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Research paper

Navigating the complexities of medicating paediatric patients: Insights from an enteral feeding tube workshop

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ABSTRACT

Enteral feeding tubes (EFT) are used to administer nutrition into the gastrointestinal tract of patients who are unable to take nutrition via mouth. A wide range of children may require enteral feeding through EFT which are also used to administer medication. However, many medicines are not licensed for administration via this route. Numerous factors can impact EFT medicine administration, including for example, dosage form properties and composition, EFT size, design and material, and operational aspects such as tube flushing. As a result, the risk of sub-optimal dosing and medication error is much higher in patients with EFT compared to those without. EuPFI organised a preconference workshop to review the current state of knowledge around aspects to be considered in the verification of EFT administration of medications to children, and considerations for EFT use, and to highlight the areas that remain challenging. Healthcare professional, pharmaceutical industry and regulatory agency perspectives were shared, and case studies discussed. It was agreed that simple and clear standardised global procedures are required for the evaluation and administration of medicines via EFT, and collaboration between all key stakeholders is recommended.

1. Introduction

Enteral feeding tubes (EFT) are critical for patients unable to maintain nutritional intake and swallow oral medications because of medical conditions or age-related limitations that may compromise swallowing or the function of the upper gastrointestinal tract. Indeed, EFT are used in many children with acute and chronic illnesses, and neurodisability, who are unable to safely swallow. It is essential that the required dose as well as safety and effectiveness of a drug product administered via an EFT are not negatively impacted through the use of this route of delivery.

EuPFI organised a preconference workshop as part of its 14th Annual Conference to review the current state of knowledge around aspects to be considered in the verification of EFT administration of medications to children, and considerations for EFT use, and to highlight the areas that remain challenging. The workshop aimed to provide perspectives from healthcare professional, regulatory agency and pharmaceutical industry representatives on current practices, issues, and requirements for the administration of products via EFTs. Participants were given the opportunity to use their existing knowledge and experience regarding EFT paediatric medicine administration to explore this topic further through group discussion. This paper provides an overview of the workshop presentations and subsequent team discussions.

2. Method

The detailed objectives of the workshop are presented in Fig. 1. Following to an introduction to the need for, challenges and risks associated with the administration of medication to children via EFTs, presentations on challenges and potential solutions were given by a healthcare professional (a paediatric pharmacist), and representatives from the pharmaceutical industry (a device engineer) and Food Drug Administration (FDA) and European Medicines Agency (EMA) regulatory agencies. The participants were distributed into two small groups, to facilitate discussion. The groups were chosen to, as far as possible, include participants who had some experience in the use of EFT or in the

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development of products intended for administration via EFT, and those who were less familiar with the topic. The participants discussed to one of the two fictional, yet realistic formulation case studies posed to them:

- the evaluation of the administration of immediate release sprinkles/granules (beads) in capsule to paediatric patients via EFT ("Farmako") [Fig. 2].
- the evaluation of a suspension under development for administration to paediatric population via EFT ("Enticillin") [Fig. 3].

Participants were asked to consider information provided by the speakers as well as their knowledge and personal experience and apply them to the case study provided and respond to the following questions:

– What formulation attributes need to be considered and how would you evaluate them?
– What preparation or manipulation, if any, might the formulation require to enable EFT administration?
– What EFT attributes need to be considered and how would you select appropriate EFT(s)?
– What studies would you perform to generate sufficient EFT administration instructions for the end user?
– Overall, what are the key challenges associated with paediatric medicine administration via EFT and what constructive solutions, if any, could mitigate them?

Each group was supported by a facilitator from the EuPFI devices workstream to provide guidance when needed and to answer any questions posed to them based on a pre agreed facilitator brief. Within the groups, the workshop facilitators asked all participants to discuss and deliberate on their delegated tasks and then present their conclusions to all workshop participants. They were also asked to provide critical comment on the feedback provided by the other breakout discussion group. Facilitators were encouraged to stimulate discussion and help the group reach its own conclusions and to avoid instructing the group as far as possible. An elected representative member from each group provided a summary of the outcome of their discussions for comment. The feedback presented by the participants was collated by the workshop facilitators and is summarised below in the results and discussion section.

