations (newborn and infants compared to adolescents).

The results presented will facilitate further discussion and research into the evidence to underpin a relevant pBCS. These results highlight the need for additional evidence and guidance in this area.

Keywords: survey; paediatric; biopharmaceutics; solubility; dissolution; permeability, BCS

1. Introduction

The biopharmaceutics classification system (BCS) was introduced in 1995 to facilitate the development of medicines for adults (Amidon et al., 1995). It has subsequently been used to justify the introduction of alternative formulations in the absence of a clinical study (EMA, 2010; FDA, 1995). A BCS-based biowaiver has become an important and cost-saving tool in the development of new medicines and approval of generic medicines (FDA, 2000).

The BCS is based on an understanding of the solubility and permeability of a drug and dissolution of the drug product. These key parameters can better assist in predicting the *in vivo* absorption of an oral medicine in adults. It is obvious that prediction of a drug's absorption in a paediatric population offers significant benefits however the extrapolation of the adult BCS is not simple (Batchelor, 2014). There has been previous discussion on this topic yet there has been no effort in defining how the boundaries should be defined for paediatric populations (Abdel-Rahman et al., 2012; Batchelor, 2014; Gandhi et al., 2014).

This paper describes a survey of those working in paediatric biopharmaceutics used to identify current thinking and consensus in the area of paediatric biopharmaceutics specifically related to a paediatric biopharmaceutics classification system (pBCS). Parameters for the adult BCS were derived based on existing knowledge of a group of experts in the area (Amidon et al., 1995). The aim of this study was to derive parameters for a pBCS using a broad range of self-selecting experts. The Delphi technique is a widely used method for gathering data from respondents within their domain of expertise; this technique is designed to gain consensus on specific issues. In a Delphi process consensus is gained by a sequential series of questionnaires. This study aimed to gain insights and determine whether consensus exists in the definition and need for a pBCS and therefore a Delphi approach was taken although this was not followed by further questionnaires as this would be the role of the regulator and therefore the value of this follow-up was limited.

Previous literature reports have highlighted knowledge gaps in paediatric biopharmaceutics and this paper aims to address these gaps by: a) verification of the need for a pBCS; b) providing a view of trends and possible criteria to implement in a pBCS and c) obtaining a comprehensive list of further research required in the area of paediatric biopharmaceutics.

2. Methods

A literature review was used to aid in the design of the survey however only four papers were identified that referred to a paediatric biopharmaceutics classification system (Abdel-Rahman et al., 2012; Batchelor, 2014; Gandhi et al., 2014; Shawahna, 2016). Key knowledge gaps in paediatric biopharmaceutics were identified by the European Paediatric Formulation Initiative (EuPFI, www.eupfi.org) biopharmaceutics workstream (a collaboration of academic and industrial pharmaceutical scientists working in paediatric medicines development) and these insights formed the basis of the survey. In line with the research objectives, a qualitative research approach was adopted. The questionnaire was constructed to minimise the burden to participants by presenting questions in a logical order with similar themes linked together. The respondents were given fixed options as well as allowed to input free text comments on each question to allow the best quality data to be generated whilst minimising the time burden to participants. A draft survey was reviewed collaboratively by the EuPFI biopharmaceutics workstream members to ensure that key questions were phrased unambiguously to maximise the value of the responses. It is acknowledged that pilot studies can improve the structure and clarity of questionnaires (Edwards, 2010), therefore, the survey was then tested online with some external experts from within the EuPFI wider network.

Key areas of questioning identified included:

- Is there a need for a pBCS, if so who should be involved in developing this?
- What are the relevant criteria to define high solubility, high permeability and rapid dissolution in paediatrics and are these values different within different age categories of paediatric populations?
- What additional information is required to enable the development of a pBCS?

Aspects of the Delphi process were considered within the design of the survey questions where consensus was sought from the respondents to identify areas of high agreement, such that these values can inform current thinking going forwards. Typical consensus levels used in Delphi approaches are 75% of participants agree on a parameter (Diamond et al., 2014). This approach was

considered to be particularly relevant in defining the criteria used in solubility, permeability and dissolution parameters.

