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# Better medicines for neonates: Improving medicine development, testing, and prescribing

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ABSTRACT

Pharmacotherapy is a powerful tool to improve the outcome of neonates. Unfortunately, the potential health impact of pharmacotherapy in neonates remains underexplored. This necessitates a structured approach to go beyond the current practice of trial and error, reflected in off-label prescription. The existing regulatory framework hereby provides a structure to reflect about aspects like pharmacokinetic models for dose selection and outcome assessment, including long-term safety. Future medicine development should also be driven by neonatal needs, diseases and pathophysiology, since surfactant is the latest product developed for preterm neonates. The potential impact is illustrated by ongoing repurposing (propranolol, allopurinol, erythropoietin, Insulin-like Growth Factor-1) projects.

Clinical researchers will be crucial to close the knowledge gap by developing dose selection tools and outcome assessment tools and by exploring pathophysiological mechanisms. The final step of such a structured approach cycle is the subsequent translation of accumulated knowledge into improved prescribing.

## 1. Pharmacotherapy in the newborn: how to get beyond trial and error?

When health care professionals administer a medicine to a newborn, it is with the intention to provide effective relief for a given indication (e.g. infection, retinopathy of prematurity, pain), while still avoiding disproportional side-effects. Clinical pharmacology aims to predict the effects of such interventions, applying pharmacokinetics (PK) and pharmacodynamics (PD) as mathematical concepts to generate predictions, including confidence intervals. PK (ADME, ***a***bsorption, ***d***istribution and elimination, through either ***m***etabolism or renal ***e***limination) estimates the relationship between a concentration at a specific site (e.g. cerebrospinal fluid, blood compartment) with time ('*what the body does to the medicine*'). PD aims to estimate both the effects and side-effects of a given medicine in relation to a given concentration ('*what the medicine does to the body*') [1,2]. Because of the fast maturational changes in neonatal life with age (postnatal, postmenstrual) and weight (birth weight, current weight) as main drivers (covariates) of this maturation, PK and subsequent PD display extensive between and within-individual variability [1,2].

The physiology-related maturation in ADME processes is reflected in changes in body composition, protein binding and subsequent compartment size changes. All phase I (e.g. cytochromes) and phase II (e.g. glucuronidation) metabolic processes of medicines mature in an enzyme specific pattern, while renal function [glomerular filtration rate (GFR), tubular absorption/excretion] also display age-dependent clearance [3]. Age-dependent PD differences are much less explored, but also relate to age and population-specific effects (e.g. caffeine to treat neonatal apnoea, oxygen and retinopathy of prematurity, cerebral palsy related to postnatal steroids) [3]. Consequently, dosing of medicines in young infants should be based on integrated knowledge concerning the specific diseases to be treated, the physiological characteristics of the newborn receiving the medicine, and the PK-PD parameters of the medicine. This makes clinical research on pharmacotherapy in neonates relevant, but also more difficult to perform [1,2,3].

Unfortunately, the potential health impact of neonatal pharmacotherapy remains underexplored. It is still very common practice to administer medicines outside their market authorization (indication in this population, off-label). Unlicensed prescription refers to the use of an approved medicine in an unapproved formulation. The most recent (2015) meta-analysis on unlicensed and off-label medicine prescription practices reconfirmed that this practice is still widespread in pediatrics, and that the youngest age category, i.e. (pre)term neonates are exposed

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**Table 1**
Number of studies and proportion of clinical studies as retrieved on www.clinicaltrials.gov (30 July 2017), using either no specific search criteria (all studies) or retrieved when 'child', 'infant' or 'newborn' were entered.

| | All studies | 'child' | 'infant' | 'newborn' |
|---|---|---|---|---|
| Worldwide | 250,710 | 55,942 (23%) | 8603 (3%) | 5451 (2%) |
| United States | 103,757 (41%) | 23,664 (42%) | 3592 (42%) | 2038 (38%) |
| Europe | 70,579 (28%) | 12,145 (22%) | 2026 (25%) | 1541 (28%) |
| Canada | 17,142 (8%) | 4180 (7%) | 784 (9%) | 409 (8%) |
| Pacific | 6216 (2.5%) | 1236 (2%) | 291 (3%) | 102 (2%) |
| South America | 8314 (3%) | 1884 (3.5%) | 263 (3%) | 167 (3%) |

most commonly (100%) to unlicensed or off-label medicines [4]. Although off-label is not always equal to off-knowledge, this practice does result in the fact that health care professionals commonly lack the availability or access to crucial information to make the best possible, informed decision and to discuss options with parents: *do we accept to continue to use this trial and error approach*? It is not because we have been using a medicine for even decades that we know enough about the medicine and how to use a given medicine effectively and safe. Oxygen or postnatal steroids may hereby serve as relevant illustrations to neonatologists. Finally, off-label practices are only one side of the coin, as this also reflects the fact that the potential health impact of neonatal pharmacotherapy remains underexplored [5].

