

# Beyond Child-Resistant Packaging for Drugs: F Value Determination for Added Child Safety

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## Background

According to the World Health Organization (WHO), acute poisoning is the third leading cause of unintentional deaths in children up to the age of 14 years. WHO estimates that each year, these episodes of acute poisoning are fatal in approximately 3,000 children and that 90% of those poisonings take place in the home.<sup>1</sup>

According to the 2016 annual report of the American Association of Poison Control Centers' National Poison Data System, the top 5 substance classes most frequently involved in all human exposures are analgesics (11.2%), household cleaning substances (7.54%), cosmetics/personal care products (7.20%), sedatives/hypnotics/antipsychotics (5.84%), and antidepressants (4.74%). The top 5 most common exposures in children 5 years of age or younger are cosmetics/personal care products (13.3%), household cleaning substances (11.1%), analgesics (9.21%), foreign bodies/toys/miscellaneous (6.48%), and topical preparations (5.07%). The overall rate of poison exposures is 660/100,000 population, with the highest rates in children of ages 1 year (8,083/100,000 population) and 2 years (7,675/100,000 population).<sup>2</sup>

Various regulatory requirements exist to prevent unintentional drug poisoning in children. The United States Food and Drug Administration (US FDA)'s Consumer Product Safety Commission's special packaging standards, also known as child-resistant packaging (CRP) standards, are applicable for most oral prescription drugs, many nonprescription drugs, and various household products. Under the Poison Prevention Packaging Act (PPPA), one of the best-documented successes in preventing unintentional poisoning in children,<sup>1</sup> any package (including blisters or pouches) containing a substance regulated under the PPPA must meet CRP standards. Otherwise, the product could be misbranded or recalled and the marketing authorization holder penalized.<sup>3</sup> The US FDA also recommends including a labeling

statement declaring the compliance of the product to the CRP standards.<sup>3</sup> Since the PPPA has been in effect, reported deaths of children from ingestion of toxic household products, including medications, have declined remarkably.<sup>4</sup> The International Organization for Standardization also published an internationally agreed standard test procedure for reclosable CRP.<sup>5</sup> In Europe, several regulatory requirements have been introduced that complement the International Organization for Standardization's standard.<sup>6,7</sup>

## What Is the F Value?

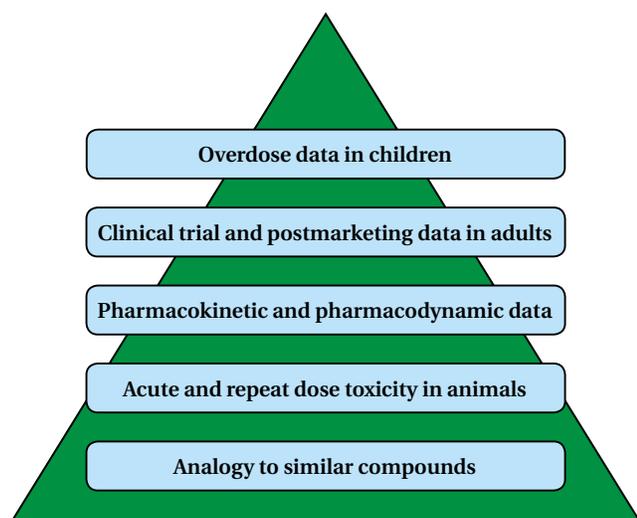
For products requiring CRP, there is also a regulatory requirement to calculate the product's F value ("failure value").<sup>8</sup> For unit dose packages, the F value is defined as the number of individual dose units of a drug that can cause serious illness or injury in a 25-lb (11.4-kg) child. Failure occurs when a 25-lb child can gain access to this number of tablets or capsules in 10 minutes. For example, if a substance will breach this toxicity threshold after exposure to 3 units, the substance is assigned an F value of 3. For highly toxic or harmful products, the F value is usually set at 1 ( $F = 1$ ), which indicates that a child's access to even a single unit is considered a failure. For less toxic or harmful products, the F value may be higher. A default limit of "greater than 8" is usually adopted in the US. Unless a lower failure limit is declared, a failure occurs when a child gains access to a ninth unit.

The F value is used to guide the design of product packaging and in the tests to evaluate safety. Products with a lower F value require reinforced (better) CRP, such as a strip pack, a blister pack, or a container with a child-resistant closure system, which are designed or constructed to be significantly difficult to open for most children younger than 5 years.

### Determining the F Value

Although guidance is available on the conduct and reporting of packaging tests, guidance is scarce on specific methods for determining the F value. Each manufacturer needs to conduct risk assessments and decide what constitutes “serious personal injury or serious illness” for their products. Acute and chronic animal toxicology data, adult clinical dose response data scaled to children, and postmarket surveillance reports of acute overdose in children are generally evaluated for this purpose. A single method for determining the F value cannot be applied to all drugs.