There was a need to balance directed responses to ensure that the survey was simple and quick to complete yet also allow scope for participants to raise issues important to them. An increasing number of surveys in different fields are conducted using the internet, although it has some advantages (e.g. no or minimum cost, fast, reliable, easy to complete by the participants) and disadvantages (many people delete the online survey without opening it, for fear of spam or virus). Importantly, an online questionnaire maintains the anonymity of participants. The online survey software, Bristol Online Survey, (www.onlinesurveys.ac.uk) was deemed most appropriate for this survey as it is specifically designed for academic research and public sector organisations and is fully compliant with UK data protection laws.

For this survey, experts were identified on the basis of their recognised experience in the fields of formulation and paediatric biopharmaceutics. No geographical limitations were placed on the location of survey participants to best capture global expertise and practise. Experts were sought with the following backgrounds:

- Academics (i.e. researchers, existing research networks and groups, scientific societies),
- Health care professionals (i.e. medical doctors, pharmacists, nurses and others working in a clinical environment)
- Pharmaceutical Industry scientists (Small and Medium Enterprises (SME) and larger companies).
- Regulators within agencies (at European and national level).

The EuPFI was used as the primary network to distribute the survey via their membership. Additional experts outside of the EuPFI collaboration were targeted via direct mail from related and interested networks including: International Consortium for Innovation and Quality in Pharmaceutical

Development (https://iqconsortium.org); Orbito (http://www.orbitoproject.eu/); APS Biopharmaceutics Focus Group (www.apsgb.co.uk)). This approach to distribution of the survey was selected as an email from an existing contact is typically less likely to be deleted (Edwards, 2010). In addition a link to the survey was placed in relevant online networks (Linked In Groups including GastroPlus™ User Group; Regulatory Professionals in the development of paediatric formulations and AAPS Formulation Design and Development Section) with a request for anyone interested to complete the survey. This non-probability based convenience sampling method was selected and individuals were left with a choice to "opt in" to the questionnaire following an invitation via any of the methods outlined above. This self-selection was used as the population of interest is of a relatively small size and random sampling would be unlikely to provide sufficient results (Fricker, 2012). The dissemination process followed would have attracted mainly European and US responses, however information on the geography of respondents was not collected. The survey included a question which enabled participants to provide details if they were willing to be contacted about their responses or for further details which would provide the research team with a sub-population to ask further questions if required.

The survey was opened and advertised in September 2014 and responses collected until December 2014.

3. Results and discussion

3.1. Literature review

The literature search revealed a total of four publications ((Abdel-Rahman et al., 2012; Batchelor, 2014; Gandhi et al., 2014; Shawahna, 2016)) discussing pBCS criteria. Dissolution parameters were not detailed in any of the publications. Permeability was aligned to adult values in three publications, using ClogP values (Batchelor, 2014; Shawahna, 2016) or based on absolute bioavailability in paediatrics where high permeability required an oral fraction dose absorbed of 90%

or more compared to an intravenous study in paediatrics (Gandhi et al., 2014). According to the BCS, highly soluble drugs are those where the highest dose (or dose unit) is soluble in 250 mL aqueous liquid at a relevant pH range (Amidon et al., 1995). The relevant volume of liquid for different paediatric populations were discussed to the greatest extent within the four papers and a summary of the information contained within these papers is included in table 1.

The justification for the 25 mL volume for all paediatric populations was not stated by Abdel Rahman et al (2012) (Abdel-Rahman et al., 2012). Batchelor (2014) and Shawahna (2016) calculated a paediatric reference volume based on literature reports that the volume of gastric fluids in the fasted state in children is approximately 0.56 mL/kg (Crawford et al., 1990) relative to the adult gastric volume of 37.1 mL and BCS adult volume of 250mL; the slight differences reported relate to differences in input reference weights for children of given ages.

