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Review article

A review of paediatric injectable drug delivery to inform the study of product acceptability – An introduction

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ABSTRACT

Aim: The EMA defines acceptability as "the overall ability and willingness of the patient to use, and their caregiver to administer, the medicine as intended" [1]. This paper seeks to outline issues of acceptability in relation to injectable therapy, namely intravenous (IV), intramuscular (IM) and subcutaneous (SC) administration routes, and to lay a foundation to identify a minimum set of data that would satisfy Regulatory Authorities when discussing the acceptability of an injectable product. In addition, it will alert drug product developers to other factors that might contribute to good practice, alternative administration strategies and overall adherence to achieve successful treatment.

Whilst the term 'parenteral' means "outside the intestine" [2,3] and so potentially covers a range of administration routes including intranasal and percutaneous administration, this review focuses on IV, IM and SC administration by injection. The use of indwelling canulae or catheters to reduce venepuncture and facilitate prolonged treatment is common and may impact acceptability [4]. This may be influenced by information provided by the manufacturer but is not always in their direct control.

Other injectable products suitable for routes such as intradermal, intra-articular, intraosseous and intrathecal, share the requirement to be acceptable but are not specifically covered in this paper [2,5].

1. Introduction

Oral administration of drugs is a convenient and widely used route of drug delivery, but the oral route may not always be practicable or desirable. Parenteral routes of administration help circumvent issues such as dysphagia, gastrointestinal disease, low enteral absorption, high first pass metabolism, instability or degradation in the gastrointestinal tract [2,6]. Injectable routes constitute one of the main modes of therapy in hospitals and emergency care especially when the oral route is not feasible, such as in neonatology and critical care of children, impaired consciousness, trauma, and when there is a need for rapid onset of drug action. Injectable routes are also used for intermittent or continuous infusion of drugs; for maintaining consistent blood levels via depot formulations; and for maintaining nutrition in severely ill patients. Although injectable drug delivery offers several advantages, it also has drawbacks in terms of higher costs, training (including avoidance of sharps injury), specialized equipment and the need to avoid microbial contamination [2,6,7,8].

Innovations in injectable formulations, devices and clinical practice have permitted sustained, targeted and controlled therapy in addition to reducing frequency of administration and adverse events thereby improving patient acceptability [2,6,9].

In the outpatient and domiciliary settings in several countries, developments in practice include the increasing use of injectable antimicrobial therapy (OPAT) for paediatric and adult patients. Injectable administration can be achieved by visiting a healthcare facility, self-

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administration by the patient, administration by a caregiver/family member or with the help of a visiting health practitioner [10,11,12].

As further discussed below, the concept of acceptability is a complex one. In order to help focus the contents of this paper a summary of the 'knowns' and 'unknowns' with regards to paediatric drug product acceptability assessment has been compiled and is presented in Table 1.

1.1. The terminology of acceptability

In relevant papers discussing 'acceptability' a variety of terminology is used and often reflects the overall acceptability of an intervention, including safety and efficacy and other components relating to overall quality of life such as convenience to both patient and carer, feasibility and cost. Several other terms used to discuss outcomes may cause confusion when determining what to measure when demonstrating 'acceptability' of a pharmaceutical product (Table 2). These include *adherence, compliance, concordance* [13,14], *preference, quality of life, safe practice, benefit-risk profile, comparative acceptability*. Acceptability of the drug product will be important in achieving these broader outcomes, but should be measured discretely.

Table 1
Gaps in acceptability information.