A weight-of-evidence approach is usually applied for calculating the F value<sup>9</sup> (Figure 1). Data on overdose in children, if available, are given the highest priority, followed by data on overdose and adverse events (AEs) in adults. As the F value is defined for children with a body weight no greater than 25 lb, a body weight scaling method is usually used in the calculation of this value. When pediatric or adult overdose data are scarce or unavailable, the maximum tolerated dose (MTD)—the largest dose of a drug a patient can take without unacceptable AEs—in adults or even preclinical data can be used. When none of the above evidence is available, overdose data about a similar compound can be used to calculate the F value. When determining the F value of a combination product, the F value for each drug is calculated and the lower value is assigned to the combination.



**Figure 1.** Recommended weight-of-evidence approach to calculate the F value.

### Challenges in Determining the F Value

Many oral drugs are not approved for use in pediatric patients; therefore, direct clinical dose response or pharmacokinetic (PK) data for a 25-lb child may not be available. In this case, the MTD in adults is usually used as a basis for calculating the F value. In the absence of pediatric data, a provisional F value

can be assigned to a product (with assumption that the nature of toxicity is similar in adults and children) until pediatric data are available. Below are some examples of our company’s experiences using various approaches to determine the F values for oral drugs.

#### *Bupropion XL*

The safety and efficacy of bupropion XL (extended-release antidepressant drug) tablets in the pediatric population have not been established. Although the MTD of bupropion for adults has not been established, bupropion overdose, with symptoms of neurologic, cardiovascular, and gastrointestinal signs,<sup>10</sup> has been reported in adults who have ingested up to 30 g of the product.

In a case report, an 11-month-old infant boy (weighing 12 kg) ingested 30 tablets of 300 mg bupropion SR (sustained release), resulting in a dose of 750 mg/kg. He developed generalized tonic-clonic seizures, dilated pupils, tachycardia, and severe hypotension with metabolic acidosis and became comatose (Glasgow Coma Scale score 7). He received mechanical ventilation, inotropic support, and extracorporeal membrane oxygenation along with other overdose management therapies. The infant was extubated on day 8 and discharged 2 weeks after extubation. Neurologic sequelae were not observed at the 12-month follow-up.<sup>11</sup>

In another case, a 7-year-old boy (weighing 21.8 kg) ingested 7 tablets of 150 mg bupropion XL (1,050 mg). He experienced vomiting, hallucinations, tachycardia, and a tonic-clonic seizure. He recovered and was discharged after 48 hours without any sequelae.<sup>12</sup> A dose of 1,050 mg in a 21.8-kg child would be equivalent to 48.17 mg/kg.

Using the body weight scaling approach, the corresponding dosage in an 11.4-kg child that could cause AEs would be approximately 549.08 mg. Based on these historical data, the F value assigned to bupropion XL 150 mg tablets is 3 and to bupropion XL 300-mg tablets is 1.

#### *Pyrimethamine*

Pyrimethamine is an antiparasitic that has a good safety and tolerability profile. Adverse events observed with pyrimethamine, including anorexia, vomiting, atrophic glossitis, hematuria, megaloblastic anemia, leukopenia, agranulocytosis, thrombocytopenia, and cardiac rhythm disorders,<sup>13</sup> are primarily due to central nervous system toxicity in acute overdose and due to folate depletion in chronic overdose. The lowest reported fatal dose of pyrimethamine is 375 mg; however, there have been case reports of pediatric patients recovering after an overdose of up to 625 mg.<sup>14</sup>

Several case reports have been published on pyrimethamine overdose in children. A 23-month-old infant girl

ingested eight 25-mg tablets of pyrimethamine (200 mg) and experienced vomiting, irritability, jerky movements of limbs, opisthotonus, and ataxia for 2 hours, but she recovered spontaneously without any interventions.<sup>15</sup>

Because the average weight of a 23-month-old infant is 11.27 kg according to the 2006 WHO child growth standards,<sup>16</sup> 200 mg is equivalent to 17.74 mg/kg. Using the body weight scaling approach, the corresponding dosage in an 11.4-kg child would be approximately 202.3 mg. Therefore, the recommended F value for pyrimethamine 25-mg tablets is 8.

### Documentation

Any package of drugs regulated under the PPPA must mention the F value of the packaged substance. Evidence-based justification and calculation of the F value is described in a report (Figure 2), which requires submission to the US Consumer Product Safety Commission. The F value report titled “F Value Calculation and Justification” is intended to provide a critical analysis of the available clinical and preclinical information about the drug, along with the conclusions and implications of the information. Literature pertaining to preclinical and clinical information is identified through a targeted literature search on databases such as PubMed and Embase. Additional relevant data are also included from databases such as Poisindex and overdose case reports.

The rationale for calculating the F value based on weight of evidence is then developed and added to the F value report. If pediatric data are not available, a temporary F value is calculated on the basis of adult data and assigned to the molecule until pediatric data become available.

