# Paediatric Microdosing

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For Discussion by the Members of the EAP Ethics Working Group

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## Introduction

Microdosing presents an alternative to traditional pharmacokinetic studies that require the use of a therapeutic dose in order to accurately measure metabolites. Both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) define a microdose as one-hundredth of the No Observed Adverse Effect Level (NOAEL) or predicted pharmacologic dose based on animal data or as 100 μg of the investigational drug, whichever dose is lower.[i] Dose linearity between the microdose and therapeutic dose is a prerequisite to extrapolate pharmacokinetic data to dosing guidelines. The extremely low dose concentrations call for highly sensitive measurements. Through the use of accelerator mass spectrometry (AMS), low attomolar to zeptomolar isotope ratio ranges can be measured such to allow for the quantification of $^{14}$C-labeled drug or metabolite concentrations in urine or plasma samples, even after at least five half-lives following a microdose. At the same time, the use of a $^{14}$C-labelled microdose presents fewer risks to the subject: the very low sub-therapeutic dose does not threaten a significant toxicological response. The addition of a a $^{14}$C-label to the formulation brings only a very low (insignificant) radiation exposure, that is, less than 10 μSv in adults, when compared with the yearly background exposure of 2.5 mSv/year in, for example, The Netherlands.[iiiii]

## The Added-value of Microdosing in Drug Discovery

Early on in the development of a drug (an 'investigational medicinal product'), it is important to characterize the molecule's toxicological and pharmacological properties:

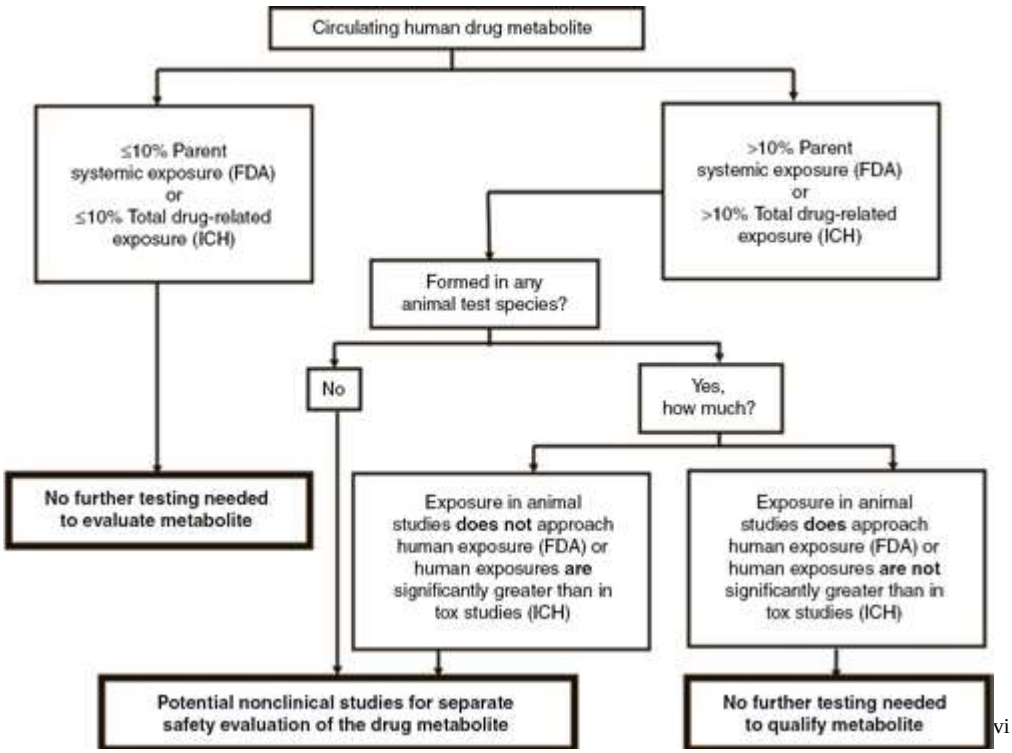
> Before any clinical trial is carried out, results of non-clinical investigations or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans. . . . Throughout drug development, emerging animal toxicological and clinical data should be reviewed and evaluated by qualified experts to assess their implications for the safety of the trial subjects. In response to such findings, future studies and, when necessary, those in progress should be appropriately modified in a timely fashion to maintain the safety of trial participants.[iv]

