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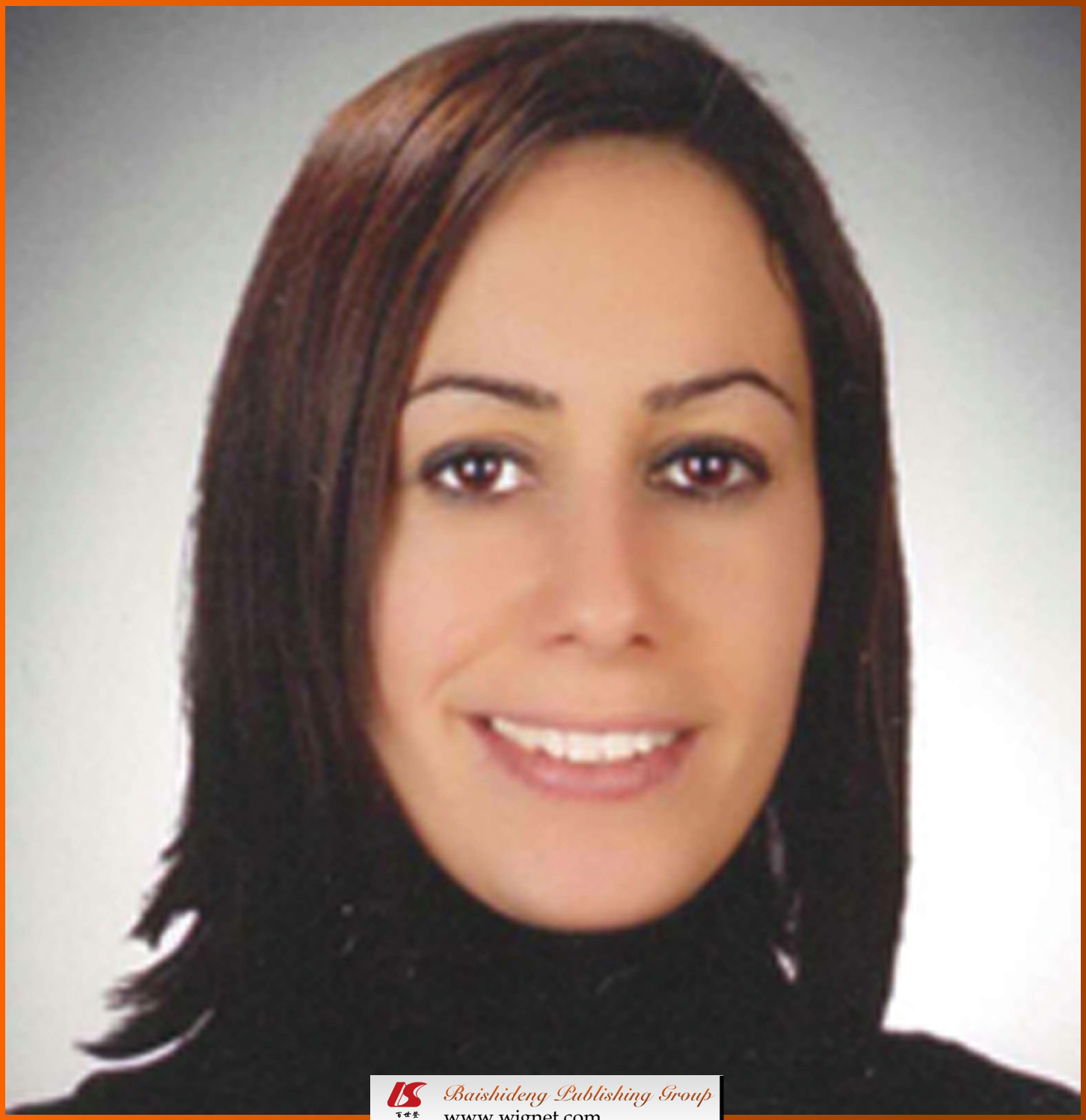

