

# Journal Pre-proof

## Acceptability of generic versus innovator oral medicines: not only a matter of taste

Catherine Tuleu, Dyfrig A. Hughes, David Clapham, Thibault Vallet, Fabrice Ruiz



PII: S1359-6446(20)30473-6  
DOI: <https://doi.org/10.1016/j.drudis.2020.11.008>  
Reference: DRUDIS 2841

To appear in: *Drug Discovery Today*

Received Date: 5 June 2020  
Revised Date: 22 September 2020  
Accepted Date: 6 November 2020

Please cite this article as: Tuleu et al., Acceptability of generic versus innovator oral medicines: not only a matter of taste, *Drug Discovery Today* (2020), doi: <https://doi.org/10.1016/j.drudis.2020.11.008>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.

# Acceptability of generic versus innovator oral medicines: not only a matter of taste

Catherine Tuleu<sup>1,5</sup>, Dyfrig A. Hughes<sup>2</sup>, David Clapham<sup>3,5</sup>, Thibault Vallet<sup>4</sup>, and Fabrice Ruiz<sup>4,5</sup>

<sup>1</sup>UCL School of Pharmacy, London, UK

<sup>2</sup>Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK

<sup>3</sup>Independent pharmaceutical consultant, Bishops Stortford, UK

<sup>4</sup>ClinSearch, Malakoff, France

<sup>5</sup>Members of the EuPFI Taste Assessment and Taste Masking workstream

Corresponding authors: Tuleu, C. (email); Clapham, D. (email)

Commented [LM1]: For AQF: please provide the email addresses for the corresponding authors.

## Research highlights

- Lack of formal scrutiny of the acceptability of generics may reduce patient adherence.

**Keywords:** generic; acceptability; palatability; swallowability; appearance; cost effectiveness.

**Teaser:** Reduced patient acceptability of generic products, especially oral ones, can undermine adherence and clinical effectiveness and, hence, compromise their potential benefits.

### Author biographies

#### Catherine Tuleu

Catherine Tuleu is a professor in pediatric pharmaceuticals at UCL School of Pharmacy, London, UK. Her research is inherently translational, ranging from formulation, process, and methodology development to clinical implementation, integrating the following themes: children-centric excipient research; reformulation and repurposing for better medicines for children; development of innovative age-appropriate dosage forms (especially for under 5s); administration issues (co-administration with food/beverages) and devices; and Sensory Pharmaceuticals™ (acceptability and *in vitro/in vivo* taste assessment). She is the founder of the European Paediatric Formulation Initiative (EuPFI), a consortium working in a precompetitive way on pediatric drug formulations.

Catherine Tuleu



Optimum use of generic products would require equivalence, not only in terms of quality, safety, and efficacy in clinical studies, but also patient acceptability to not jeopardize treatment success because of nonadherence which would *de facto* limit the potential cost saving anticipated by their use. Although acceptability is a requirement for the authorization of pediatric innovator products, our survey of European Union (EU) regulatory authorities showed that few have a formal process for assessing patient acceptability of generic products during the registration processes. The current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) focus on unifying guidance for the development and scrutiny of generics but should include acceptability alongside the other factors being considered for harmonization.

#### Introduction

Once a medicine is no longer under patent protection and the period of market exclusivity has expired, it is likely that a generic version will become available. The lower acquisition cost of generic medicines is a strong incentive for prescribers, pharmacists, and healthcare systems to use them in preference to the innovator product, all other factors being equal. Indeed, in some jurisdictions, there is financial pressure on prescribers and pharmacists to supply the cheapest licensed product available. In others, generic substitution, even when a product is prescribed by brand name, is encouraged or even mandated [1]. In England, for instance, 84% of all drugs in primary care are prescribed generically, potentially generating significant savings for the National Health Service (NHS) [2].

In France, pharmacists must provide a generic product even if the written prescription has a proprietary brand name. The prescriber can only object to this substitution in the following three circumstances. First, if the medicine has a 'narrow therapeutic index' (NTI), such as levothyroxine, phenytoin, or theophylline, and the patient is already effectively stabilized with a particular brand. Second, for children <6 years of age, if there is no generic drug in an age-appropriate dosage form available. And, finally, the original medicine can be prescribed if it does not include an excipient, present in all available generic medicines, to which patients have a demonstrated contraindication [3]. If these conditions are not met and the branded product is supplied, the reimbursement process can become complex for the patient [4]. If all generic products were equally as acceptable as the original product this would be less of an issue. However, this is not always the case.