The sooner and more completely drug pathways (pharmacokinetics) and potential drug toxicity (toxicokinetics) in humans can be identified, the more accurately the drug's potential pharmacological effects (pharmacodynamics) as well as appropriate dosing ranges can be estimated for the provision of the safe and efficient administration of the drug.

Prior to the introduction of a new pharmaceutical into humans, the drug is traditionally studied in animal models in order to assess the molecule's exposure and toxicity. Potential risks and initial dosing ranges for humans are determined by analysing the drug plasma concentration levels and systemic exposure in animals. This allows for the identification of potential risks for humans as well as the development of more specified monitoring plans for clinical studies.

> The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.[v]

The nonclinical safety studies are considered adequate when the metabolic profiles in the animal models are considered equivalent to the metabolic profile in humans, both quantitatively and qualitatively. Both the International Conference on Harmonization (ICH) and the US Food & Drug Administration (FDA) have set standards for Metabolites in Safety Testing (MIST) in order to ensure the safe introduction of new chemical entities into clinical trials with humans. The following decision tree provides an overall schema for MIST studies:


[vi]

The characterization of metabolites is a critical component for identifying drug pathways and toxicology. The more completely a potential drug pathway is characterized, the more reliable the pharmacokinetic description we will have of the molecule. However, it is not always the case that in vitro testing and animal models sufficiently identify or adequately describe all clinically relevant metabolites. There exists a potential for 'disproportionate drug metabolites' that will remain unidentified or inadequately described through animal models alone:

> This situation can occur if the metabolite is formed only in humans and is absent in the animal test species or if the metabolite is present at disproportionately higher levels in humans than in the animal species used in the standard toxicity testing with the parent drug.[vii]

Early on in drug development it is important to characterize as fully as possible the metabolic pathways of a drug, identifying both its potential toxicology profile as well as its potential prophylactic or therapeutic clinical profile. And while animal models are able to identify metabolites affected in drug metabolism, the extrapolation from animal models to humans remains fraught with risks of inaccuracy and oversight.

> Human in vivo metabolism studies usually have been conducted relatively later in drug development, but we strongly recommend in vivo metabolic evaluation in humans be conducted as early as feasible.[viii]

It becomes thus important to identify early in the development of a drug any metabolic differences between animals used in nonclinical toxicity studies and the (potential) use of the drug in humans. The discovery of disproportionate drug metabolites late in the development of a candidate medicine will delay the further development of the drug and potentially threaten its viability for marketing authorization.

Microdosing introduces a relatively new methodology for more fully identifying and describing the metabolic pathways of a drug in humans. By administering a subtherapeutic dose, minimally 1/100$^{th}$ of the NOAEL, the drug can be introduced in clinical settings to patients or healthy volunteers and followed by a tracer across the full range of metabolic pathways in human biology. This provides researchers and sponsoring companies a safe environment in which they can adequately describe the pharmacokinetic properties of a drug far below any toxic risks to the research subjects. This overcomes the potential for entering therapeutic level studies in humans based solely on animal models that risk later findings of 'disproportionate drug metabolites' in humans.

### *The Challenge of Clinical Studies in the Paediatric Population*

Although in recent years the study of new medicines as well as existing medicines in children has been increasingly advanced (by regulators, industry, researchers, and patient groups), still many of the medicines currently administered to children have not been adequately studied regarding their safety and efficacy specifically in children. Children have often been viewed as a particularly vulnerable population for which it was considered usually more appropriate to extrapolate findings from clinical studies in adults.