3. Results

3.1. Participants

Ten participants from six countries (Belgium, France, Germany, Nigeria, Sweden, and UK), excluding the workshop organisers and speakers attended the pre-conference workshop. The majority (7) were from the pharmaceutical industry whilst two participants were from academia, and one was from a children's hospital.

3.2. Presentations

3.2.1. Healthcare professional perspective

Administration of medications through an EFT is a reasonably common nursing intervention that entails several skills, including preparing the medication, verifying the tube position, flushing the tube, and assessing for potential complications. It also involves making many informed decisions including the form of medication to select (solid or liquid), modifications needed and what tube/syringe size to use. Tube blocking is a particular concern for healthcare professionals, the risk of which increases with number of drugs administered enterally and dose administrations per day [1] In addition, risk of medication error is significantly higher in patients with EFTs compared to patients without, often due to failure to flush tubes adequately [2]. It was noted that most medicines are not licensed or designed for administration via EFT and hence are given "off-label" resulting in greater liability on the healthcare team. In addition, manipulation of the dosage form, for example tablet crushing or capsule opening followed by dispersal in liquid is often required. Several issues are associated with the preparation of solid oral dosage form-based suspensions for enteral tube administration. For example, such manipulated products may be clinically unsafe for the patient, such as extended release or enteric coated products, e.g., lansoprazole, where crushing may destroy the modified release mechanism resulting in decreased therapeutic effect [3]. A number of drugs may be potentially toxic to the carers crushing the tablets, by inhalation of the powder, such as cytotoxic, carcinogenic or teratogenic drugs [4]. Inadequate or inappropriate crushing or dispersing can result in tube

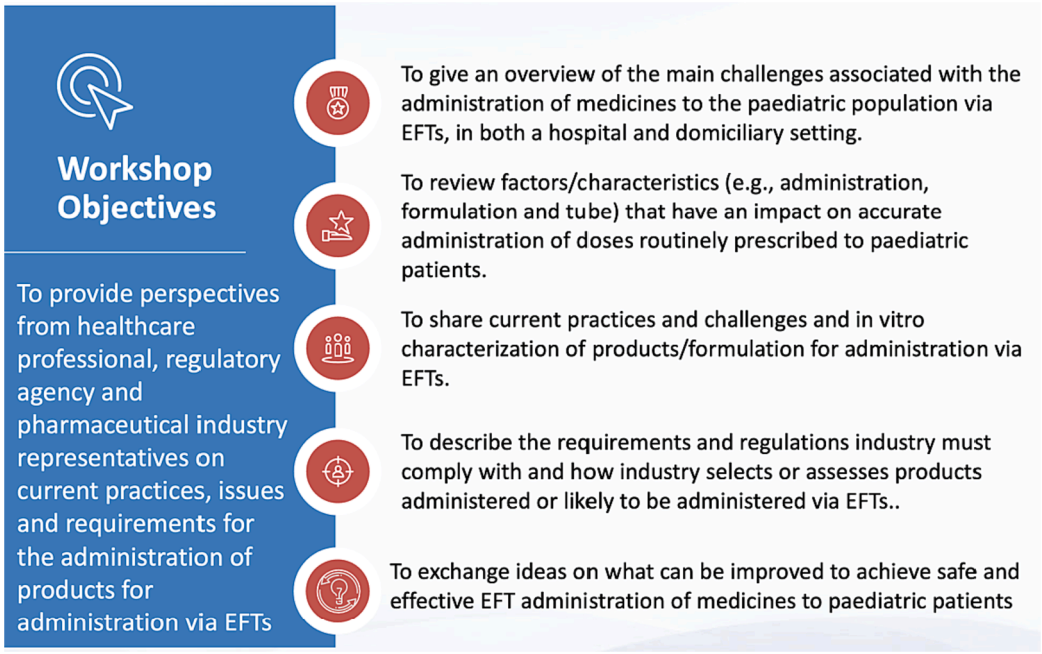

Fig. 1. Workshop objectives.