What do we know?
Information about the potential acceptability of an injectable product and its route of administration (IV, IM, SC) is important for product design and development. Paediatric patients and caregivers may have perceived preference for a route of administration.
Regulatory authorities expect discussion of the acceptability of proposed dosage forms to be included in paediatric investigation plans and confirmation of acceptability from clinical studies. There is useful information in guidelines about product attributes that should contribute to product and patient acceptability but no regulatory guidance on how acceptability should be determined.
The definitions of 'acceptability' in European guidelines concerns product and patient or caregiver acceptability but the term is also used in relation to overall acceptability of healthcare interventions.
Product acceptability may involve the child patient, parent or caregiver, and the health professional caregiver with different importance or priority for different aspects of acceptability. For example, the child patient may prioritise avoiding pain on injection but the caregiver may have to contend with a complex administration technique.
There is a growing amount of scientific literature on patient and caregiver acceptability of oral dosage forms and products for children. There is sparse literature directly concerned with the range of outcomes that might be measured to study acceptability of injectable products and no published tools that might be used. However, some features that make up 'acceptability' have been well studied and reported in different contexts. For example, pain scoring in different age groups for assessing the efficacy of analgesia.
Companies and regulators should have information about the studies required to confirm patient and caregiver acceptability of injectable products but information and outcomes have not been published.
Acceptability should be measured discretely – withdrawal from a clinical trial could be as a result of pain of administration but there are other reasons for withdrawal that may not be related to the drug product.
What do we need to know?
What information about acceptability is required for a paediatric investigation plan?
What developmental changes in anatomy, physiology and psychology in childhood may affect the acceptability of an injectable product?
What are the attributes of an injectable product for children that should make it acceptable for patients and caregivers?
Is it possible to extrapolate from acceptability demonstrated in studies with adult patients?
What should be studied in clinical trials/studies to demonstrate acceptability to patients and caregivers, of an injectable product?
Can the experience of companies and regulators about methodology and outcomes of studies on acceptability of injectable products for children be harnessed to provide guidance?
Can studies be designed to measure acceptability related specifically to characteristics of the drug product and discriminated from other aspects of the intervention?

Table 2
Terminology.

Term	Definition/comment	Reference
Acceptability	The quality of being tolerated or allowed.	[15]
Acceptability *(patient; care giver)*	The overall **ability and willingness** of the patient to use a medicinal product as intended and its care giver to administer the medicine as intended.	[1]
Acceptability *(patient; care giver)*	The **ability and willingness** of a patient to self-administer, and also of any of his/her lay or professional caregivers, to administer a medicinal product as intended.	[16]
Acceptability *(cost)*	The **ability and willingness** of the provider to pay for the treatment	[17]
Acceptability *(intervention)*	The term is also used in relation to overall health care interventions	[14]
Adherence	The extent to which the patient's behaviour matches **agreed** recommendations from the prescriber. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the prescriber's recommendation.	[18]
Appropriateness	A set of pharmaceutical design characteristics of a drug product that determines within a specific target patient population if a patient and/or its caregivers can use the pharmaceutical drug product as intended.	[19]
Benefit-risk	In relation to pharmaceutical dosage forms, consideration of the advantages and disadvantages of the product in relation to efficacy and safety.	[20]
Comparative acceptability	The attributes determining acceptability of two or more dosage forms or interventions are ranked and may allow preference to be expressed	[14]
Compliance	The extent to which the patient's behaviour matches the **prescriber's** recommendations.	[18]
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which prescriber and patient **agree** therapeutic decisions that incorporate their respective views, but now includes patient support in medicine-taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.	[18]
Health-related quality of life	The patient's ability to enjoy normal life activities. Quality of life is an important consideration in medical care. Some medical treatments can seriously impair quality of life without providing appreciable benefit, whereas others greatly enhance quality of life.	[21]
Medicines optimisation	A person-centred approach to safe and effective use of medicines, to ensure people obtain the best possible outcomes from their medicines. Medicines optimisation applies to people who may or may not take their medicines effectively. **Shared decision-making** is an essential part of evidence-based medicine, seeking to use the best available evidence to guide decisions about the care of the individual patient, taking into account their needs, preferences and values.	[22]
Preference	Something one would like to have or do rather than something else. May be used when comparing the attributes of drug	[15,23]

(*continued on next page*)

Table 2 (*continued*)

Term	Definition/comment	Reference
Safety *(medication safety; safe medication practice)*	products but also when considering other treatment-related factors such as different routes of administration, frequency of dose, safety and efficacy. In relation to pharmaceutical dosage forms, consideration of the attributes of the product and the way it is used and actual or potential effects on accepted standards of practice and harm to the patient.	[24, 25]

2. Literature review

Much of the literature relevant to assessment of product acceptability relates to products used for adults and may not be directly relevant to children. Some of the literature and discussion concerns the overall acceptability of a health care intervention and quality of life.