> The issue of testing medications in children presents a dilemma. Society wants to spare children from the potential risks involved in research. But children may be harmed if they are given medications that have been inadequately studied. Research that is carefully designed and conducted should help to protect children, but studies — particularly studies of medications whose safety has not been established — cannot be risk-free.[ix]

In addition, the paediatric population often (though not always) represents a significantly smaller population for which medicines are intended than the adult populations, making specific paediatric clinical studies less financially interesting as an investment for the pharmaceutical industry. Further, the paediatric population is a complicated population from the perspective of drug metabolism and dose ranges. And this is particularly so in younger age ranges where drugs are metabolized in significantly different ranges.

The very important MIST studies described above have been nearly exclusively developed in the context of introducing a new molecule into the adult population. The MIST studies are then followed by early phase studies (particularly Phase 1 studies) performed almost solely in adult populations. If the pharmaceutical is then studied in children, it is usually introduced to the paediatric population in Phase 2 dose-finding studies or even later in Phase 3 studies largely focused on efficacy. So, with the exception of medicines that specifically addressed diseases restricted to childhood, children have been (and largely remain) dramatically under-represented in the clinical study of medicines.

In 1997 the US Congress introduced the Food and Drug Administration Modernization Act[x] that required the FDA to request pediatric-specific dosing information on drugs widely used in the paediatric population that should carry paediatric labelling. In 2007 the Food and Drug Administration Amendments Act[xi] included the Pediatric Research Equity Act (Title IV,

2007 [originally from 2003]) and Best Pharmaceuticals for Children Act (Title V, 2007 [originally from 2002]). Alongside this, the European Union's Paediatric Regulation of 2006 (effective 2007) significantly impacted this rather traditional approach, promoting the clinical research of existing medicines used in paediatric care as well as going further and requiring new medicines submitted for marketing authorization to address adult health conditions, but that also may have a potential benefit a health condition in children, related to that in the adult or not, be studied in the appropriate paediatric population(s).[xii]

The Paediatric Regulation, in particular, required that these studies be performed within a Paediatric Investigation Plan (PIP) for new medicines, or medicines for a new indication, that will identify the safety and efficacy parameters of the medicine in children. This is a comprehensive requirement that pharmaceutical companies can only avoid in their application for a Marketing Authorisation (MA) when they can show a reasonable expectation that the medicine will not be used in children, for the indication for which a MA is being made or for another indication in childhood disease for which the medicine might be applicable. In these latter cases, the application for an MA must be accompanied by a PIP Waiver. The Regulation also requires a PIP for the study of medicines to be exclusively used in the paediatric population. Similar requirements also developed in the US and are currently reflected in the 2006 FDA Draft Guidance Pediatric Study Plans.[xiii]

### *The Vulnerability of Children and Research Ethics in Clinical Trials*

One of the major reasons for hesitating to study medicines in children is the risks that are associated with introducing new medicines in children or using medicines studied principally in adults in children. The developing biology of children alongside their varying metabolisms of medicines make the paediatric population particularly difficult to predict with regard to the the metabolism of drug molecules. Without this information, predicting appropriate dosing in children, even where there is relative confidence in safety and efficacy parameters, becomes more challenging.

In addition, children are largely seen as incapable of fully consenting to their participation in a research protocol, and even their assent is mired with difficulties and skepticism when it comes to providing sufficient justification for their participation in clinical trials. Thus, the hesitancy to study medicines in children is not only due to the vulnerabilities of the developing physiology and metabolism of children, but also due to the vulnerability of their developing capacity for understanding and self-determination.