- A new product (**Farmako**) is being developed for the US and European markets.
- The proposed formulation is immediate release sprinkles/granules filled into hard gelatin capsules. The capsules can be opened, and the contents mixed with soft food for administration, or may be swallowed whole by older patients.
- The granules comprise microcrystalline beads onto which drug and a pH-sensitive taste-masking coat have been applied, resulting in an approximate bead size of 300-400 µm. The granules are filled into capsules to provide three different dose strengths: **3 mg** (300 mg granules), **2 mg** (200 mg granules), and **1 mg** (100 mg granules).
- You have been requested to evaluate the administration of Farmako granules to paediatric patients via EFT.

Product Information

The product is to be administered **once a day**.

The target age group is **6 months and above**.

Final doses are to be confirmed, but are estimated as follows:

Dose (mg)	No. Capsules	Age
6	2 x 3 mg	12-< 18 years
4	2 x 2 mg	8 – 12 years
3	1 x 3 mg	6 – 8 years
2	1 x 2 mg	3 – 5 years
1	1 x 1 mg	6 months – 2 years

Fig. 2. Case study 1 – Farmako: Evaluation of the administration of immediate release sprinkles/granules (beads) in capsule.

- You are a paediatric product development scientist with EntMeds pharmaceuticals PLC. You have been asked to produce a suspension formulation of Enticllin a broad-spectrum antibiotic with an excellent broad spectrum against both Gram +ve and Gram –ve bacteria that has a multi-year history of safe use in adult populations. There are generic versions of Enticillin available and you are persuing the development under the PUMA regulations.
- The suspension under development may be used for administration to paediatric population via nasogastric tube.
- You have been requested to conduct a risk assessment to assess the potential of clogging during administration.

- **Product Information**
  - API solubility 0.5 mg/mL in water
  - Formulation strength – 100mg/5mL
  - Target age group is <7 years
  - Dosing frequency is bd

Dose (mL)	Age
5	5 – 7 years
2.5	2 – 5 years
1.5	0 – 2 years

Fig. 3. Case study 2 – Enticillin: Evaluation of a suspension under development for administration.

blockage, and it has been reported that crushing method can have an impact on the safety and dose of non-dispersible tablets delivered via EFTs. The opening of capsules or crushing of tablets may lead to an increase in the surface area of the active drug in the dosage form and hence increase the rate of drug absorption. There is a need for evidence-based standardised protocols that provide guidance and assurance that the tablet crushing method produces a suspension that will not cause tube obstruction and will deliver the intended dose.

Liquid formulations also have their own unique challenges regarding administration through EFTs, and some liquid medicines may be unsuitable for administration by this route. For example, ciprofloxacin suspension readily occludes feeding tubes. In addition, syrups may interfere with feeds and cause clumping and blockage. Obstruction of a feeding tube due to the interactions between a liquid medicine and nutrition products due to the pH of the medicine is known. Examples of drug and enteral feed interactions include phenytoin, digoxin, carbamazepine, penicillin, and rifampicin. However, compatibility information with feed can be limited and may vary according to different formulations of the same drug as well as different drugs. Appropriate administration techniques are required to prevent incompatibility (between medications and enteral feeds or food) and tube occlusion. It should be noted that some excipients currently used within oral liquid formulations are not appropriate for paediatric use, including via EFT administration, or should be used with caution, for example ethanol and sorbitol.