Ghandi et al (2014) calculated a paediatric reference volume based on body surface area (BSA), relative to the adult volume of 250 mL and adult BSA of 1.73 m^2. The values presented in Table 1 are based on average weight and BSA reported in the BNF-C (Committee.).

Data from International Commission on Radiological Protection (ICRP) (Valentin, 2002) provided intestinal dimensions for a wide range of age groups; when correlated to height, weight and body surface area of children the small intestinal surface area reported correlated best to body surface area in paediatric populations, height consistently overestimated and weight consistently underestimated paediatric intestinal surface area (Batchelor and Marriott, 2012). Therefore the use of body surface area to calculate gastric volumes may be appropriate, although this results in far higher values than those used when calculating according to weight. The data presented by Crawford et al (1990) includes paediatric data on gastric volumes and therefore is currently the most appropriate source for extrapolation.

The information from these papers was used to inform the response options within the questionnaire; particularly the lower limits of the solubility volume and dissolution volumes that could be selected for the age-range of interest.

Five additional publications made reference to paediatric biopharmaceutics within the article title, abstract or keywords however they did not refer to a pBCS ((Batchelor et al., 2014; Debotton and Dahan, 2014; Giacoia et al., 2012; Purohit, 2012)).

3.2. Survey results

The survey questions can be seen in appendix A.

3.2.1 Participant demographics

Sixty individuals completed the survey. It was not possible to calculate a response rate due to the opt-in dissemination pathway used to promote the questionnaire. The distribution of the types of institution where the participants are employed is shown in Figure 1. It was important that the survey was completed by the relevant range of individuals encompassing those in industry, regulatory positions and academia.

It was important in interpreting the resulting data, that those participating had the relevant expertise to ensure that the output is informed by experts in the area. Questions about experience working in paediatric medicines and paediatric biopharmaceutics were used to identify the level of expertise of those completing the survey 27 % had greater than 5 years' experience in both paediatric medicines and biopharmaceutics. The relatively recent experience of those participating is likely to be a consequence of the area of paediatric formulation and biopharmaceutics being relatively new having grown since the regulations requiring a paediatric product were introduced the past ten years (Committee for Medicinal Products for Human Use (CHMP), 2006; EMA, 2011).

Subsequent analysis confirmed that the views of those with greater experience were similar to the overall views; there were insufficient numbers of highly experienced individuals to allow for statistical comparative analysis.

3.2.2 General findings on the need for a pBCS

The majority of respondents agreed that a pBCS was needed. The need was considered to be higher for younger patients as shown in figure 2.

In cases where participants did not consider that a pBCS was required it was typically as they did not see the value of a pBCS and felt that alternative tools, specifically physiological based pharmacokinetic modelling was superior to the crude nature of a pBCS. The reduced need for a pBCS in older age groups was typically related to the perception that older children are more like adults in terms of gastro-intestinal physiology and therefore the existing adult BCS would be valid in these populations. Three participants commented that solid dosage forms are infrequently used in the youngest populations and therefore the relevance of a pBCS would be limited. Although solid dosage forms are less common than liquids for children's medicines there is interest in the use of solid dosage forms other than conventional tablets in children including: mini-tablets; granules; sprinkles; chewable and orally dispersible tablets (Liu et al., 2014). The data presented suggests that further work is required to develop a pBCS for children the need was greater in younger populations with >75 agreement (which meets typical consensus levels used in Delphi approaches (Diamond et al., 2014)) in children up to 5 years of age and high agreement for children aged 6-11 years of age. There was general agreement that adolescents are similar to adults and therefore can follow the existing BCS.

The survey asked a question about why a pBCS would be useful and asked participants to rank their level of concern about the lack of a pBCS against three reasons: inefficient drug development process; drug efficacy and child safety. The results are shown in figure 3.

Many respondents commented that the drug efficacy and safety would be measured directly in clinical trials and that their concerns were not associated directly with a lack of pBCS. It was also noted that two respondents stated that is was a lack of understanding of paediatric biopharmaceutics rather than the lack of pBCS that caused them greatest concern.