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EDITORIAL

Neonates need tailored drug formulations

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Abstract

Drugs are very strong tools used to improve outcome in neonates. Despite this fact and in contrast to tailored perfusion equipment, incubators or ventilators for neonates, we still commonly use drug formulations initially developed for adults. We would like to make the point that drug formulations given to neonates need to be tailored for this age group. Besides the obvious need to search for active compounds that take the pathophysiology of the newborn into account, this includes the dosage and formulation. The dosage or concentration should facilitate the administration of low amounts and be flexible since clearance is lower in neonates with additional extensive between-individual variability. Formulations need to be tailored for dosage variability in the low ranges and also to the clinical characteristics of neonates. A specific focus of interest during neonatal drug development therefore is a need to quantify and limit excipient exposure based on the available knowledge of their safety or toxicity. Until such tailored vials and formulations become available, compounding practices for drug formulations in neonates should be evaluated to guarantee the correct dosing, product stability and safety.

Key words: Drug formulation; Newborn; Excipient; Safety; Quality control

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INTRODUCTION

Extensive variability is the essence of neonatal clinical pharmacology. This mainly is due to both weight related differences and maturational changes, while non-maturational covariates also further contribute to this within and in between variability, including disease severity, co-morbidity or enzyme polymorphisms[1-4]. Neonates admitted to neonatal intensive care have a weight between below 500 g and up to 5000 g, already resulting in at least one log value of variability in weight between patients. The impact of maturational changes on drug absorption, distribution, metabolism and excretion (ADME, pharmacokinetics) relate to changes in body composition (*e.g.*, body water and fat content, protein binding characteristics), organ weight and also function (*e.g.*, renal maturation, hepatic maturation)[1-4]. Since these processes do not mature linearly or simultaneously, standardized dosing (*e.g.*, mg/kg) is inadequate in neonates. In addition to these anticipated developmental changes in early infancy, there are other, non-maturational contributors (*e.g.*, co-morbidities like renal failure or hepatic failure, co-medication with interactions) to this extensive between individual variability in drug dosing[1-4]. The clinical translation of this extensive variability in drug dosing needed in neonates is the obvious need for tailored drug formulations in neonates.

Obviously, "tailoring for neonates" does not mean that the general basic concepts of drug formulation should be neglected, such as including valid data on product stability, palatability and compatibility[5-10]. Neonates, and also children, are still commonly treated with medicines that have not been designed, developed or

evaluated in the relevant pediatric age groups. As a consequence, this approach puts them at risk of unpredictable or suboptimal (too low, too high or too variable) dosing and side effects from potentially toxic ingredients, including excipients[5-10].

This need for dosing variability is reflected in the use of extemporaneous formulations or drug manipulations. Both professional and non-professional caregivers are forced to split and divide adult formulations and mix them with food or a liquid in order to deliver an appropriate dose for an individual child. For intravenous formulations with "high" concentrations, this may mean that consecutive dilutions are needed[6]. All these manipulations introduce additional dosing inaccuracies. Sometimes, "extemporaneous" formulations will be provided by a pharmacist based on a medical prescription for an individual patient. Although this likely results in somewhat improved reproducibility, this is still a long way from having fully tested formulations ready for use. Moreover, practices and guidelines for extemporaneous formulations differ among different pharmacists or regions, introducing the risk of additional uncertainties or errors[5,6,11]. The need for validation of commonly applied compounding practices has been recently described, based on the evaluation of different paediatric oral formulations with a low proportion of hydrochlorothiazide, assumed to be suitable for use in neonates. Santoveña *et al*[12] observed that following the evaluation of 5 suspensions of hydrochlorothiazide (2 mg/mL) at present applied by pharmacists, only one guaranteed the correct administered dose and stability after 3 wk of storage at 5 ℃ and light protection.