In addition to formulation factors, EFT size and tip location are the important factors to consider. Some medicines are only licensed for administration using certain tube sizes and materials and it should be noted that the internal diameter of EFTs may vary according to material. For example, silicone tubes have thicker walls and hence a smaller inner diameter compared to polyvinylchloride or polyurethane EFT of the same French size. It is recommended a 30 mL volume of water for

irrigation is used when giving medications or flushing small diameter nasoenteral tubes to reduce the number of tube occlusions. However, this volume may not be appropriate for paediatric patients, and hence the lowest necessary volume required to clear the tube should be used for neonates, paediatric patients, and fluid-restricted patients. For example, a volume of 2 mL may be sufficient for short EFTs.

Enteral (ENFit®) syringes should be used with EFTs, although there may be concerns regarding dose accuracy. Care is required since they have a substantial dead-space at the tip, which should not be allowed to fill with liquid medicine as the contents of this dead space are not included within the measured dose. Therefore, if this space fills with liquid, there is a risk of medicine overdosage and / or leakage (with resulting medicine waste and contamination of the area). Dosing errors for legacy and low dose tip (LDT) enteral syringes increase as the nominal capacity of syringe decreases or when the dose delivered is lower than the nominal capacity of the syringe. The dead-space can be prevented from filling by using appropriate bottle adapters or medicine straws which are available from the syringe manufacturers.

3.2.2. *Industry perspective*

Prior to the preparation of a paediatric medicine for administration through an EFT, patient age groups are carefully considered to avoid food intolerances when selecting dispersing vehicles. Appropriate tube materials and sizes readily available in a hospital environment are selected, following EMA guidance ensuring regional preferences and requirements are considered [5].

The feasibility of different dispersion vehicles is assessed, based on the list provided in the FDA draft guidance for industry Use of Liquids and/or Soft Foods as Vehicles for Drug Administration [6], and by evaluating the effect of vehicle volume, dispersion time and temperature. While water is the primary vehicle of choice, stability of the dispersion must be proven, and the hold time evaluated for any vehicle selected, results may necessitate selection of an alternative vehicle. In this case clinical considerations such as patient needs, age, and potential condition as well as regional preferences all influence the selection.

The sample preparation method and homogenisation will be optimised, i.e., crushing, suspending, or dissolving the drug product in the selected vehicle, taking into account the limited volume to be used for administering to paediatric patients (maximum 15 mL) or neonates (maximum 3 mL). Larger syringes (20 mL or more) are preferred to avoid the risk of rupturing the EFT while administering the liquid. A feasibility study evaluates potential sedimentation in the syringe which could cause clogging of the EFT during administration. In addition, redispersibility of the product is evaluated after the maximum proposed holding time of the drug product, using the same syringe. When applicable, different syringe materials must be evaluated and subsequent evaluation of the compatibility of the formulation with the entire dosing administration set (e.g., adsorption) performed.

While total liquid volumes are restricted, minimum volumes for priming the EFT, dosing the medicine, rinsing the dispersion syringe, and flushing the EFT have to be used. Both the EFT and the syringe will be visually examined for any traces of drug product adhering to the tube materials or aggregation of the product in the dispersion vehicle and clogging of the syringe and EFT. Finally, dose recovery testing will confirm the required dose has been administered.

3.2.3. *Regulatory agencies perspective*

The feasibility of administering medicinal products via EFT should be evaluated in line with regulatory agency requirements, instructions defined and verified, and presented in drug product labelling [7,8,9,10].

Various types of EFTs are available, for example nasogastric, nasoduodenal and gastrojejunal, and they differ in diameter, tube composition, inner tube geometry, number of ports and configuration and connector type. Tube size (outer diameter) is measured in French (Fr or CH) where 3 Fr = 1 mm, and commonly used tube materials are polyvinylchloride (PVC), polyurethane and silicone.