2.1. Summary of method and results (see further information in supplementary material S1)

From mid-August to mid-September 2020, Pubmed was searched with the following keywords (acceptability [Title/Abstract]) AND (parenteral [Title/Abstract]) and 76 results were obtained.

On screening, 10 papers were judged relevant, with 4 concerning paediatrics. This search was verified on 25-Apr-22. 82 results were obtained, without finding any additional papers of interest for this review. Further searches were carried out on Google scholar. The search was widened to include all age groups. Detailed information on search terms is provided in supplementary material S1. Cited references of the selected studies/systematic reviews were hand-searched for any additional relevant articles. In addition, citation chaining searches were undertaken on Google Scholar using the "Cited By [# results]" link below the link to the paper.

A first table with 194 references was constructed. When the abstract mentioned "acceptability" but only concerned adults the reference was kept (to be able to compare children vs adults methods). When it was collected from "preference" or "pain" search terms, only references related to children were kept unless there was no access to the full article to check if it also concerned children. At the end of the process, 105 references were selected and are tabulated in supplementary material S2. The table provides summary information under the following headings: title; drug/device/acceptability factor studied; device/route, or formulation; age and age group; acceptability objective; method or tool used; summary of results.

3. Results

None of the studies directly addressed the issue of drug product characteristics in relation to acceptability which might be required by regulators for drug products early in their authorisation life cycle. However, there is information of relevance to preparing guidance within the references such as the use of pain scoring tools when comparing routes of administration; collection of data from lay and professional carers; importance of factors like convenience and care setting.

3.1. Age groups

Where the age of participants was defined in the paper, the data was coded into six categories shown in Table 3. There were 29 papers where the age of the participants was not included in the paper and 29 papers where adults only were studied. Five papers included information from parents or carers; one of which included preference for route of administration used for morphine for their baby from their perception of the effect on breast feeding.

Table 3
Number of papers relevant to acceptability according to age of patient.

Classification	Details	Number of papers
Younger child	<6 yrs	1
Older child	>4–18	16
Child	0–18	11
Mixed	children (and views of parents/carers)	5
Mixed	children and adults	14
Adults	(>16 to adult)	29
Age not defined		29
Total number of papers		105

3.2. Types of studies

Twenty reviews of the literature were found, including 4 systematic reviews. There were many clinical studies including randomised controlled trials where the aim was to compare the efficacy of the active drug by different routes of administration or injection device - acceptability or preference was determined by a variety of methods as a secondary objective. Inspection of the summaries shows the diversity of study types.

3.3. Focus of papers

When the papers are divided into study areas the main areas of focus are shown in Table 4. The majority of studies examined the acceptability of different devices used in the administration of drug products. Examination of the acceptability of or preference for different routes of administration was also frequently studied. Many of the selected papers concerned insulin or growth hormone and a comparison of different injection devices (pens) or were recording preferences for different routes of administration such as SC versus IV. Others concerned overall health care interventions such as OPAT and methods of achieving safe but convenient homecare, e.g., for rheumatoid arthritis, febrile neutropenia.

4. Conclusions

The literature review confirmed that there are few publications of direct relevance to determining what studies should be undertaken to describe the acceptability of individual injectable products for children. Regulatory guidance [1,16,26] and experience of the authors shows that information about injectable products relevant to acceptability is required in applications for marketing authorisation and that acceptability should be confirmed during clinical studies. Further work is required to gather information from pharmaceutical companies and to propose structures for pre-clinical and clinical studies to guide pharmaceutical development and product registration.