Here, we explore more formally the level of scrutiny of the acceptability aspects of generic product development and highlight the added value of generics if non-inferiority is achieved in terms of acceptability as well as bioequivalence (BE). We discuss the findings of a purposive literature review of the relative palatability of generic products and corresponding impacts on medication adherence. We also present the findings of a survey of several regulatory authorities, to establish whether the relative acceptability of generic products is one of the factors considered as part of marketing authorization. The outcomes of the review and the implications for product development are discussed.

Although this paper focuses largely on oral medication, as the most commonly used mode of administration, the topics addressed are applicable to all product types, although each has their own critical acceptability criteria and challenges. Given the expertise of the authors and the crucial part that acceptability has in pediatric medicine use, we focus mainly on this patient group. However, the main points are also applicable to some extent to all medicine users and, in particular, to other vulnerable patient groups such as older patients and those with particular

formulation needs (e.g., those who experience swallowing difficulties or those with cognitive issues) [5,6]. We have included occasional references to these groups where they serve to illustrate a particular point. Given that the focus of the paper is mainly on oral pediatric medicines, many of the examples given are for antibiotic formulations because they are a class of medicines frequently prescribed for children [7,8] and often have challenging organoleptic characteristics. These are illustrative of the issue as a whole.

#### **Potential advantages of generic products**

Generic products can offer several advantages over their innovator counterparts, not least in relation to cost. A product that is normally a tablet might be easier to swallow, whereas a capsule can improve ease of administration for patients who need to mix the medication with food or disperse in water and administer via an enteral tube. As another example, a liquid dosage form of a product that is usually a tablet can aid dose measurement. The packaging is also unlikely to be exactly the same, potentially offering scope to provide a product that the patient would prefer to handle or that is easier to differentiate from other medicines.

Finally, there might also be scope for improving continuity of supply if generic products are available from several different manufacturers. However, the counter to this is that, if there are several generics available, different products might be supplied on different occasions, with implications that are discussed later.

Where such benefits arise, the mechanism and logistics of specifying a particular generic for supply to the patient and issues around reimbursement are likely to be problematic for the patient, prescriber, and dispensing pharmacist. For example, there is currently no formal mechanism for allowing a doctor to prescribe a particular generic or for the pharmacist to supply one from a particular supplier and to obtain reimbursement above and beyond the reference price should that particular generic be more expensive. Even where the pharmacist does choose the generic product that will be stocked in their pharmacy, it is unlikely to be economically viable to stock multiple versions.

Although a specific generic could have enhanced acceptability to a particular patient relative to the innovator product, experience and literature reports suggest that the opposite is the case [9,10]. A lack of consideration of the acceptability of generic products could undermine the potential considerable cost saving and other advantages that could be achieved by promoting their use. As with all medicines, it might be possible (but by no means certain) that acceptability could be improved by patient/provider education. However, this is unlikely to be particularly effective for young children, the main focus of this paper, or for patients with cognitive or functional impairments.

#### **Bioequivalence considerations**

Generic products must be bioequivalent with the innovator or receive a waiver, for example, based on the Biopharmaceutical Classification System (BCS) class of the active pharmaceutical ingredient (API) or meeting specified requirements for certain dosage forms or products [11–13]. To be bioequivalent, a suitable pharmacokinetic (PK) study (e.g., a randomized crossover or parallel design) in healthy volunteers needs to show, for both peak drug concentration (C<sub>max</sub>) and area under the curve, that the 90% confidence interval of the ratios (generic:reference) lies between 0.80 and 1.25 [11]. To meet this requirement, the variation in PK parameters between the generic and the reference is small [14], but nonetheless might have important implications, especially for medicines with a low therapeutic index (TI). In these cases, the BE requirements are tighter (0.90–1.11) and C<sub>max</sub> control might also be required. However, differences in acceptability between both products could have a detrimental effect on adherence, because very simply, 'drugs don't work in patients who don't take them' [15].

It is important in this context to remember that BE studies are generally performed in adults in controlled environments even for pediatric formulations, when it will be children that will be taking (or not taking) them in a domestic setting.

#### **Acceptability considerations**

Currently, legislation and regulation-related guidance from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mandate the development of formulations for children concurrently to those for new 'innovator' products for adults. Among other criteria, the acceptability of the formulation itself needs to be demonstrated [16]. As per EMA definition, acceptability is an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorized) [17].

