Development of Oral Liquid Products for Neonatal Patients

Quotient Sciences
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INTRODUCTION

The objective of the development programme was to design an age-appropriate multi-dose liquid product suitable for the neonate population (up to 28 days old). The API-salt is an odourless white crystalline powder that converts to free acid in an aqueous environment. A Quality Target Product Profile (QTPP) for the pediatric liquid is detailed in Table 1.

Table 1: QTPP for Pediatric Oral Liquid

Quality Attribute	Target
Dosage form	Multi-dose oral liquid (sugar-free solution, syrup or suspension) for once daily dosing to neonatal subjects (birth to ~4 weeks old) as an anti-infective therapeutic.
Active ingredient concentration	Target 1 mg/mL - The concentration of drug in the liquid is to be optimised at a suitable level to minimize the volume the patient receives, whilst supporting accurate measurement using the dosing system by the caregiver.
Assay	Release: 90.0% - 110.0% of label claim
Shelf-life	24 months (including climatic zone IV)
Microbiological Limits	Meets pharmacopoeia acceptance criteria

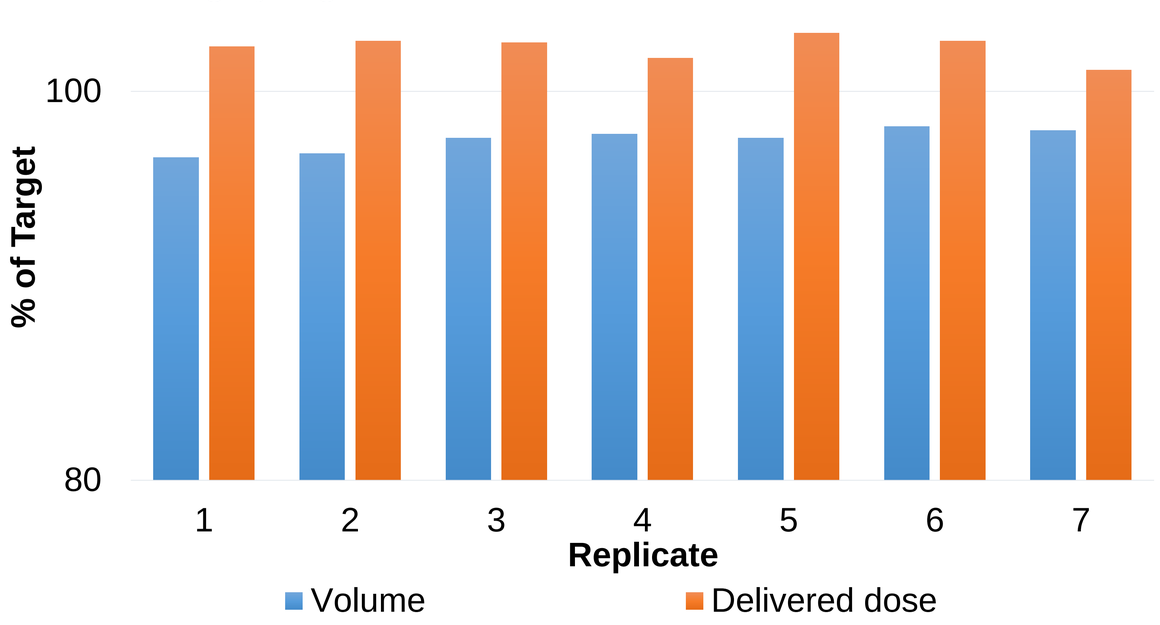
MATERIALS AND METHODS

The design of the formulation and selection of excipients took into consideration the guidance provided by the European Medicines Agency (EMA) [1],[2] for pediatric formulations. Additionally, the levels of excipients used were guided by the EC Notice to Applicants Guideline [3].