In terms of those involved in developing a pBCS the respondents reached consensus, in that >90% agreed that regulators, academic and industrial pharmaceutical scientists should be involved. Only 65% of participants felt that healthcare professionals should be involved in the development of a pBCS. In general comments that related to the need for multidisciplinary teams highlighted the belief that data on the relevant parameters is scattered and needs to be consolidated and the need to engage regulatory agencies throughout the process.

3.2.3 Criteria to classify a drug as highly soluble in a pBCS

Survey participants were asked to state what volume they felt was most appropriate as a criteria to classify a drug as highly soluble for a range of paediatric age ranges. The typical volume proposed for solubility increased with age as shown in figure 4.

The paediatric reference volumes in which the highest dose or dose unit should be soluble to classify a drug as highly soluble within a pBCS showed reasonable agreement between the participants of the survey although consensus, in typical Delphi terminology, was not obtained (<75%).

Comments relating to reference volumes highlighted that there was insufficient evidence to propose or agree with those values suggested, some respondents commented that the two age groups for children were still very large and that further subdivisions may be useful. Comments also highlighted that it was the volume of liquid the child was likely to take that should be used to guide this value

and this should be the focus of further research. Typically information with in children's medicines (as per the BNFc) state that the product should be consumed with half a glass of water (Truvada ® tablets; Rufinamide tablets) or a full glass of water (FasTab®; Elvanse®; Risedronate sodium tablets; Etravine tablets; alendronic acid tablets); a full glass means at least 150mL (Committee.). A small study conducted reported that mean values of liquids reported to be consumed with tablets were 82mL for 14-15 year olds and 109mL for 9-10 year olds (Batchelor and Marriott, 2013).

The survey results did not match any of the previously reported literature values in determining the volume for a highly soluble drug. The fixed value of 25mL by Abdel Rahman et al (2012) (Abdel-Rahman et al., 2012) was reasonably similar to the most popular values for newborns and infants yet this was much lower that the values proposed for all older age groups. Using body weight linked to fasted gastric volumes as a ratio to propose relevant volumes for the pBCS ((Batchelor, 2014; Shawahna, 2016)) gave values that were within those suggested by the survey participants for age groups up to 6 years; above 6 years this estimation gave lower volumes than those suggested within the survey. Ghandi et al (2014) related volume to body surface area; this gave a better fit to the survey data in children over 6 years. Consensus was not achieved for volumes relevant to use in paediatric populations, this finding highlights the need for additional research in this area to determine both the actual relevant volumes present within the intestinal tract of children as well as additional details on the typical volume of liquid taken with medication.

3.2.4 Criteria to classify a drug as highly permeable in a pBCS

Highly permeable drug classification within the BCS states that drugs where greater than 90% is absorbed are classified as highly permeable (Amidon et al., 1995); in terms of paediatrics and classification for a pBCS the survey asked whether this classification should remain the same or

whether the 90% should be raised or lowered. The most popular selections for each age group are shown in table 2.

The results highlighted that as the age of the child increased the confidence in similarity to adult absorption increased with consensus on absorption criteria for older children and adolescents being reached (as equivalent to adult values). There was more variability in the younger age groups; many comments referred to the conservative nature of the existing 90% criteria and proposed that lower values (down to 80%) are reasonable; many others commented on the existing methodology to assess permeability and the limitations of these techniques. More recent draft guidance from the FDA has reduced high permeability criteria to greater than 85% which reflects the responses found within this survey (FDA, May 2015). It was surprising that some participants suggested an even more conservative approach in classification of a highly permeable drug with absorption values even higher than 90%, there was only one comment provided to justify this which related to the overall permeability and the risk of faster transit in paediatric populations requiring the need for a more conservative estimate of permeability and the impact on clinical performance. Participants were provided with an option to suggest alternative criteria or provide comments which are listed as "other" in Table 2. Typical comments included suggestion of values of 80% (2 responses) as the clinical impact of permeability measurements is unknown and the existing value in adults was considered by participants to be overly conservative. Another comment left as "other" was that this should be calculated based on the drug in question and the clinical risk associated with that compound.