Oral dosage forms may require manipulation to enable their delivery via EFT, for example dissolution or dispersal of solid oral dosage forms within a suitable vehicle, or dilution of an oral liquid. A key risk associated with EFT drug delivery is tube occlusions; the incidence of clogged feeding tubes has been reported to be up to 35%, which can lead to incomplete delivery of the medicine and the need to remove and replace the tube [11]. Factors such as the presence of insoluble ingredients, use of inappropriate dispersion or dilution vehicle, stability in the vehicle, repeat dosing and inadequate tube flushing before and after drug administration can increase the risk of occlusion. In addition, tube size (diameter), material of construction and design (number and position of ports) can affect clogging (blockage). For example, lansoprazole delayed release orally disintegrating tablets were found to cause blockage of EFT as well as syringes due to dissolution problems and were subsequently withdrawn from the market.

Guidance on studies to be performed to demonstrate the feasibility of EFT drug delivery has been provided by EMA and the US FDA, as summarised in Table 1.

EFT sizes used for in vitro studies should be selected based on the intended population, for example, 4-6Fr for neonates and 8-12Fr for children and adults. Dose recoveries above 90% are preferred. It is suggested that small tube sizes are used to assess tube blockage, whilst small dose volumes (for example 1–3 mL for neonates) and large lumen tubes should be used for dose recovery studies, since these represent the worst-case scenarios. A design of experiments approach may be used for these studies. Dose recovery in various tube materials may be used to assess physicochemical compatibility of the drug product with the tube; extractable and leachable studies are not usually necessary due to the transient contact time. Aspects such as risk of accidental aspiration and possible effects on the bioavailability of the drug product should be also considered.

It should be noted that generic products require comparative EFT data with the originator/reference listed drug (RLD). The behaviour of the generic product should be comparable with the originator/RLD, i.e., the products should be interchangeable. For example, generic esomeprazole magnesium delayed release granules required labelling changes before approval since unlike the innovator product, the pellets adhered to the syringe and aggregated in the tube causing a blockage. It is important that EFT delivery is fully investigated for all products to enable successful administration via this route, and clear information provided in the label.

Table 1
Summary of recommended studies to demonstrate the feasibility of administering an oral drug product via enteral feeding tubes.

European Medicines Agency	United States Federal Drug Agency
• Ease of administration (use of finger pressure for enteral syringe). • Product modification (dispersal, dissolution, dilution, vehicle type and volume). • Tube blocking/clogging, including after repeated use. • Dose recovery and flush volumes. • Physicochemical compatibility (dose recovery in various tube materials).	• Recovery testing: water at pH 5.5–8.5 or apple juice, three different tube types (material/ design), repeat dosing. • Sedimentation volume and redispersibility testing. • In-use stability in designated dispersion media • Particle size distribution for suspensions and modified release products. • Acid resistance testing for drug products with an enteric coat. • Dissolution testing for extended-release drug products.
Source: Quality of medicines questions and answers: Part 2 [5]	Source: Oral drug products administered via EFT: in vitro testing and labelling recommendations guidance for industry (draft) [10]

4. Group discussion feedback

The group discussions on each case study identified various formulation and EFT attributes that should be considered regarding administration of medicines via EFTs, as well as dosage form manipulation that may be required and studies to be performed to generate sufficient information to enable effective EFT drug administration. In addition, key challenges, and potential solutions regarding medicine administration via EFTs were highlighted by the groups.

The outputs of each group are summarised in Tables 2 and 3 below.

Both groups reported that the key challenge regarding medicine administration via EFTs is the high number of variables that can have an impact on the dose received by the patient. It was noted that the process should be simplified to make it easy and clear and that a global solution is required.

5. Discussion

The workshop provided an opportunity for participants to learn about healthcare professional, pharmaceutical industry, and regulatory agency perspectives on the administration of medicines via EFTs, and to share their own and learn from other's experiences in this subject. The fictional yet realistic case studies gave rise to valuable group discussions on what factors should be considered and evaluated to enable effective EFT medicine administration. Various formulation and tube attributes were identified, for example particle size, viscosity and tube dimensions and material of construction [3,12,13]. In addition, differences in clinical practice and techniques and the patient can affect EFT medicine administration.