### *First-in-Children Studies*

The introduction of new molecules in the human population, First-in-Human or Phase I clinical trials, are particularly sensitive because *in vitro* and animal model studies cannot always fully predict pharmacokinetic (absorption, distribution, metabolism, and excretion [ADME]) and toxicological responses in humans. Thus, these studies are usually carried out in a limited healthy adult population under strictly controlled and highly monitored conditions. As a rule, phase I studies are performed first or exclusively in adults. Only after the molecules have been confirmed for safety in adults, and more usually after the completion of phase 1 through phase 3 studies for both safety and efficacy confirmation in adults, are the molecules introduced for testing in the paediatric population. Exceptions are made for medicines to be used exclusively in the paediatric population or at times in vaccines or instances of public health crises.

> When paediatric patients are included in clinical trials, safety data from previous adult human experience would usually represent the most relevant information and should

> generally be available before initiation of paediatric clinical trials. The appropriateness and extent of adult human data should be determined on a case-by-case basis. Extensive adult experience might not be available before paediatric exposures (e.g., for paediatric-specific indications).[xiv]

The reticence to introduce new molecules into children and the reluctance to perform comprehensive studies in children is further exasperated by the fact that there exist large metabolic heterogenicity in children between age groups, often with significant metabolic differences in small age ranges among very young children. Thus, even where new molecules (or new indications for molecules with an existing MA) have been successfully studied regarding their safety and efficacy profiles in adults, there is a reasonably founded caution with regard to introducing these molecules into the paediatric population or, more correctly from a child biological development perspective, the paediatric populations. This is even more the case when, for example with vaccines, the medical research community has good reason to want to study these molecules in populations of healthy children.

### *Distinguishing Standard Treatment from Clinical Research in Children*

Although many medicines currently used in the treatment of children have never been the subject of clinical trials specifically in children, it would be wrong to decry their usefulness, including their safety and efficacy that often have a strong basis in wide clinical experience. At the same time, it is increasingly evident that the safety and efficacy profiles of the use of these medicines could be increased in many cases by well-designed clinical trials that take into account differences in age ranges among children as well as between children and adults. With regard to the medicines already consistently used in paediatric medicine, we can say 'We know they work.' But we cannot sufficiently say 'We know just how much and why they work.'

So, while there has been a widespread call to investigate new medicines and new indications for already marketed medicines in children, there is also an increasing interest in having medicines already widely used in paediatric care studied in controlled clinical trials in specific paediatric populations. This is particularly important because drug metabolism differs not only between adults and children, but also among various age ranges in children, particularly in age groups between < 36 weeks of gestation to 23 months.

### *Drug Metabolism in Children*

As the number of clinical trials in children increases, there has been an increased awareness of, and attention to, age differences in children. Traditionally, medicines have been administered to children based largely on extrapolation from studies and prescribing behaviour in adult populations. This method is still recommended, though with increased caution and attention to differences in disease pathogenesis, disease progression measurements, pathophysiological, histopathological, and pathobiological considerations. Importantly, the extrapolation should be dynamic in assessing the differences between the reference (adult) population and the paediatric populations. Furthermore, specific attention needs to be given to safety in the different paediatric populations:

> When efficacy in the pediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the pediatric population may be utilized; however, additional pediatric safety data are usually required, as data in adults may only provide some information about potential safety concerns related to the use of a drug in the pediatric population. [ICH E11 (2000) Section 2.4].[xv]

Similar to the expression of 'disproportionate drug metabolites' found between animal models and humans, expressions of 'disproportionate drug metabolites' can also be found between children and adults as well as between various paediatric populations. Children go through various stages of development: from new-born infant through childhood through adolescence and into maturation in young adulthood.

