Pediatric Drugs—A Review of Commercially Available Oral Formulations

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Received 19 January 2007; accepted 22 May 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21101

ABSTRACT: Pediatric oral formulations can be quite scientifically challenging to develop and the prerequisites for both a measurable dosage form to administer based upon bodyweight, and also taste-masking are two of the challenges unique for pediatric oral formulations. The physicochemical and organoleptic properties of the active drug substance such as solubility, chemical stability, and taste along with the intended dose can determine which formulations are feasible to develop. Oral pediatric formulations are available in 17 different varieties and can be either a ready-to-use formulation such as a solution, syrup, suspension, tablet, scored tablet, chewable tablet, orally disintegrating tablet, or thin strip, or can also be a formulation that requires manipulation such as a powder for constitution to a suspension, tablet for constitution to a suspension, powder for constitution to a solution, drops for reconstitution to a suspension, concentrated solution for dilution, effervescent tablet, bulk oral granules, bulk oral powder, or solid in a capsule to mix with food or drink. Recently there has been an increase in pediatric formulation development inspired by increased regulatory incentives. The intent of this review is to educate the reader on the various types of formulations administered orally to pediatrics, the rationale in deciding which type of formulation to develop, the excipients used, development challenges, the in-use handling of oral pediatric formulations, and the regulatory incentives.
J Pharm Sci 97:1731–1774, 2008

Keywords: pediatric; formulation; suspensions; physical stability; oral drug delivery; excipients; chemical stability; solid dosage form; solid-state stability; regulatory science

INTRODUCTION

Recently there has been an increase in pediatric formulation development inspired by increased regulatory incentives. Pediatric formulations can be quite scientifically challenging to develop due to unique requirements and limitations. Pediatric formulations are delivered by many routes of administration including oral, rectal, nasal, buccal/sublingual, topical/transdermal, injectable, pulmonary, ocular, and ear drops. Pediatric formulations are obviously designed to be administered to infants and children, but can also be administered to adults who desire the ability to

Abbreviations: AUC, area-under-the-curve; BMS, Bristol–Myers Squibb Company; b.i.d., twice-a-day; C_{max}, maximum concentration; EDTA, ethylenediaminetetraacetic acid; EU, European Union; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; HIV, human immunovirus; HBV, hepatitis B virus; HPC, hydroxypropylcellulose; HPMC, hydroxypropyl methylcellulose (hypromellose); ODT, orally disintegrating tablet; PEG, polyethylene glycol; q.d., once-a-day; q.i.d., four times-a-day; RT, room temperature; t.i.d., three times-a-day; TPGS, d-α-tocopheryl polyethylene glycol-100 succinate; UK, United Kingdom; USA, United States of America.

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Journal of Pharmaceutical Sciences, Vol. 97, 1731–1774 (2008)

adjust their dose, for ease of swallowing, or to achieve a desired pharmacokinetic effect such as a shorter onset of action or higher maximum plasma concentration (C_{max}) compared to the conventional formulation such as a tablet.

This review focuses on commercially available oral pediatric formulations[1] and the challenges in their development. Table 1 is a listing of excipients used in commercially available pediatric oral formulations. Tables 2 and 3 are selected lists of commercially available pediatric oral formulations arranged by formulation type and then alphabetically by the drug's generic name, which is followed by the trade name. Oral pediatric formulations are available in 17 different types of formulation and can be a ready-to-use formulation (Tab. 2) such as a solution, syrup, suspension, tablet, scored tablet, chewable tablet, orally disintegrating tablet, or thin strip. An oral pediatric formulation can also require manipulation such as a powder for constitution to a suspension, tablet for constitution to a suspension, powder for constitution to a solution, drops for reconstitution to a suspension, concentrated solution for dilution, effervescent tablet, bulk oral granules, bulk oral powder, or solid in a capsule to mix with food or drink (Tab. 3). Figure 1 is a bar chart showing the occurrences, as identified in this review, of the 16 different types of prescription pediatric formulations. The intent of this review is to educate the reader as the various types of formulations administered orally to pediatrics, the rationale in deciding which type of formulation to develop, excipients used, development challenges, the in-use handling of oral pediatric formulations, and regulatory incentives.

REGULATORY INCENTIVES

In December 1994 the Center for Drug Evaluation at the Food and Drug Administration (FDA) issued the first of what are commonly referred to as "The Pediatric Rules," as a response to the observation that approximately 75% of prescription drugs in 1992 had inadequate pediatric use information. Thus the FDA began to encourage pharmaceutical companies to consider the pediatric population during two time periods: throughout a drug's development up to approval and during marketing (www.fda.gov/cder/pediatric; accessed May 21, 2007).

Since pediatric formulations may have low sales volume, the Food and Drug Administration Modernization Act of 1997 and the Best Pharmaceuticals for Children Act of 2002 added an economic incentive to industry. Specifically "The Pediatric Exclusivity Rule," also known as the "Pediatric Rule of 1998" grants the sponsor company an additional 6 months of patent life on the active moiety if a pediatric formulation is marketed or pediatric dose information is provided. However, the United States law granting pediatric exclusivity is scheduled to sunset in October of 2007. In addition, under the Pediatric Research Equity Act of 2003 the FDA can require pediatric studies of a drug submitted in a new drug application if the FDA determines the product is likely to be used in a substantial number of pediatric patients. These incentives seemed to have accomplished their intended purpose since nearly 100 medicines for sale in the United States of America (USA) have received pediatric labeling since the late 1990s, and 250 clinical studies have been conducted on 124 products as of July 2005.[2] As of May 2007 the FDA has granted pediatric exclusivity to 136 approved drugs (www.fda.gov/cder/pediatric/exgrant.htm; accessed May 21, 2007).

In Europe a legislative framework came into force January 2007 by the European Commission and was published in the Official Journal of the European Union (EU) as regulation number 1901/2006 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf; accessed May 21, 2007). The European legislation is inspired by observations that Europe has 100 million children, which is 20% of the total population, but there is a lack of suitable pediatric formulations and dosing guidelines. European hospital dispensaries commonly extemporaneously manipulate many adult drugs. The European legislation also contains the incentive of 6-month patent extension, but is more rigorous than the USA regulations in that the EU proposal also requires that the sponsor at the time of the marketing authorization application to provide data on the use in children, and also to market the pediatric formulation for the approved indication within 12 months. The EU proposal also provides incentives for off-patent medicines.

CLINICAL CHALLENGES

Clinical trials in pediatric patients are challenging due to pharmacokinetic variations with age, potentially different doses for different age groups, dose calculated based upon body-mass,