Acceptability of a medicinal product is likely to have a significant impact on the patient's adherence and, consequently, is likely to impact the translation of a product into clinical effectiveness (i.e., the performance of a medicine when used in the context of routine care) [18,19]. It is driven by the characteristics of the user (e.g., age, individual health status, behavior, disabilities, background and culture, and prior expectations) and by the characteristics of a medicinal product. For example, for oral dosage forms, these would be: (i) palatability (e.g., taste, flavor, sweetener, mouth feeling, product texture); (ii) swallowability (e.g., size, shape, 'stickiness', integrity of dosage form, film-coating); (iii) appearance (e.g., color, size, shape, embossing); (iv) complexity of modification before administration (if required); (v) required dose (e.g., dosing volume, number of dose units, scoring); (vi) required dosing frequency and duration of treatment; (vii) Selected administration device (if any); (viii) primary and secondary container closure system; and (ix) how the dosage form is to be taken and how often it is to be administered.

Anecdotal evidence suggests that generic products (in particular oral liquid dosage forms often used in pediatrics) might not/do not receive the same level of regulatory scrutiny as do innovator products in terms of their acceptability.

Although not always the case, this can lead to generic products being approved with poorer acceptability, which in turn can influence their clinical- and cost-effectiveness via reduced adherence [20] as discussed.

The lack of scrutiny of acceptability factors does not only affect pediatric medicines. The situation is no better in the context of polypharmacy in older people, where patient-centric drug design should, but does not always, consider their needs, ability, and preferences. It is crucial to consider administration-related factors (e.g., difficulty in swallowing, handling, and palatability) to ensure that efficacious treatments in clinical trials are effective in practice. As an example, size is an important acceptability driver for older patients [5]. Similarly, taste masking should not be neglected for older patients even if it is often thought that older people are less sensitive to palatability issues [21]. Thus, acceptability factors should be considered when assessing the suitability of particular formulations in meeting patients' needs regardless of their age.

A further aspect that should perhaps be considered when developing any medicine and, in the context of this paper, generic versions of innovator products, is their pharmaceutical elegance (i.e., those aspects of the product that the patient perceives as indicating its quality) and the expectations that this might produce within the patient. There is a corpus of literature concerning the interaction between patients' expectations produced by the packaging, the product, the environment, and their prior experiences, on their subsequent perception of the acceptability of the final product and, hence, the likelihood that they will take it as intended. Extensive discussion of this aspect is beyond the scope of this current paper, but a few references are given to illustrate the concept [22,23].

If there are multiple generic versions of a product available, then although some generics are formulated to match (as far as possible) the appearance and properties of the innovator product, this is not universally the case because they will be approved regardless, provided the product complies with all required standards of quality, safety, and efficacy. Even if the individual generic products are acceptable in their own right, they can still differ significantly both from the innovator and each other, including the possibility to differ in pharmaceutical form (e.g., tablet versus capsule, tablets of different size, shape, color, etc). Given the supposed interchangeability of (generic) drugs, it is possible for a different formulation to be supplied on different occasions (or between different pharmacies). This can lead to frequent changes to the type, appearance, storage, dosing, administration requirements [24], or organoleptic properties of medicines dispensed to the individual, which can lead to confusion and present a further barrier to adherence. There is an additional risk of medication error, should the patient take more than one formulation of the same API at the same time, with obvious therapeutic and toxicological sequelae.

#### **What actually happens in practice?**

To explore the issues concerning the acceptability of generic medicines, we conducted a purposive literature review that focused mainly on pediatric populations; and conducted a survey of European regulatory authorities' approaches to assessing the acceptability of generic medicines during their marketing authorization reviews. We also present our understanding of the regulatory situation outside Europe.

##### *Purposes of this review*

A search was performed in PubMed up until June 2019 using the search terms: (acceptability OR palatability OR taste) AND (drugs; generic OR drugs; non-proprietary) to identify publications that discuss the relative acceptability of innovator and generic versions of medicines. Therapeutic areas where acceptability issues are known to be a significant in pediatrics were also investigated, namely antibacterial agents OR corticosteroid, as exemplars of the issues discussed. These categories cover the most frequently prescribed oral medicines in children. Asthma treatments are not considered because these tend to be delivered via the pulmonary route.

In addition, some publications highlighting the impact of formulation and presentation changes on the acceptability of an API were identified from a broad personal database, updated since 2014, which gathers papers on medicine acceptability in vulnerable populations. Herein, we discuss 24 key references that had a direct relevance to this paper. Table 1 lists those key references and provides reasons for the few not discussed further.