3.2.5 Criteria to classify a drug product as rapidly dissolving in a pBCS

An immediate release drug product is considered rapidly dissolving when 85% or more of the labelled amount of the drug substance dissolves within 30 minutes (a very rapidly dissolving product will need to do the same within 15 minutes, within a volume of 900mL or less at a pH range from 1 to 6.8 (EMA, 2010; FDA, 1995). The criteria for volume of media, timeframe for 85% dissolution and

pH range for a paediatric population were surveyed and the most popular responses are recorded in table 3.

Many comments on dissolution referred to the lack of biorelevance of the test for the adult population and therefore the limited value in a direct translation into paediatrics(EMA, 2010; FDA, 2000). The recent draft FDA guidelines propose reducing the volume from 900mL to 500mL (FDA, May 2015) which is aligned to many comments made within the survey. There were several comments highlighting the lack of reliable data on anatomy and physiology of the paediatric intestine which made this question difficult for many people to answer. The full pH range was also questioned by some participants as the gastric pH in the youngest population is reported to be higher than that in adults; this was reflected in responses where 25% of respondents felt that the pH range for newborns and infants can run from 4.5 to 6.8 rather than starting at a lower pH value.

3.2.6 Proposed areas within paediatric biopharmaceutics for further research

The survey participants were asked to list up to three priorities for research in paediatric biopharmaceutics as it was recognised that this is an under-researched area and there are many knowledge gaps. The resulting answers were themed and then prioritised according to the frequency with which each suggestion was made; the results are presented in table 4.

Previously literature reports have prioritised paediatric information of interest including gastrointestinal volume and pH, enzyme differentiation and transporter maturation, particularly identifying information related to carrier-mediated drugs (Abdel-Rahman et al., 2012; Batchelor et al., 2013; Gandhi et al., 2014); this survey of experts provides end-user input into future areas of research and it is important to match academic aspirations with the application of their findings.

Conclusions

This survey confirmed the desire for a pBCS. The survey approach allowed access to those currently working in the area of paediatric biopharmaceutics and exposed the relatively new knowledge base within this groups as there were only 27% with more than 5 years' experience in the field. However, reaching 60 individuals was considered by the authors to be a representative proportion. It would be interesting to repeat this survey in the future when there are more experienced individuals working in paediatric biopharmaceutics to demonstrate whether there is a change in thinking as more knowledge becomes available. The results also showed discrepancies in pBCS criteria proposed within the literature and current thinking of those working in the area; this may be a reflection of the relatively recent literature and the lack of a definitive evidence base. Although consensus was not reached in many questions the data presented here highlights the gaps in current knowledge and provides indications of the most appropriate methodology to use in measuring the *in vitro* performance of paediatric medicines. The proposed criteria limits are prudent and based on incomplete knowledge therefore additional research is required to generate sufficient, robust evidence to underpin a pBCS. However, biowaivers to justify formulation switches for BCS I and III drugs where the formulation switch is to a paediatric product need to be undertaken with caution due to the dose number adjustment in switching from an adult to a child as well as the lack of knowledge in permeability differences. A pBCS would enable a more reliable system on which to justify biowaivers for paediatric populations once appropriate boundary criteria have been defined. The BCS is known to be prudent therefore it was not surprising that proposed criteria for paediatric populations were conservative. This may also be influenced by the greater perception of risk of inequivalence in vulnerable paediatric populations.

It is recognised by the authors, and also the survey respondents, that BCS criteria are frequently used during drug development to risk assess decisions; in developing paediatric products a pBCS would help in this process. Specific areas were pBCS classifications would be useful include:

- Early strategic planning of formulation design (specifically dose:solubility ratio); this can influence formulation design strategy (and subsequent resource) and dictate whether an enabled formulation is required

- Determining target limits for dissolution using biopredictive methodology: biopredictive rather than biorelevant methods are specifically sought due to the absence of an IVIVC in most cases for paediatric products. A biopredictive dissolution method would allow better understanding of the critical quality attributes of a paediatric solid dosage form to support QbD risk assessment.