4.1. What is 'acceptability' in the context of an injectable medicine?

The EMA guideline on the pharmaceutical development of formulations for paediatric use [1] defines 'patient acceptability' as *'the overall*

Table 4
Number of papers according to the focus of the study.

Focus of the acceptability study	Number of papers
Device	57
Route of administration	33
Formulation type	6
Needle length or geometry	6
Regulatory	1
Not defined	2
Total papers	105

ability and willingness of the patient to use a medicinal product as intended and its care giver to administer the medicine as intended'. The guideline explains that '*the suitability of the chosen method to test the patient's acceptability and the appropriateness of the limits to be applied should be discussed and justified in terms of risk to benefit considerations, including risks at population level (*e.g. *emergence of microbiological resistance due to poor acceptability of different preparations with antibiotics). The characteristics of the target age group(s), the condition relevant to the paediatric medicine, single or multiple use, the duration of treatment and any co-medication should also be considered'*. The guideline frequently uses the terms 'acceptability, acceptance, suitability' and the requirement to discuss attributes of the pharmaceutical product in relation to them but does not attempt to quantify or to discuss methods for determining the acceptability of injectable products.

In a recent Reflection Paper on the pharmaceutical development of medicines for use in the older population [16], patient acceptability is similarly defined *as 'the ability and willingness of a patient to self-administer, and also of any of his/her lay or professional caregivers, to administer a medicinal product as intended'*. Much of the information in the reflection paper is also applicable to paediatric patients. It goes on to say that *'patient acceptability is likely to have a significant impact on patient adherence, which can have an impact on the (perceived) patient and caregiver quality of life, institutional or hospital medication safety systems and/or the medicine's benefit-risk profile. Patient acceptability is mainly determined by the interplay of the multi-dimensional requirements of the medicinal product (design) and the characteristics of the patient and, where relevant, his/her caregiver (patient product interface)'*. Examples of product characteristics influencing patient acceptability are given which are generally applicable to the paediatric situation but again there is no focus on injectables. The reflection paper notes that *'adequate patient acceptability can be demonstrated by different means (*e.g. *using data from clinical trials, representative simulated use studies, human factor studies with healthy volunteers or patients, market experiences, literature)'* and that *'selection of the method and acceptance criteria is left to the company.'*.

These two EMA definitions of acceptability link the drug product characteristics and those of the patient and/or caregiver, indicating the multi-dimensional evaluation required and that this product-patient interaction is but part of an intervention to achieve health and well-being of the patient (and carer) and contributes to the acceptability of the overall intervention. Injectable drug products should be acceptable to the paediatric patient but should also be acceptable to the carer (professional or relative) since many injections will be administered by a carer rather than the patient.

Using the EMA guidelines and the Reflection Paper [1,16] and Kozarewicz's paper outlining regulatory perspectives on acceptability of dosage forms in children [26], Table 5 below outlines potential acceptability characteristics.

Table 5
Potential acceptability characteristics derived from paediatric guideline on pharmaceutical development of medicines [1], older people reflection paper [16] and Kozarewicz [26].

	Paediatric guideline [1]	Reflection paper – older people [16]	Kozarewicz [26]
Patient characteristics			
Age and weight	✔	✔	✔
Individual health status	✔	✔	✔
Disease type			✔
Disabilities	✔	✔	✔
Behaviour	✔	✔	
Background and culture	✔	✔	
Perception and previous experience	✔	✔	
Medicine characteristics			
Route(s) of administration	✔	✔	
Dosage form	✔	✔	
Dosing needs/flexibility; frequency and total number of doses	✔	✔	
Excipients (suitability and acceptability)	✔	✔	✔
Stability issues (including shelf life and storage conditions)	✔	✔	
Measuring and administration devices; equipment for accurate delivery; instructions	✔	✔	✔
Medication error potential	✔	✔	
Site of injection	✔	✔	
Physicochemical properties; dose volume, administration rate	✔		✔
Duration of administration			✔
Preparation prior to administration	✔	✔	
Packaging and container size	✔		
Ease of use; container closure system; device		✔	
Complexity of dosage instructions; readability of the package leaflet (PL; text and figures) and the completeness of information		✔	
Appearance		✔	
Other			
Setting in which the product is used	✔	✔	
Need for caregiver assistance		✔	