> A better understanding of the various physiologic variables regulating and determining the fate of drugs in the body and their pharmacologic effects has dramatically improved both the safety and the efficacy of drug therapy for neonates, infants, children, and adolescents. During childhood, these changes are dynamic and can be nonlinear and discordant making standardized dosing an inadequate means of effective drug dosing across the span of childhood. The impact of these changes is largely related to function of organs important in metabolism (e.g. the liver) and excretion (e.g. the kidney) and changes in body composition (e.g. body water content, plasma protein concentrations).[xvi]

Children are not a homogenous population for pharmacology. Indeed, due to the ongoing development of their biology, from a pharmacokinetic and dosing perspective they are far more diverse than the general target population found in adult clinical trials. In particular, dose determinations in relation to age is complicated in the paediatric population:

> The following age classification is suggested in the ICH and CPMP guidelines: preterm newborn infants, term newborn infants (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 – 11 years) and adolescents (12 to 17 years). . . . It should be noted that this classification is used to discuss characteristics of the paediatric population in different developmental stages. Some age classes are wide and include a large range of maturation levels. The identification of which age range to study should be medicinal product-specific and justified. The assessment of efficacy and safety should not be based on the specific age classes per se, but on the available documentation within the studied age range. In addition to age, the classification of the population may be based on other variables such as gestational age, renal function, metabolic function etc.[xvii]

Chronological age alone is not a sufficient basis for the categorising of developmental subgroups in paediatric studies. Recent draft guidance to supplement ICH E11 emphasises the point:

> [T]he arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study.[xviii]

Pharmacologically relevant target age ranges need to be identified on the basis of PK-PD and toxicological evidence that appropriately the paediatric population into relevant metabolic and dose categories.

The core objective is to provide evidence that supports the safe and effective use of drugs in the paediatric population. As the US FDA points out, the approach may vary according to the adequacy of the evidence presented in previous adult studies or based on evidence derived directly from paediatric populations.

> The identification of the appropriate ages to study and decisions on how to stratify data by age are drug-specific and require scientific justification, taking into consideration developmental biology and pharmacology.[xix]

A major challenge in streamlining clinical trials in children, and arriving at sound and efficient FDA Initial Pediatric Study Plans (iPSPs) and EU Paediatric Investigation Plans (PIPs), is stratifying studies across the metabolic ranges in various age groupings of children, particularly very young children, in order to demonstrate representative ADME evidence for dosage developmental age groups for children.

> Growth and developmental changes in the paediatric population will create substantial changes in ADME. PK measures and parameters for a drug or biologic may need to be described as a function of age and be related to some measure of body size, such as height, weight, or body surface area (BSA).[xx]

Microdosing provides an avenue for researchers to investigate, in parallel, the metabolic pathways of drugs in the various developmental and biological age ranges of the paediatric population that comprise pharmacologically disparate target populations.

### *The Added Value of Microdosing for iPSPs and PIPs*

It is against this background of challenges, cautions, and vulnerabilities in paediatric clinical trials that this select group of experts in developing medicines for children gathered to examine the potential added value of microdosing to the development of iPIPs and PIPs for submission to regulatory authorities in the United States, Europe, and other countries and regions in the world. The added value from incorporating microdosing studies in early drug development for children is specific and evident: microdosing provides a highly safe methodology for determining the MIST and potential toxicological effects of pharmaceuticals across paediatric developmental and biological age ranges. In addition, microdosing studies have now been demonstrated to be both feasible and accurate in paediatric populations, including in the youngest and most vulnerable populations. Introducing microdosing studies as either 'First-in-Children' studies of early-on Phase 0 studies for existing medicines can reduce the risk of unforeseen adverse toxicological injury to the child-participants and increase the accuracy of pharmacokinetic (PK) and toxicological analyses of (potential) medicinal molecules across the wide developmental range of childhood biology, In certain cases these studies may prove to be both scientifically and financially more expedient, while also increasing the ethical confidence we can have in paediatric medicines development plans.