Many studies have demonstrated differences in palatability between distinct formulations of an API. As early as 1984, differences in children's taste ratings were demonstrated among three different oral suspensions of bacampicillin as well as two penicillin syrups [25]. Two years later, Uhari *et al.* [26] similarly highlighted acceptability differences for penicillin and erythromycin mixtures, varying in terms of sweeteners and flavors. Indeed, an erythromycin mixture, flavored with cherry/sodium citrate was significantly better than the mixture flavored with pineapple/menthol, both on the basis of the time required to give the medicine to the child (as recorded by a nurse), and the subjective score of drug acceptance given by the nurses. Such acceptability variation because of flavor were also observed for pivampicillin mixtures [27] and ondansetron syrups [28].

A study of US-approved antibiotic suspensions highlighted that the generics were rated lower or equal in taste to the respective innovator products [9,10]. The originator product tasted better than the generic product for trimethoprim sulfamethoxazole, whereas there was no taste difference in relation to cephalexin and erythromycin sulfisoxazole suspensions [10]. It is not clear in the latter case whether this was because all formulations were equally acceptable or equally unacceptable. Similar findings were observed for the acceptability of antibiotics approved in France [29,30]. Although there was no significant difference between amoxicillin innovator and generic products, differences in palatability and acceptability between Augmentin and other co-amoxiclav products appeared significant [29,30]. These findings underlay a specific problem of oral generic antibiotic drugs; that is, their

acceptability to children and, hence, adherence to treatment courses [31–33]. Differences among reference and generic products have also been highlighted for other therapeutic contexts, such as corticosteroids, which are frequently related to poor taste [34]. Although these results were based on human testing (e.g., child's evaluation and observer reports), innovator and generic formulations could be also distinguished using biomimetic taste-sensing systems [35]. These instrumental results were often correlated with those from gustatory sensation tests performed by well-trained adult volunteers [36–38].

In pediatrics, differences in acceptability between innovator and generic products appeared to be mainly because of taste and this, in turn, can be influenced by age. Bagger-Sjoberg and Bondesson showed in 1989 that taste differences could be driven by the age of a patient: two pediatric formulations of phenoxymethylpenicillin were differentiated by grade-schoolers (6–10-years old) but less so by preschoolers (3–5-years old) [39].

Other aspects identified in the search that had an influence on overall acceptability that differ between generics and innovator products in children include administration devices [40] and physical attributes, such as size of solid dosage oral form (SODF) [41].

Similarly, taste issues have often been overlooked in older patients, another vulnerable population. Recent research using a multivariable approach initially developed for pediatrics [42,43] then transposed for the older population [44], highlighted that taste/palatability remains crucial for the acceptability and, therefore, correct use of oral liquid pharmaceutical products, especially in older women [6,21]. As for pediatric patients, studies of many aspects of the characteristics of a medicine are needed to better understand overall acceptability, from taste to administration device [40] or physical attributes, such as size of the SODF [41].

Even for SODFs, where taste is less of an issue, the name, packaging, appearance, size, shape or pharmaceutical form (i.e., tablet or capsule) could cause confusion for some patients [45]. Acceptability could also be affected by swallowability [45]. The potential for confusion, along with variability of presentations, were raised as the main disadvantages of generic products by general practitioners, who suggested that drug composition and packaging could be made uniform to mitigate some of the drawbacks associated with generics, while taking advantage of their lower cost [46]. A recent cohort study supported this conclusion [47]. Based on >200 000 cases in the USA, researchers highlighted that switching to a generic identical in composition and appearance to the innovator drug product was associated with lower switchback rates compared with switching to generic drug products that were different to the innovator [47]. Although low, there was still a degree of switchback from the 'identical' generic to the innovator product.

Although generic medicines have the same API as the innovator product and must be bioequivalent and of equal quality, they can differ in term of excipients and, consequently, in taste/palatability.

For pediatric products, innovator products have to be tested to confirm acceptability during product development [17] because it is widely accepted that medicine acceptability could impact effectiveness. In theory, an 'identical generic' could be assumed to have identical acceptability to that of the innovator product. However, producing a generic that is truly identical might prove to be a significant challenge. For example, sourcing exactly the same flavors might be problematic and simply using similar ones might lead to significant organoleptic differences either initially or over the shelf life of the product as the flavor ages.