- Risk assessing inequivalence in paediatric populations compared to adults to enable root cause analysis on inequivalence to understand whether the differences observed are related to the formulation or the patient anatomy/physiology.

The limitations of a pBCS were highlighted as this is recognised to be a crude estimation of product performance yet as outlined above is of value during the development of paediatric medicines. A great emphasis was placed on developing age-appropriate biorelevant tools to better predict the in vivo performance of paediatric medicines. PBPK is a growing area and the need for a pBCS may be superseded by the development of validated models that use the understanding of pBCS inputs to better predict in vivo absorption of medicines in children. The same evidence and knowledge is required to further develop both parameters for a pBCS and validated PBPK models so these tools are likely to be developed in parallel as the evidence base increases. Current paediatric medicines development work involves the use of preclinical animal models as well as a range of in vitro and in silico tools; additional research is required to understand the relative benefits and limitations of each method and its value in predicting clinical performance in paediatric populations.

Dissemination of these results is critical to promote further research and discussion in this area. Furthermore, competent authorities should use this information to inform future guidelines.

Acknowledgments

We would like to thank the experts for their contribution to the survey and for those who assisted in the distribution of the survey.

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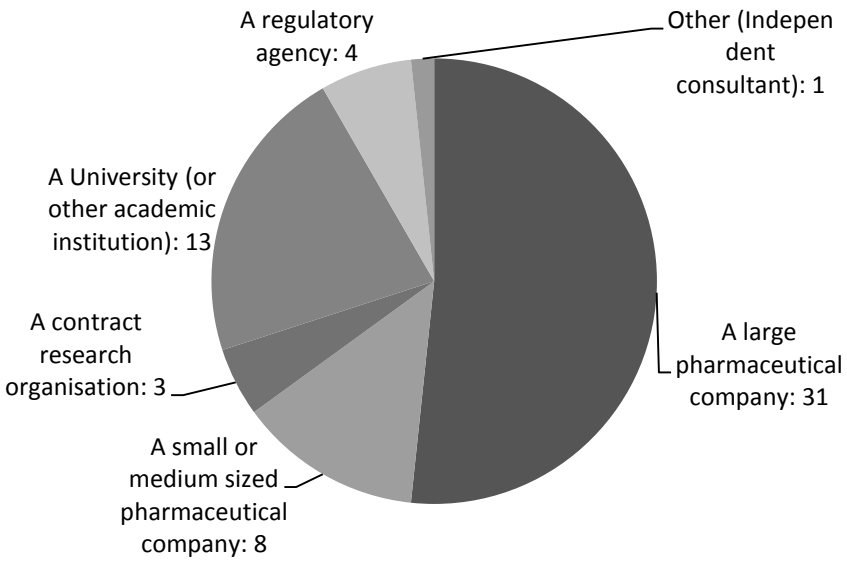