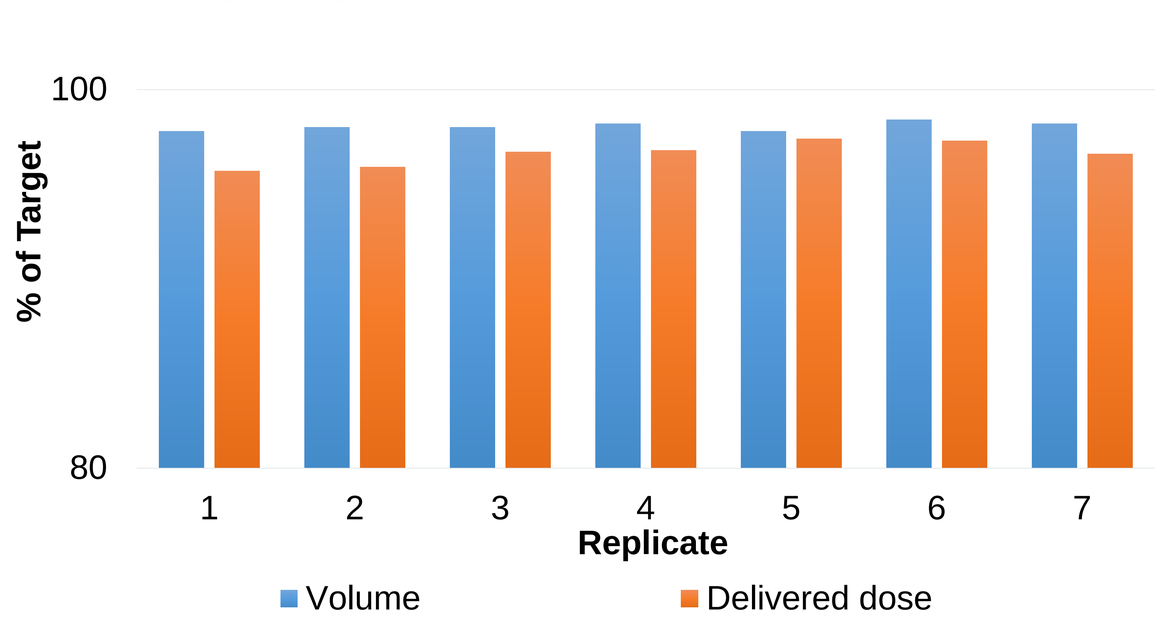
Following evaluation of alternative combinations of appropriate pH modifiers, vehicles/diluents, sugar-free sweeteners, and thickening/suspending agents, the lead formulation(s) was identified by combining material science techniques (such as X-Ray Powder Diffraction and optical microscopy) with short-term stability screening studies. To retain the salt form of the API in the liquid format, non-aqueous vehicles were selected as part of a simple two-component system. The increase in API concentration (up to 5mg/mL) enabled the reduction in the dosing volumes to deliver the target dose whilst improving the ease of administration.

Delivered dose evaluation studies were used to assess the accuracy and consistency of the administration of target dose using oral dosing syringes (see Graph 1 and Graph 2).

Graph 1 - Volumes and doses delivered using oral dosing syringes: Oral suspension formulation



Graph 2 - Volumes and doses delivered using oral dosing syringes: Oral solution formulation



RESULTS

The output of the development program resulted in two age-appropriate, non-aqueous oral liquid prototype formulations (oral suspension and oral solution) in line with the QTPP. The simplicity of the two-component systems made it possible to achieve preservative-free formulations that cater for neonate patients. The associated manufacturing processes make them suitable for scale-up using conventional processing technology.

The salt form of the API was retained and no crystal growth or particle agglomeration was observed during storage at accelerated conditions. The formulations demonstrated consistent homogeneity, content uniformity and acceptable in-use stability (measured for up to 28 days) and could be administered satisfactorily using oral dosing syringes.

CONCLUSION

There was a specific need for the development of a pediatric formulation of a novel anti-infective therapeutic medicine for very young children. Based on the knowledge of the physicochemical properties of the drug substance, consideration of regulatory guidance and the selection of appropriate excipients, it was possible to design liquid formulations that would provide flexibility of dosing to neonate patients less than 28 days old. The lead candidate formulations were then scaled-up and assessed in an adult healthy volunteer clinical study as part of the overall development program to evaluate and verify PK prior to proceeding into patient trials.

REFERENCES:
1.EMA Reflection paper: formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005)
2.EMA Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)
3.EC Notice to Applicants Guideline: Excipients in the label and package leaflet of medicinal products for human use (SANTE-2017-11668)