The presentations from the stakeholders identified some common themes, for example, challenges regarding appropriate dosage form handling/manipulation to enable EFT administration and concerns with tube blocking. However, some interesting different viewpoints also emerged, illustrating the complexity of this topic. For example, from a regulatory perspective, a minimum dose recovery of 90% should be achieved, using a realistic number of tube flushes (e.g., 1–2 mL). However, from a clinical perspective, it was noted that less than 90% may be acceptable, provided that the achievable dose recovery was stated in the product label. Indeed, it was noted that information on % recovery according to different numbers of flushes and different flush volumes would be of value to clinicians. It was remarked that taste masking is not required for an EFT-administered product and a healthcare professional expressed a preference for the taste-masked granules to be crushed to reduce the risk of tube blocking. However, there were concerns from pharma industry participants that this may impact *in vivo* product performance.

As stated above, EFT tube clogging (blockage) is a key concern [14,15,16]. It is important that medicine EFT administration procedures are reproducible and that mitigation strategies for blockages, such as extra flushing, are in place. It was noted that clinicians may not always follow instructions, for example, not flushing between medications which can increase the risk of blocking [17].

It is recognised that only a small number of individuals participated in the workshop and that representations from key stakeholders, i.e., healthcare professionals, pharmaceutical industry, and regulatory agencies, were not equally represented. Nevertheless, the workshop succeeded in achieving its aims.

Table 2
Case Study 1: Farmako granules (beads) in capsule group discussion output.

Formulation Attributes	Bead pH sensitive and taste masking coating. Excipient solubility. Bead particle size (wet and dry). Compatibility with the vehicle (water is first choice). Dispersibility/sedimentation in the vehicle.
Formulation Preparation/ Manipulation	Assume internal diameter of EFT is > 400 μm (bead size). Open capsule, disperse contents in vehicle (water or feed). Timescale from capsule opening to administration. Consider pH and source of water.
EFT attributes	Size range of tube (length and diameter) – target stomach for low pH. Tube material – compatibility – worst case and flush volume.
Studies to perform	Identify minimum volume for dispersion versus dose. Materials and mixing to form a dispersion. Particle size distribution (wet and dry). Sedimentation and redispersibility. In-use stability in designated vehicle. Identify minimum flush volume versus dose. Check flow through tube.

Table 3
Case Study 2: Enticillin oral suspension group discussion output.

Formulation Attributes	Age-appropriateness of excipients. "Stickiness" of excipients. Viscosity. Ready to use/ reconstitution and shaking. Drug particle size. Compatibility with feed.
Formulation Preparation/ Manipulation	Dilution (if too viscous) and volume of diluent required.
EFT attributes	Length, internal and external diameter of tube (start with smallest). Number of ports, presence or absence of balloon (tube design). Tube material Geographic differences.
Studies to perform	Viscosity/dilution of suspension. Stability under specific storage conditions. Sedimentation time and uniformity. Tube studies – flush volume.

6. Conclusions

The workshop successfully enabled healthcare professional, pharmaceutical industry, and regulatory agency perspectives regarding the administration of medicines via EFT to be elucidated, and the sharing of participants' experiences on this topic. Key formulation and EFT attributes were highlighted as well as administration factors. Studies for generating sufficient EFT administration instructions were discussed.

The workshop exemplified the high number of variables that need to be considered when administering a medicine via and EFT and illustrated potential differences in the opinions and needs of different stakeholders. Collaboration between these groups may help refine EFT administration practices.

7. Disclaimer

The views expressed in this article either represent opinions of workshop participants or they are the personal views of the authors. All views expressed in this article may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or FDA.

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Declaration of Competing Interest

The authors declare that they have no known competing financial

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Data availability

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

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