Figure 1. Demographics of survey participants

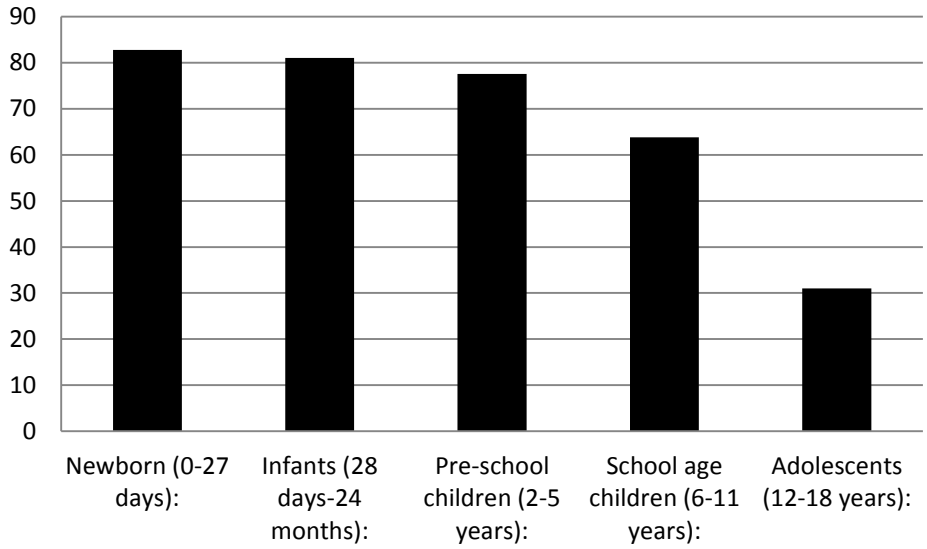

Figure 2. Percentage of respondents that agree a pBCS is required for the range of age groups.

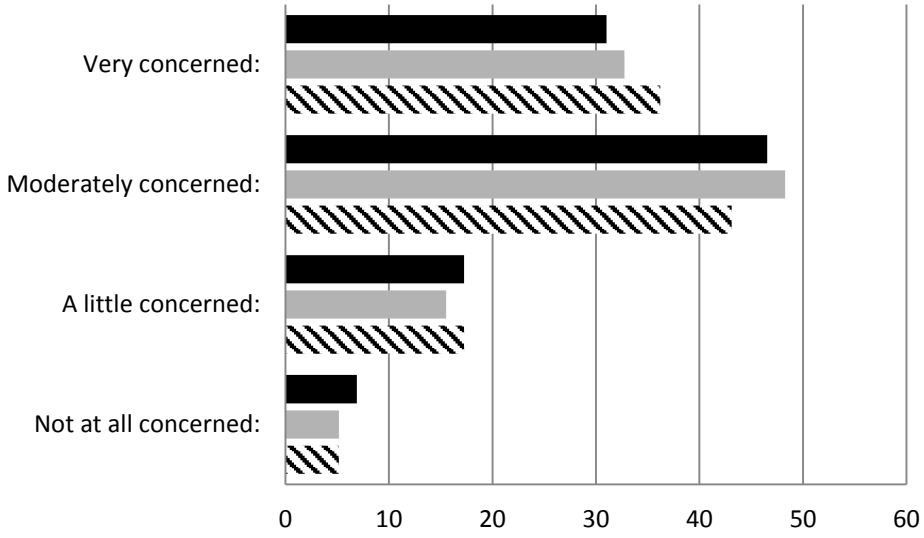

Figure 3. Percentage values of participant levels of concern about the lack of a pBCS (black bars represent concern with regard to an inefficient drug development process; grey bars drug efficacy and striped bars child safety).