If a generic is not identical in all respects to the innovator drug product, the same acceptability testing as that required for the innovator should be considered by regulatory authorities. As discussed in the following section, this might not always be the case.

Unacceptable medicines can impede the benefits of even the most effective drug, yet many parents and other carers are faced with the daily challenge of getting their children to take their treatments. 'I don't like the taste' remains the number one challenge for children in taking medicines (>60% of 652 respondents in a recent survey) [48].

#### *Approach taken by European regulatory authorities*

To understand the current position of various regulatory authorities as regards to their requirements for acceptability testing of generic formulations, 31 national EU regulatory agencies were emailed, either via personal contacts or via the EMA Paediatric Committee (PDCO) list, during the summer of 2019 [49]. The project was introduced, and the following questions were asked: (i) does your country allow marketing approval of generics of different oral dosage forms to that of the innovator product? (ii) Do some formal or informal discussions take place regarding acceptability of generic versus originator medicines? And (iii) What relevant regulatory documentation does your country use when considering this area?

Responses were received from 14 (45%) regulatory agencies. Belgium, Croatia, Denmark, Estonia, Greece, Iceland, Ireland, Latvia, Netherlands, Slovakia, Slovenia, Spain, Sweden, and UK all answered that they allow marketing approval of generics of different oral dosage forms, if the conditions of Article 10 of the Directive 2001/83/EC are fulfilled [50].

The responses varied from the very detailed to the very brief, but were sufficient to provide a good level of understanding of the situation in Europe. As presented in Table 2, only three respondents (from UK, The Netherlands, and Croatia) affirm that there was some level of formal scrutiny around acceptability of generic versus originator medicines at least for pediatric submissions. Based on anecdotal data, it is probable that informal discussion of these aspects might be more widespread, particularly in terms of tablet dimensions and shape. However,

it appears that discussion about the choice of flavoring is less common and formal requests for data on these aspects are rare.

Surprisingly, only three agencies reported that they routinely formally consider acceptability when evaluating generic products, given that differences between generic products and their originators products should be considered as part of the Risk Management Plan (RMP), as detailed in the EMA position paper *Potential Medication Errors in the Context of Benefit Risk Balance and Risk Minimization Measures* [51]. This concludes that 'If a product containing the same active substance as an authorised/established one, but which is different in some aspects, including new indications, patient populations etc., is developed, the potential for medication errors caused by confusion with the authorised/established product, should be considered in the development and presentation of the product.'. The guidance does not specifically reference acceptability, but perhaps it should do so.

It appears that the risk of administration errors has been more formally recognized in the case of formulations for older patients [52]. This reflection paper notes that patients 'commonly recognise oral preparations by their size, shape, color, embossing, rather than by reading the product label, whereas preparations for other routes of administration may be recognized by their immediate container closure system', and that even carers, whether in the home or in an institutional setting, 'are also likely to administer medicinal products to the mainly older patients by a visual verification of the product appearance'. It acknowledges that confusion based on these factors and changes in them can lead to medication errors. Therefore, innovators are encouraged to ensure that they 'carefully compare the appearance and user instruction of their own product versus others on the market (e.g., sound or lookalikes)' and where relevant, to introduce 'appropriate measures in the product characteristics such as the formulation, packaging or product information' to mitigate risk. Given the highlighted issues, we encourage generic manufacturers to also ensure that their products 'have the same key visual appearance (i.e., color, size, etc.) and user instruction' as that of the originator product; the latter should be up to date and address older people's specific needs. As we point out elsewhere in this paper, although this is highly desirable guidance, it is not mandatory and not always applied in practice.

#### Regulatory landscape outside Europe

Our survey confirms that, in the EU, competent drug regulatory authorities might allow a generic drug and its reference product to be different oral dosage forms if the product meets bioequivalence criteria. In the USA, this is not the case. The FDA does not allow a generic drug and its reference product to be different oral dosage forms (e.g., tablets and capsules). In fact, the FDA guidance on *Size, Shape and other Physical Attributes of Generic Tablets and Capsules* [41] recommends generic oral tablets and capsules to be of similar shape and size to the reference product (brand leader or originator product). 'Similar' can be interpreted as not identical, allowing some increase in dimensions and weight. However, this guidance does not mention testing of acceptability. There is also an earlier FDA guidance on *Size of Beads in Drug Products Labeled for Sprinkle* [53]. This provides guidance on the maximum, but not minimum size of granules to be used in such 'sprinkle' products to avoid them being chewed and applies to all such formulations. However, there is no requirement for either the formulation or the granule size to be the same for generics and the innovator product with clear potential for the organoleptic acceptability to differ. This might be more important if such products are administered via a nasogastric tube.