To a certain extent, formulation science aims to catch up with the legislative environment for formulations and pediatric pharmacological evaluation. European legislation and similar legal initiatives in other parts of the world made companies develop pediatric formulations for new compounds coming on to the market that could potentially be used in children as part of the drug registration process. Similarly, regulatory agencies became aware that guidelines on issues, like excipients or subpopulation specific, preferred formulations having to undergo revision because of newly emerging information, conflicting opinions or unfeasible requests[13,14].

The need for an appropriate balance between dose, volume, drug manipulations and dose flexibility in neonates calls for dedicated, tailored formulations. We will first discuss issues related to dosage forms for neonates. A second focus of interest is excipients, *i.e.*, the solvents and additives, needed as co-solvents, surfactants, preservatives, colorants and/or sweeteners that are part of the formulation. During formulation development, there is an obvious need to quantify and limit excipient exposure based on the currently available knowledge on their safety or toxicity. Until such tailored formulations become available, compounding practices for drug formulations should be evaluated to guarantee correct dosing, product stability and safety.

DOSAGE FORMS TAILORED FOR USE IN NEONATES

A formulation allows an active pharmaceutical ingredient to be combined with other ingredients in a dosage form according to standardized practices, with the aim to result in predictable and safe exposure. When applied to age-appropriate dosage forms for neonates, commonly administered formulations are intravenous formulations and oral liquid (*e.g.*, drops, suspension or syrup) formulations[5,13,15]. The rectal route is only rarely used because of variability in bio-availability.

Intravenous formulations

During intravenous administration, volume overload should be avoided. However, administering very low volumes may also result in additional dose inaccuracy. These conflicting issues related to concentration need a balanced approach since serial dilutions in order to achieve the required dose should be avoided if all possible. It has repeatedly been documented that serial dilutions are prone to errors, while such errors can be avoided by providing appropriate concentrations based on a population specific dedicated formulation. Serial dilution also results in additional dose inaccuracy. The impact of a "pediatric vial" on dose inaccuracy has been quantified in neonates[16,17]. Using population pharmacokinetics in a cohort of 254 preterm neonates, the unexplained variability in amikacin clearance in neonates is in part related to the vial used. A pediatric vial (50 mg/mL, 2 mL) resulted in a relevant reduction (8%) in unexplained variability when compared to an adult vial (250 mg/mL, 2 mL)[17].

Nunn *et al*[16] reported on the clinical practice to manipulate medicines to provide accurate doses, including in neonates. Over a 5-d period, 5375 drug administration events were recorded in neonatal and pediatric patients in one regional children's hospital. Despite this specific regional children's hospital setting, 10% of the prescriptions were judged to require manipulation or needed a small volume (< 0.2 mL). Measured doses below 0.1 mL (oral or intravenous) accounted for 25% of the manipulations, most commonly (60%) in the neonatal intensive care unit[16]. To further illustrate the practice and the need for sequential dilutions, reference doses (mg or mg/kg) in preterm and a term neonate (1.5 and 3 kg) were compared to intravenous formulations available on the Belgian market (Table 1).

Formulations suited for the enteral route

Enteral administration can be achieved by different types of formulations. Because of the specific characteristics of neonates (*e.g.*, inability to swallow solid unit dosage formulations) and the need for dose flexibility, oral liquid formulations (*e.g.*, syrup, drops, suspension) are preferred in neonates and young infants[5,13,15]. Specific aspects of relevance in (pre)term neonates that remain commonly underexplored are the potential interactions with (human) milk and issues related to the use of feeding tubes (*e.g.*,

Table 1 Reference doses (mg/kg) compared to intravenous formulations to illustrate the need for sequential dilutions in neonates