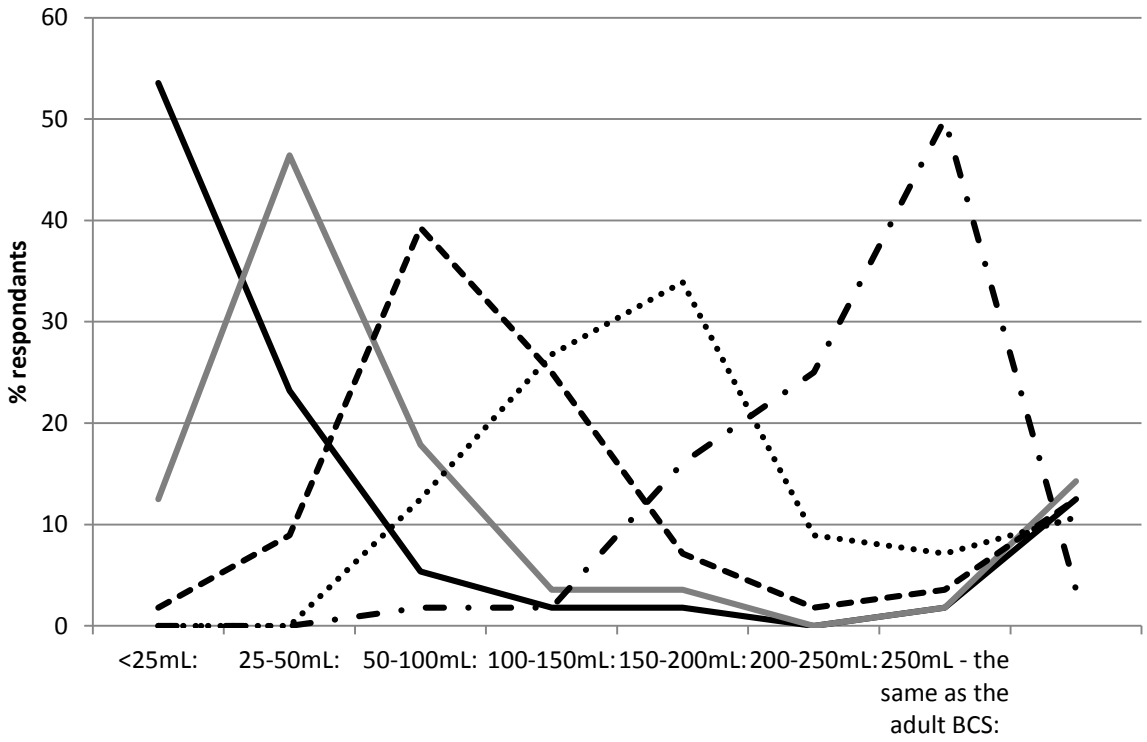

Figure 4. Percentage of respondents who selected the paediatric reference volumes in which the highest dose or dose unit should be soluble to classify a drug as highly soluble within a pBCS. (Black line = neonates; grey line = infants; dashed line = children aged 2-5 years; dotted line = children aged 6-11 years and the dot-dash line is adolescents (12-18 years)).

Table 1. Comparison of reported values for the volume in which the highest dose or dose unit should be soluble to classify a drug as highly soluble within a pBCS

	Volume to use (mL)				
Reference	**Neonate (1 month)**	**Infant (12 months)**	**Child (3 years)**	**Child (10 years)**	**Adolescent (14 years)**
(Abdel-Rahman et al., 2012)	25	25	25	25	25
(Batchelor, 2014)	13.2	37.7	56.6	111.4	188.7
(2014) (Gandhi et al., 2014)	34.7	67.4	93.9	159.0	220.3
(Shawahna, 2016)	14.9	38.9	54.0	121.0	192.0

Table 2. Frequency of responses selected for the classification of a drug as highly permeable reported by age category. *Represents answers where consensus was reached (>75% of participants agreed).

	Frequency of response (%)			
Age	**> 90% absorbed - the same value as the adult BCS**	**A higher % absorbed compared to adults**	**A lower% absorbed compared to adults**	**Other**
Newborn	57	9	26	8
Infant	60	11	23	6
Child (2-5 years)	66	11	16	7
Child (6-11 years)	*79	4	12	5
Adolescent (12-18 years)	*90	0	7	3

Table 3. Most frequent responses selected for the most appropriate dissolution conditions for paediatric products. *Represents answers where consensus was reached (>75% of participants agreed).

Age	**Volume (mL)**	**Time (minutes)**	**pH range (1-6.8)**
Newborn	<250	15 mins	As per adult
Infant	<250	15 mins	As per adult
Child (2-5 years)	250-500	15 mins	*As per adult
Child (6-11 years)	500-900	*15 mins	*As per adult
Adolescent (12-18 years)	900	*15 mins	*As per adult

Table 4. Prioritised proposed areas for research in paediatric biopharmaceutics

Suggestion	**Frequency**
Better characterize physiology and anatomy of the GI tract in paediatric patients	25
Characterize age-specific changes in drug permeation across the intestinal membrane	16
Development of biorelevant media that better reflect the composition and pH of GI fluids in paediatric patients	11
Development of biorelevant dissolution tests	11
Validation of PBPK *in silico* models	10
Understand bridging from adult to paediatric formulations	7
Understand the food effect	3
Measure minimum and maximum of drinking volumes	1
Understand which animal models can be used as models for paediatric intestinal tract	1