## Recent Studies and Recent Findings Regarding Microdosing in Children

The workshop examined two recent microdosing projects in children that provide 'proof of concept' regarding the science, the practicalities, the ethics, and the results of microdosing in children. One project involved microdosing studies of $^{14}C$ paracetamol and midazolam in neonates and infants carried out by the Paediatric Accelerator Mass Spectrometry Evaluation Research Study (PAMPER) Consortium. A second and similar project also involved a set of microdosing studies of $^{14}C$ paracetamol, this time in infants 0 to 6 years of age. The PAMPER Project was carried out by a consortium of United Kingdom, Estonian, Polish, Dutch, and Belgian researchers and funded by PRIOMEDCHILD ERA-NET while the other study was carried out by a consortium of Dutch researchers and funded by the Netherlands Organization for Health Research and Development (ZonMw). Both sets of studies followed similar scientific methodologies, encountered similar practical challenges, addressed similar ethical questions, and arrived at similar results.

### *The PAMPER Consortium's Microdosing Studies*

The aim of this study was to examine whether therapeutic dose PK parameters (using $^{14}$C-APAP mixed in a therapeutic dose as a microtracer) of APAP in infants and neonates are similar (comparable) to PK parameters for an isolated microdose. The objectives were:

1. to operationalise the conduct of a microtracer/microdose study in children up to the age of two;
2. to validate a microtracer of $^{14}$C-APAP incorporated in a therapeutic dose using noncompartmental analysis (NCA) and extant data; and
3. to compare NCA PK parameters for an isolated microdose and a microtracer.

The overall aim of the study was to demonstrate 'proof-of-concept': that the PK analysis of a microdose in early childhood populations would provide comparatively valid results to a PK analysis of a therapeutic dose in the same populations. The project's objectives included, not only the more purely scientific objective of demonstrating PK similar results between a microdose and a therapeutic dose of a well-used drug in paediatric medicine but also the following objectives:

- to obtain all necessary ethical and regulatory approvals;
- to prepare 14C-labelled probes;
- to recruit neonates and young infants; and
- to compare PK parameters from microdosing (isolated dose of labelled probe) with microtracing (labelled probe administered with unlabelled probe)

The study recruited at two paediatric clinics between January 2013 and December 2013 in Liverpool, United Kingdom (Alder Hey Children's NHS Foundation Trust, recruiting a total of 34 babies) and in Tartu, Estonia (University of Tartu Children's Hospital, recruiting a total of 20 babies). The youngest baby recruited was 35.6 weeks postmenstrual age and the oldest 127 weeks (see Table 1 and Table 2). Ten babies in total received either an enteral or intravenous microdose of $^{14}$C-APAP alone with no concomitant therapeutic APAP dose.

Data was obtained from 10-15µl plasma that was analysed for Paracetamol and its sulphate and glucuronide metabolites, which were quantified at therapeutic and microdose levels. The microdose used was 106-fold lower than that of the therapeutic dose. The AMS analysis demonstrated that the PK parameters between the microdose and the therapeutic dose were within a factor of 2-3 when dose normalized. At the same time, plasma profiles were shown to have a similar shape between the microdose and the therapeutic dose (sulphate > glucuronide concentration).

Overall the study was able to conclude the following:

- No major problems were encountered in recruiting patients or obtaining the necessary approvals from ethics committees and regulatory authorities.
- The use of a microdose appears to give comparable results to a microtracer in a therapeutic dose.
- Microdosing using AMS can play a significant role in the early stages of drug development programmes for children.
- In cases where there is a demonstrated simple elimination of the drug (e.g. unmetabolized renal), microdosing studies may not provide added value.
- Microdose studies could be particularly valuable for drugs with complex metabolic pathways that cannot be simply extrapolated from animal or adult models.

[i] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals EMA/CPMP/ICH/286/1995, Pages 3 and 14.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

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[iv] ICH E8 General Considerations for Clinical Trials. Page 1..
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf

[v] ICH guideline M3 (R2) on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, p. 5.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf

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[viii] FDA Safety Testing of Drug Metabolites: Guidance for Industry 2016. Page 4.
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[xiv] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals EMA/CPMP/ICH/286/1995, Page 20

[xv] ICH Harmonised Guideline Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11(R1), Step 1, 25 August 2016. Page 9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf

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[xviii] Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population. E11(R1). 2016. Page 7. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf

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