There is a legal framework and ongoing initiatives to generate knowledge on neonatal pharmacotherapy to improve this setting. To quantify and put these activities into perspective, studies in infants and in newborns cover 3 and 2% of all registered studies respectively, with a similar spread throughout different regions (Table 1). Unfortunately, 42% of pediatric studies ($n$ = 44, 2007–2014, submitted to the Food and Drug Administration (FDA) failed to document efficacy ($n$ = 39, 86%) or safety ($n$ = 7, 16%) due to inaccurate dosing ($n$ = 10) or failure to sufficiently consider the differences in the pediatric vs adult disease ($n$ = 8) [6]. Neonatal pharmacotherapy is lagging even further behind when compared to other pediatric populations [7]. Stiers and Ward recently reported that only a limited number of label changes (24/406, 6%) included labelling changes for neonates (1997–2010, FDA), claiming that newborns were one of the last therapeutic orphans to be adopted. This seems to relate to inaccurate dose selection and insufficient assessment of neonatal pathophysiology. As additional weaknesses, the majority of studies were single center studies (58%), and industry was sponsor in a limited number (23%) of the registered trials [8]. Additionally, the traditional control trial design, especially for the extremely preterm neonates is often perceived not to be feasible [9]. However, in a recent analysis on studies in neonates registered within the clinicaltrials.gov application, Desselas et al. concluded that placebo versus drug randomized controlled trials (RCT) represent 34 (146/423)% of the registered neonatal trials with steroids, erythropoietin and nitric oxide as the most commonly evaluated medicines [10].

The existing regulatory framework hereby provides a structure to reflect about aspects like PK models for dose selection and outcome assessment, including long-term safety. Future medicine development should also be driven by neonatal needs, diseases and pathophysiology, since surfactant is the latest product developed for preterm neonates. The potential impact is illustrated by ongoing repurposing (propranolol, Insulin-like Growth Factor-1, allopurinol) projects [1,12,13]. Contributions of health care professionals active in neonatal care will be crucial to enable the best use of the regulatory framework, to generate the knowledge needed to develop dose selection tools and outcome assessment tools and to explore pathophysiological mechanisms. The same health care professionals will also be crucial to enable the final step of such a structured approach cycle: the subsequent translation of the accumulated knowledge into improved prescribing.

## 2. Current regulatory framework for medicine development program applied to neonates

Both the FDA and European Medicines Agency (EMA) have converted pediatric legislation to initiatives to optimize medicine evaluation in pediatric populations with the intention to result in label changes, including in neonates as recently discussed in this journal [5,14]. Such efforts should be based on the neonatal study decision tree [Fig. 1] as applied by these authorities to assess neonatal medicine development plans [15]. Such a medicine development plan can be defined as the aggregate of individual studies conducted in the course of the product development cycle, and can include studies on efficacy, safety, PK or PD, and tolerability [6].

As mentioned earlier, diseases may be specific to neonates, the impact of immaturity and rapid developmental changes in early life is important, and medicines may have short and long-term effects including developmental toxicity. Consequently, a neonatal study decision tree is useful to reflect about potential scenarios. *Scenario 1* is appropriate when extrapolation of the exposure-response is possible and the dose-exposure (PK) is to be documented (e.g. antibiotics for sepsis, antifungals), including safety. *Scenario 2 or 3* are appropriate

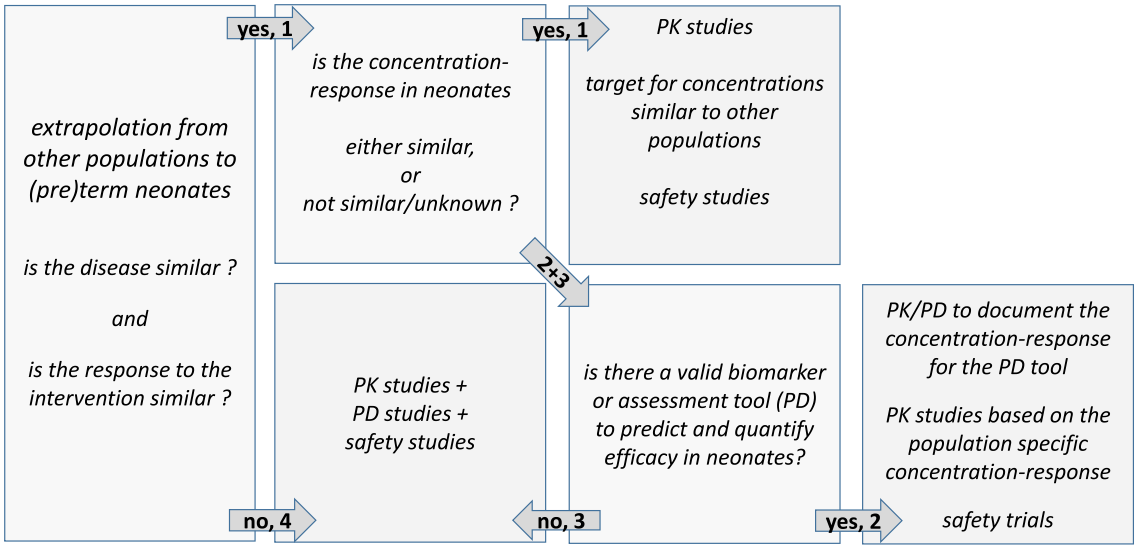


**Fig. 1.** Pediatric medicine study decision tree as applied by the authorities to assess neonatal medicine development plans, adapted from Pons and Manolis [15].