4.2. Interplay of product characteristics for patient and care givers

The characteristics of the injection dosage form such as pH and osmolality may have a direct bearing on patient acceptability if, for example, it irritates at the site of injection and causes pain. However, the technique of administration – for example, by repeated direct venepuncture versus injection into an indwelling catheter - may not be within the control of the manufacturer yet the former injection technique is likely to be more painful than the latter. Equally, if pain on direct injection is predicted or observed the manufacturer may recommend dilution before administration or injection into a fast-flowing intravenous infusion or injection through a central venous catheter only and include this information in the SmPC and patient/carer information. Patient acceptability may be improved (as measured by pain on injection for example) but acceptability to the carer may decrease because of increased complexity and the benefit-risk profile may be decreased if central venous catheterisation is obligatory.

Many IV injections are not given by direct injection through a needle into a vein. When several injections are required over a period of time (which may be over minutes, hours, days or months) or infusion of injectable products is indicated, a short cannula into a peripheral vein, a longer catheter into a central vein or a subcutaneous reservoir linked to a central vein via a catheter can be used. If possible, the decision over which device will be used should be the focus of a discussion between the health care practitioner and the family or carer of the child. The injectable product is then administered into tubing or taps attached to the catheter or via special needles into the subcutaneous reservoir. Such administration techniques are commonly used in treatment of cystic fibrosis, in cancer care, for postoperative analgesia and for intravenous feeding but may be preferred for short courses of treatment in many children because of the preference over repeated direct venepuncture or IM injection [27,28]. Advantages and disadvantages of different approaches to reducing the need for direct venepuncture is beyond the scope of this article but further information is available [4].

Pharmaceutical developers should be aware of these techniques of intravenous administration and take steps to ensure that adequate product information is made available to enable safe and effective administration to the child, which is acceptable to the practitioner. Examples will include minimum and maximum concentrations, suitable carrier fluids, potential for interaction with administration apparatus,

stability of diluted product, duration of injection or infusion, suitability of peripheral versus central venous administration and compatibility information where available.

4.3. Acceptability challenges and considerations

During formulation development the desired PK profile, biopharmaceutical considerations and/or physicochemical properties of the active drug may drive selection of one injectable route over another.

For the product developer there are challenges in paediatric formulation development such as avoidance of potentially toxic excipients [29] compounded by the lack of knowledge concerning acceptability and safety of medicines with respect to the age and developmental status of children.

Confirmation of the acceptability of a pharmaceutical product is a critical feature in the pharmaceutical development of all medicines. Acceptability needs to be evaluated in a manner that assures patient compliance in taking their medicine and will be a significant feature in developing concordance between patient, family carers and health care practitioners.

Table 6 below outlines some of the main challenges and considerations related to paediatric injectable drug product development, including potential impact on product acceptability.

4.4. Acceptability assessment

In accordance with the guideline on pharmaceutical development of medicines for pediatric use, applicants must demonstrate to the regulator the acceptability of their new product in the targeted population [1]. In the context of injectable treatment, the drivers of acceptability are heterogeneous in terms of product and patient characteristics and of clinical practice. Local policies and practice may influence injection and administration technique (including direct SC or IM injection, venepuncture, IV or SC cannulation and use of indwelling catheters). For a new drug product relatively early in its clinical studies the criteria may relate to that specific product with standardized method of administration but later in the product life cycle, for those assessing the risk and benefit of health technologies, acceptability may be judged within broader health care interventions where other factors such as cost and quality of life are introduced, as well as acceptability compared to that of other products. Having an acceptable pharmaceutical product is an important contribution to the overall acceptability of health care interventions and hence on overall therapeutic outcomes.