Active agent	Available concentration	Reference doses	Preterm, 1.5 kg	Term, 3 kg
Amikacin, adult vial	500 mg/2 mL	15-20 mg/kg	130 mg, 0.12 mL	50 mg, 0.2 mL
Amikacin, pediatric vial	100 mg/2 mL	15-20 mg/kg	30 mg, 0.6 mL	50 mg, 1.0 mL
Enoxaparin	40 mg/0.4 mL	1 mg/kg	11.5 mg, 0.015 mL	13 mg, 0.03 mL
Erythromycin	1000 mg/20 mL	5-10 mg/kg	12 mg, 0.24 mL	25 mg, 0.5 mL
Fentany[1]	100 μg/2 mL	1-3 μg/kg	13 μg, 0.06 mL	16 μg, 0.12 mL
Insulin	300 U/3 mL	0.1-1 U/kg per hour	10.3 U, 0.03 mL	10.6 U, 0.06 mL
Midazolam	15 mg/3 mL	0.1 mg/kg	10.15 mg, 0.03 mL	10.3 mg, 0.06 mL
Paracetamol	500 mg/50 mL	10 mg/kg	15 mg, 1.5 mL	30 mg, 3 mL
Phenobarbital	200 mg/1 mL	5 mg/kg	17.5 mg, 0.0375 mL	115 mg, 0.075 mL
Propofol	200 mg/20 mL	1-3 mg/kg	2 mg, 0.2 mL	4.5 mg, 0.45 mL
Ranitidine	50 mg/2 mL	0.5-1 mg/kg	11.5 mg, 0.06 mL	13 mg, 0.12 mL

Formulations were sorted alphabetically and reported as available in Belgium, not necessary reflecting the setting in another country. A dose in a 1.5 and 3 kg newborn has been used for illustrative purposes. [1]Initial volumes ≤ 0.2 mL.

particle size, viscosity, volume, osmolarity, compatibility with the plastic of the feeding tube)[5,13,15].

EXCIPIENTS IN NEONATAL FORMULATIONS: NEVER PRESCRIBED, COMMONLY ADMINISTERED

Excipients are commonly added to a drug formulation, *e.g.*, to ensure stability over a given shelf life, to improve palatability or to facilitate solubility or to bulk up formulations that otherwise contain highly potent active ingredients, and are referred to as preservatives, sweeteners, fillers and solvents, coating materials or coloring agents[18-20]. Examples of excipients are lactose, aspartame, ethanol, propylene glycol, benzyl alcohol, sorbitol, xylitol, mannitol and poly-ethylene glycol. Some of these excipients cause specific harms in specific, rare diseases. Examples include lactose in the setting of lactase-deficiency, aspartame in patients suffering from phenylketonuria or fructose containing formulations in the setting of fructose intolerance. More recently, the concept of "functionality" has been introduced by adding excipients to enhance product performance[18-20]. Illustrations of such a "functionality" approach or relevance in early neonatal life are liposomal amphotericin, to reduce exposure of renal tubular cell and the subsequent toxicity, or the use of an oil-in-water emulsion as an adjuvant to improve the efficacy of influenza vaccines in infants.

Although medicines are formulated with excipients that are Generally Regarded As Safe ("GRAS" status), such a "GRAS" status does not consider the population specific aspects and neither are such claims based on well-validated prospective studies in neonates. History provides us with different case observations on the deleterious effects of excipient exposure in neonates. Excipients can be harmful to neonates, since benzyl alcohol, propylene glycol and polysorbate 80 co-administration resulted in different toxicological syndromes in neonates[21-24].

Fatal benzyl alcohol related poisoning has been described following co-administration of this compound as a bacteriostatic with normal saline in preterm neonates[21,22]. Following at least a minimal exposure to 130 mg/kg per day of benzyl alcohol, neonates developed metabolic acidosis and a raised anion gap from the second day of exposure onwards. This was followed by progressive bradycardia, gasping and clinical seizures[21]. Similarly, toxicity to propylene glycol has also been reported following exposure of up to 3000 mg/d for at least 5 consecutive days[22,23]. Such a significant exposure was due to high concentrations of propylene glycol as a co-solvent in parenteral nutrition solutions. The toxicity was both biochemical (*e.g.*, hyperosmolarity, lactic acidosis, plasma creatinine, bilirubin) and clinical (seizures). Finally, E-ferol containing high concentrations of vitamin E and high concentrations of Polysorbate 80 resulted in another clinical syndrome and was reported shortly after its introduction[24].