Our review is based on a Western developed world perspective. Although many other territories follow either European or US regulatory standards and guidance, this is not always the case. It was outside of the scope of this review to locate specific relevant guidance on the evaluation of the acceptability of generics in significant markets, such as China, Africa, and India, and emerging markets. However, it appears likely that a lack of the scrutiny of acceptability of generics also applies in these markets. Given issues of access and cost, generic acceptability might be even more important in these territories than in Europe and the USA.

#### Why does all this matter in clinical practice?

Generic medicines are licensed in the EU in line with the requirements of Directive 2001/83/EC as amended [50]. Article 10 of the directive provides for three main categories of 'generic' where a change of pharmaceutical form may result: (i) 10(1) a 'true' generic medicinal product; (ii) 10(3) a hybrid application; and (iii) 10(a) well-established use (WEU; not actually a generic application, rather a formal recognition of medicines with a long and safe history of use).

EU countries that allow marketing approval of generics base their assessment on the bioequivalence of the generic to the innovator, with acceptability having a significantly lesser role at present. Although 'a generic medicinal product' is defined as 'a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies', article 10.1 goes on to state that 'the various immediate-release oral pharmaceutical forms include tablets, capsules, oral solutions and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10.' This is also reflected in the Notice to Applicants (2A, chapter 1, section 5.3.2.1) and the *Bioequivalence* guideline [11].

As a consequence, there is no requirement for generic medicines to be the same color, shape, size, and so on, or to bear the same embossing as the reference product. Neither does the pharmaceutical form need to be the same. A



generic tablet (article 10.1) referencing a capsule, or oral suspension, or oral solution originator (or vice versa) would be acceptable and could obtain a marketing authorization provided all other requirements are met.

More changes are allowed in other article 10 applications. Some recent examples serve to illustrate the point: (i) a 10.3 hybrid application for hydrocortisone granules in capsules for opening (Alkindi®) referring to hydrocortisone tablets [54]. The main differences in Alkindi® compared with the reference medicinal product are: change in pharmaceutical form; change in strength; and indication in replacement therapy in pediatric patients only; (ii) a 10.3 hybrid application for an orphan drug indication for mercaptopurine in the treatment of lymphoblastic leukemia. The generic oral suspension formulation references Puri-Nethol tablets [55]; (iii) Sialanar® is an oral liquid dosage form containing glycopyrronium and is a 10a WEU application. Glycopyrronium has been licensed for many years. Before Sialanar® oral liquid, there were injections and SODFs licensed. The Sialanar® WEU application has resulted in new indications and a new dosage form for this drug substance [56].

The implications of this presumption of equivalence and, hence, presumed 'substitutability' between various immediate-release formulations is clearly not necessarily true in terms of acceptability.

#### What are the product development implications?

Based on the aforementioned published findings in the literature and information provided by the responses to the survey, it is possible to provide some detailed discussion for each of the individual factors that influence overall acceptability.

##### Palatability

At least some regulators are aware of the literature showing potentially significant differences between formulations; for instance, one quoted the study referred to earlier that found that several brands of generic co-amoxiclav tasted worse than the innovator (Augmentin) [29]. This study, which acknowledged financial support from the former French medicines agency (Afsaaps until 2012), called for the evaluation of palatability of future drugs (generics and references) before granting of the marketing authorization, because, particularly for active substances of poor taste, palatability has a significant role in adherence to the treatment, especially in children.

It is also acknowledged that other antibiotics also pose palatability challenges [33]. For example, Floxapen®, the brand leader formulation of flucloxacillin, has very poor palatability. Anecdotally, many generic flucloxacillin brands are equally unpleasant. This issue of poor palatability is highlighted in some hospital formularies. For example, the formulary of Evelina Children's Hospital, London, states: 'Flucloxacillin liquid is not very palatable' [57]. The impact on adherence of unpalatable antibiotics is discussed on forums such as MumsNet and acknowledged internationally (e.g., pharmacists in Canada have suggested tips for giving antibiotics to children [58]).