Under these conditions, the selection of a harmonized set of judgment criteria to objectively measure acceptability will be challenging, particularly in the youngest populations. In addition, as acceptability is a multi-faceted concept and the analysis of the measures observed could be complex, the criteria should be analyzed in all these dimensions. Otherwise, the establishment of clearly defined algorithms would be required to manage cases where criteria, such as reduced pain or discomfort versus need for frequent hospitalization, might give opposite signals [23].

5. Conclusion

In addition to the challenges associated with the development of medicines for children there is a distinct lack of guidance or internationally agreed harmonized methodologies for determining the acceptability of injectable products. This brief review is intended to flag some of the issues in this area and to start a conversation on the development of such guidance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 6
Drug product development considerations related to acceptability of injectable drug delivery for paediatric patients.

Considerations	Impact on Product Acceptability
Product Design	
Physicochemical properties of active	May determine administration vehicle, route and dosage form.
Formulation design (e.g. immediate release or long-acting)	Impacts number of injections required. May impact administration setting (home or hospital). May impact safety profile of the product.
Product concentration(s)	Determines injection volume. May impact dose accuracy if very small volumes have to be administered (e.g. neonates). Large volumes may not be suitable for fluid restricted patients.
Excipients	Type and daily exposure need to be suitable for target patient population.
Formulation properties (pH, osmolality, viscosity etc.)	May potentially be linked to discomfort on administration [30–32]. May be linked to requirements for additional dilution or administration via central vein catheters.
Stability (including in-use)	May result in need for additional manipulation steps (e.g. reconstitution of lyophile); shorter in-use periods; refrigerated storage conditions or protection from light
Size of primary container/product volume in container	May increase the potential for dosing errors (e.g. accidental overdose if multiple doses can be withdrawn from the container). Re-use of single-dose vial may occur if several doses can be withdrawn and the product is costly.
Cost	The cost of a product must be seen as cost effective.
Device (hospital and home use)	Potential risk of dosing errors because of incorrect use (e.g. insufficient training or unclear -instructions for use). Risk of non-compliance because of device complexity, or because device is otherwise not acceptable.
Product Administration/Use	
Complex calculations and product dilutions	Potential for dosing errors; higher risk of microbial contamination / infection if multiple preparation steps required; length of time required for dose preparation. Higher training burden.
Dose volume	Linked to product concentration and requirements for product dilution prior to use. May be impactful if patients are fluid restricted (e.g. neonates) or are receiving multiple medications. Small dose volumes can result in inaccurate dose delivery.
Accuracy of dose delivery	Linked to dose volume, complexity of dose preparation, and training.
Needle geometry/type	Needs to be appropriate for patient population and route of administration to minimise pain and allow dose delivery to the target area (e.g. vein, muscle, subcutaneous tissue). Is usually selected by the healthcare professional (HCP), unless it is supplied as part of a device (pre-filled syringe, autoinjector).
Place in complex therapy; co-administration of several treatments	Simultaneous administration of multiple treatments/parenteral nutrition/hydration can be challenging when vascular access is limited; co-administration through the same lines can lead to incompatibilities resulting in potential line blockage and patient safety concerns.
Care setting and type of vascular access	Care setting is determined by the therapy regimen and delivery site. If this is complex, a clinical care site may be required, however if this is less complex, it may be possible that the therapy is delivered by a visiting health care professional or by the patient or carer themselves with potential acceptability and pharmacoeconomic benefits.
Product storage	Determined by product stability. Refrigerated storage may be challenging in some settings.

(*continued on next page*)

Table 6 (*continued*)

Considerations	Impact on Product Acceptability
Product Design	
Training/education	Availability of (age-)appropriate education materials, training and Instructions for Use (IFU) for paediatric patients, caregivers and HCPs.
Effect of foreseeable handling errors	Care setting and training

the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpb.2023.04.010.

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