Unfortunately, the side effects of excipients still do not receive sufficient consideration in contemporary neonatal pharmaceutical care and are not just historical events. To illustrate this, the United States Food and Drug Administration notified healthcare professionals in March 2011 of serious health problems that had been reported in premature babies treated with Kaletra (lopinavir/ritonavir) oral solution. This oral solution contains relevant amounts of ethanol and propylene glycol and a link was made between these excipients and the toxicity observed[23]. Moreover, recent observations on contemporary exposure to potential toxic excipients (*e.g.*, propylene glycol, ethanol, benzyl alcohol) have confirmed the almost uniform exposure to such excipients in the United Kingdom and Estonian cohorts of neonates admitted in neonatal intensive care units[25,26]. In our opinion, collaborative research projects on excipients are urgently needed and some initiatives are already ongoing. In addition to improving knowledge on the clinical pharmacology of active compounds, there is a similar need to optimize the knowledge on clinical pharmacology of excipients in neonates[14]. Illustrations of such initiatives are the Safety and Toxicity of Excipients for Pediatrics (STEP) database and the European Study of Neonatal Excipient Exposure (ESNEE) research initiative[27,28].

The STEP database aims to improve the availability and access to published information on excipients, including information on excipient toxicity and tolerance in neonates[27]. The ESNEE research initiative aims to develop a platform for the systematic assessment of excipients in neonates[28]. The first step of this program is to establish which excipients are in use and how much of each excipient is included in medicines given to neonates. The second step of the ESNEE program is to determine what is known about the effects of excipients in neonates and juvenile animals. The third step of the program is to measure systemic concentrations of key excipients in neonates using dry blood spots and plasma samples. The final step is to integrate the work into a systematic assessment of safety for each excipient. A generic framework for the assessment of excipient safety in neonates will be developed, with the aim to illustrate how this can be applied by prescribers, pharmacists, manufacturers and regulators. Based on the Leuven propylene glycol research project, we recently illustrated that such studies are indeed feasible and of clinical relevance[23].

NEONATES ARE IN NEED OF TAILORED DRUG DEVELOPMENT

Although the principles of drug disposition also apply in neonates, their specific characteristics warrant focussed assessment. As a consequence, tailored drug development for neonates and clinical research should therefore focus on both new and already existing compounds. Adequate prescription involves assurance that the drug administered is of sufficient pharmaceutical quality, that an appropriate formulation is used, and that there is sufficient knowledge on pharmacokinetics/dynamics and safety of compounds administered.

We aimed to stress that tailored, personalized clinical pharmacology for neonates also needs to consider to neonatal formulations[5,10,11,13]. We paid particular attention to excipients with different case series on toxicity[21-24]. Further progress can be made in collaborative efforts between industry, caregivers, academia and regulatory agencies[27,28]. These efforts need to focus on product availability (tailored formulations), integration and dissemination of currently available information about existing age-appropriate formulations, an evidence-based approach to risk assessment of excipients, and the validation of procedures and practices on compounding with dissemination of validated procedures[6,15,18].

A roadmap to further improve the current setting includes: (1) a more appropriate balance between dose, volume and drug manipulations; (2) the quantification and limitation of excipient exposure; (3) focussed studies on the clinical pharmacology of excipients in neonates; and (4) the validation of compounding practices for drug formulations in neonates.

We should be aware that drugs are very strong tools used to improve outcome in neonates. In contrast to tailored perfusion equipment, incubators or ventilators for neonates, we still commonly use drug formulations initially developed for adults. At the least, there is still a lot of potential for further product improvement in neonatal drug development and formulation related issues should be part of such a product improvement approach.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2219-2808/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

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