A recent example that is a good illustration of the need for generics to have acceptable palatability concerns two new licensed omeprazole products (two strengths). Although the manufacturer intended this solution formulation to be used for administration via use with enteral tubes, because it is the only licensed formulation, it is being prescribed for oral use in the community. However, the Neonatal and Paediatric Pharmacists Group (NPPG) blog reported recently [59] that 'children don't like it saying that it does not taste nice and 'burns'.' Some consider it 'utterly revolting' and cases of emesis following swallowing of the dose have been reported. Some children have asked to go back to their old (unlicensed) liquid formulation.

Despite the known issues of poor palatability of legacy, and some new, products, some survey respondents were not aware of a major objection preventing the marketing of a product on the basis of poor palatability having ever been raised. However, our survey reported one instance (personal communication) where a generic oral liquid product that was formulated at a higher concentration than the originator, presumably to reduce the dose volumes, and which the applicant originally proposed for use in both children and adults, was restricted to use in adults only because its palatability was demonstrated to be worse than the more dilute reference product [60].

Poorly acceptable legacy products rely on voluntary reformulation by the marketing authorization holder (MAH) because there is currently no regulatory instrument that would support a request for reformulation. The pediatric-use marketing authorization (PUMA) procedures have not incentivized alternative taste masked dosage forms.

Modern regulatory procedures, such as pediatric investigation plans (PIPs), along with such regulatory guidance as EMA guidelines on pediatric development pharmaceuticals, and their requirements for age-appropriate, acceptable formulations will prevent unpalatable innovator medicines for children in the future and force the development of alternative formulations if taste cannot be masked. For innovator products, acceptability/palatability studies will be performed as part of product development, probably as part of the clinical studies that companies will need to undertake in any case. However, performing such studies in patients might not always be a requirement for generic product developers. If the API/product is BCS class I or III or an oral solution, then they might not even need to undertake a bioequivalence study and, thus, will have no obligation (or opportunity) to demonstrate the palatability of the product. If they do undertake bioequivalence studies, there is no requirement to include palatability assessment as part of those studies and, even if palatability studies are conducted, the data will be generated in adults rather than children or older patients. Including taste studies will of course increase the cost. Thus, the level of scrutiny applied to innovator and generic versions of those products is different.

Perhaps the subjectivity of taste and lack of defined methodology contribute to regulatory uncertainty in this area. A range of possible methodologies have been proposed and various groups, including the European Paediatric

**Commented [LM2]:** For AQF: please add the details of the person with whom this personal communication occurred e.g. 'J. Smith, pers. commun. 2020'



Formulation Initiative (EuPFI) and IQ Consortium, and some regulators have begun discussions on identifying and agreeing unified methodologies for assessing the palatability and overall acceptability of pharmaceutical products, but these efforts have yet to bear fruit.

#### *Swallowability*

SODFs are being used increasingly for children. The *Guideline on Pharmaceutical Development of Medicines for Paediatric Use* [17] states that 'The size and shape of a tablet are fundamental to the ability of a child to swallow it. Therefore, the acceptability of the size and shape of tablets by the target age group(s) should be justified, and where relevant supported by appropriate studies or clinical evidence'. Generic versions of a SODF might be a different shape or size and, thus, could be less acceptable, especially if they are physically larger, or appear to be so. This might be especially so if one product is a capsule whereas the other is a tablet, and this will cause difficulties in generic substitution.

Given that it is currently permissible, at least in Europe, for a generic to be a different pharmaceutical form to that of the innovator, swallowability might be improved by changing from a SODF to a liquid. However, taste issues might then be made worse and aspects such as portability and dose measurement might need to be considered. It is not yet clear whether the risk of medication error is increased or reduced in such cases, and this will likely vary on a case by case basis.

#### *Appearance*

Enhanced acceptability has been suggested as one reason for inclusion of colors in medicines, especially for children. The inclusion of color either on packaging or in the dosage form itself can also be used to help differentiate strengths.

Differences in color can exist between innovator and generics products (and among different generics); in some cases, particularly over-the-counter (OTC) medicines, the same basic formulation might exist as either a colored or color-free presentation. Although there is some evidence that adherence with prescribed therapy can be influenced by color [61], there is a clear risk that differences in appearance (including form, size, shape, embossing, and color) could lead to elevated risks of medication errors. These include selecting the wrong product at the pharmacy, patients taking the wrong tablets or wrong strength of tablet/wrong dose, taking multiple doses, and so on. This is potentially more problematic for patients taking long-term treatments who might receive several different generic products over time.

