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LETTER TO THE EDITORS

In reply to: Knowledge of developmental pharmacology and modeling approaches should be used to avoid useless trials in children

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We agree with de Wildt et al. on the need to take children's developmental changes into consideration when assessing the clinical evidence in order to waive additional studies.

In reviewing the available evidence on the use of proton pump inhibitors (PPIs) in the treatment of gastroesophageal reflux disease (GERD) in children, we focused on the age ranges for which no labeled indication was approved in the EU [1]. For example, in the case of omeprazole (authorized for the treatment of GERD in Europe for children ≥ 2 years), we searched for scientific literature based on children younger than 2 years. We found four trials entirely dedicated to children aged 0–2 years. The remaining two trials, although not strictly dedicated to that target population, also enrolled children between 0 and 2 years.

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Our review intended to deal with the general issue of off-label use of drugs in the pediatric population, to verify whether drugs not formally approved for use in a specific population may nonetheless present sufficient evidence supporting their (off-label) use. If the 0- to 2-year range is still considered too large to take into account the impact of developmental changes on a drug risk/benefit profile, further studies focusing on more specific age groups are clearly needed. Prior biological knowledge, or new data, are critical factors in deciding whether the available evidence is insufficient to guide clinical practice in a specific population sub-group.

However, we should also use a pragmatic and prioritizing approach, considering that requiring separate trials for each patient sub-group—in pediatrics as well as in other populations—may not be always feasible. For instance, in the case of the elderly, the combination of different age strata, co-morbidities, and concomitant use of different drugs may create an enormous number of potential different groups. The issue of how to generalize data deriving from a specific population to a wider population is inevitably to be considered on a case-by-case basis. Mathematical modeling may provide a contribution though, again, the applicability of existing evidence to different patient groups will continue to carry various degrees of uncertainty.

With regards to who should assess the use of off-label medicines in children, we agree on the importance of regulatory agencies in reviewing the available evidence to support clinical practice and to identify research priorities (a "to do" list). In the effort to deal with this issue, different strategies and approaches have been used at the regulatory level. In Europe, the EMEA Paediatric Committee has identified the needs in different therapeutic areas where there should be research and development of medicinal products for children [2]. In the U.S., the FDA has recently

released specific guidelines allowing drug manufacturers to distribute reprints of articles from medical journals that describe unapproved uses of their products, a practical attitude that can be of help in regulating evidence-based off-label drug use [3].

Competing interests The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the Italian Medicines Agency or the Medicines Evaluation Board.

References

1. Tafuri G, Trotta F, Leufkens HG, Martini N, Sagliocca L, Traversa G (2009) Off-label use of medicines in children: can available evidence avoid useless paediatric trials? The case of proton pump inhibitors for the treatment of gastroesophageal reflux disease. Eur J Clin Pharmacol 65(2):209–216
2. EMEA (2007) Assessment of the paediatric needs—gastroenterology. EMEA/527934/2007. EMEA, London
3. Mello MM, Studdert DM, Brennan TA (2009) Shifting terrain in the regulation of off-label promotion of pharmaceuticals. N Engl J Med 360:1557–1566