The F value report should also be a useful reference to the clinical safety information, especially pediatric overdose case reports, for regulatory authorities. The F value report is a

succinct report of the prescribing information, AEs, overdose information, and the implications of these data for child safety. For a single product, the document is typically 30 pages long; for combination products, it could be longer. When exhaustive information about the molecule is available, tables may be used for brevity.

The F value report includes the following sections and subsections.

- Introduction and background
  - Physiochemical properties and pharmacologic class of the drug
  - Mechanism of action, such as receptor binding; onset and/or offset of action
  - Clinical indications
  - Approved dosage, formulation, and administration
- Animal toxicology
  - An overview of the pharmacologic, PK, and toxicologic evaluation of the product in animals such as rats, mice, rabbits, guinea pigs, hamsters, dogs, and monkeys
  - The onset, severity, and duration of the toxic effects; their dose-dependency and degree of reversibility; and species- or gender-related differences
  - The effect of the drug observed in nonclinical studies in relation to that expected or observed in humans
  - The MTD and no observed adverse effect level, whenever available
- Effects in humans
  - Brief overview of the PK and pharmacodynamics (PD) data:
    - PK data include comparative PK in healthy individuals, patients, and special populations; extent of absorption; distribution, including binding with plasma proteins; excretion; time-dependent changes in PK.

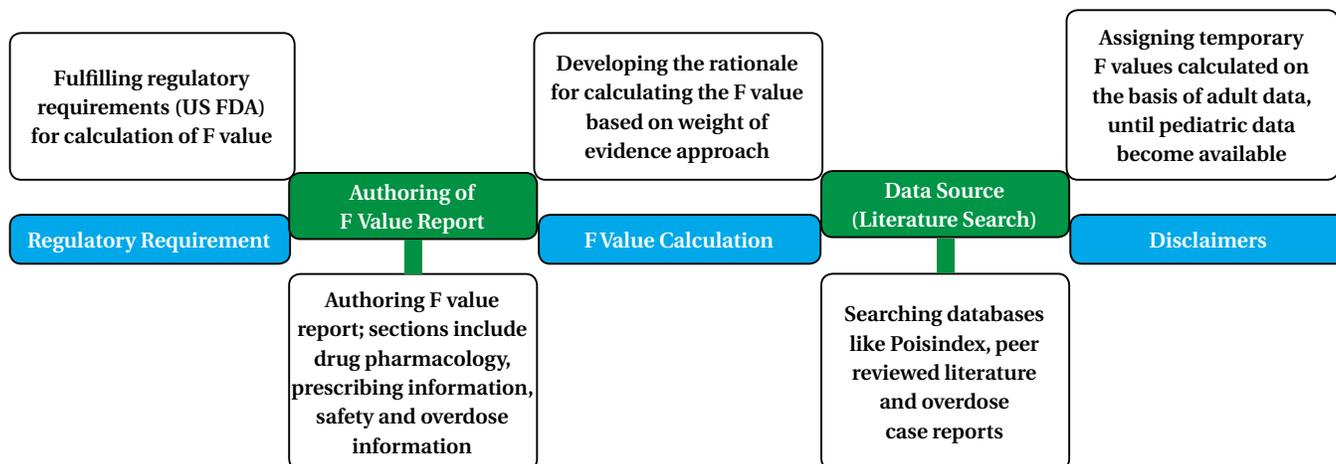


Figure 2. Process flow for authoring of the F value report.

PD data include information on the mechanism of action and the relationship of favorable and unfavorable PD effects to dose or plasma concentration (ie, PK/PD relationships).

- Adverse events reported during clinical trials and post-marketing studies:

Nature, absolute number, and frequency of common, nonserious, and serious AEs, including deaths, and other events leading to discontinuation or dose modification are to be included in this subsection. This information is generally included from the prescribing information of the molecule substantiated by published literature.

- Case reports of overdose in adults and children:

The age, weight, and health status of the patient; dose of the ingested product; and the nature, severity, and frequency of the observed AEs should be discussed in this section. Any conclusions regarding a causal relationship (or lack thereof) to the product and laboratory findings should be mentioned. The potential for dependence, rebound phenomena, and abuse should be discussed. Management and outcome of overdose cases should be included.

- Rationale for F value calculation
  - Interpretation of the data and evidence (the case report or the MTD) used as the basis for calculating the F value is included here.
  - A justification for using the chosen case report followed by the calculation of an appropriate F value is discussed in this section.
- Conclusion
  - The conclusion mentions the F values assigned for the various strengths of the drug.

## Conclusion

Despite the regulations and standards for CRP, guidelines on determining the F value of oral pharmaceutical products are unavailable. This article discusses how our company has implemented best practices to determine F values amid various challenges, especially lack of pediatric data. Further scientific discussion is necessary to critically evaluate the various approaches used. Furthermore, the use of data and the required documentation processes should be standardized to effectively fulfill this important regulatory obligation.

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