Another aspect that deserves consideration in this regard is that different colorings might be used either to attempt to match the color of another formulation or to provide an entirely different color. Although reasonably rare, some patients can be allergic to one or more of the dyes/lakes/colorants used to produce the colored product [62–64]. The variation in excipients used can be beneficial if it allows a patient to avoid those colors to which they react, but could clearly be an issue if a change of generic leads them to be exposed to a color that they do not tolerate, even if the appearance is the same. Indeed, this could be a bigger risk if the appearance does not alert them to the fact that the colorants might have changed.

Although medicines are provided in labeled packaging, for some patients, their medicines might be placed in multi-compartment compliance aids (MCAs). Changes in the appearance of medicines can be particularly confusing where they are separated from the packaging.

Similarity of these aspects among all versions of the same product might help avoid these issues and facilitate safer generic substitution.

#### *Complexity of modification before administration*

Given that a generic product can be different to the originator in terms of the formulation and even the pharmaceutical form, the ease of dose preparation before dosing (e.g., reconstitution or dispersion in water/food to aid administration) might be different. As an example, a capsule might be easy to open for the content to be dispersed in water, whereas the tablet form might require crushing even if this is not allowed in the summary of product characteristics (SmPC). Although there are occasional instances where it is legitimate practice to crush tablets for this purpose (e.g., clobazam, L-cysteine, or liothyronine), it might be more convenient to patients and carers to open a capsule than to crush a tablet. Similarly, a powder for reconstitution that requires more vigorous shaking could lead to a poorer patient experience or even dosing errors from undispersed material.

Sometimes, it is necessary to dilute liquid preparations before administration via narrow enteral tubes (e.g., to reduce viscosity). Given that generic versions can vary with regard to excipients, it is possible that ease of administration via enteral tubes might vary between products. It is also possible that one might need dilution whereas another does not. Increased complexity is clearly more likely to result in error, as well as being less acceptable to carers. The EMA has published guidance on instructions for enteral tube administration, taking into account the properties of the formulation [65].

Another example is where the innovator product or some generic versions are scored to aid dose adjustment, but other versions are unscored or unlicensed for subdivision [66]. This might require unlicensed manipulations or the need for a specific make of a medicine, which can adversely affect generic substitution.

#### *Required dose*

It is possible that the costs of formulating and registering specific generic products for various pediatric patient groups are not commercially worthwhile. Unlike the case for the innovator, there is no compulsion for generic products to cater for all users and, thus, generic manufacturers might simply choose not to seek authorization for use of their products in certain subgroups or may delete indications for use in younger children if issues regarding suitability for use in these groups are raised. Some regulators have termed this 'age-upping' and are concerned because the direction of travel should be increased availability of licensed medicines for all age ranges, especially the youngest.

As an example, given the relatively small market represented by neonates, it is possible that generic manufacturers will not specifically develop formulations for all age groups but rather seek to adapt their adult or pediatric formulations for all age groups. Very small volumes of oral liquid medicines are sometimes required for neonates. Carers can struggle to measure such volumes. Even though official guidance provides help on minimum volumes to be measured with devices, there is still the possibility that a specifically formulated product for neonates will be a different concentration to one adapted from an adult or pediatric formulation for a wider age range, leading to different dose volumes. The smaller the dose volume, at least as a percentage of the overall volume of the dosing device (e.g., an oral syringe), the bigger the risk of dosing error, even if the dose is within 'acceptable' limits. If the therapeutic index is narrow, this could be even more problematic.

These differences in the age ranges of generic products compared with the innovator do not aid generic substitution. They might also dilute the economic benefit of using generics, given that it might be necessary to use one formulation (innovator) in some patient populations while being able to use another (generic) one in others, complicating inventory requirements and costs in the pharmacy or increasing unintentional off-label use of some medicines.

#### *Devices*

The *Guideline on Pharmaceutical Development of Medicines for Paediatric Use* [17] states 'unless otherwise justified liquid pediatric medicines should be supplied with a measuring device' and 'the age appropriateness of an administration device should be discussed'. There is also an EMA questions and answers (Q&A) document on gradations on oral liquid dosing devices [67]. However, there is no requirement for any administration device provided to be similar between formulations even of the same API. Clearly, the ease of use of the device supplied can both influence acceptability and dose accuracy. A proliferation of devices could lead to confusion and the wrong dose being administered.

Some respondents to our survey stated that the supply of measuring devices with products that are inaccurate or inappropriate for the age range/dose volume is a common assessment issue with generic applications, as illustrated by the need for advice to applicants on this [67]. If the application is subsequently approved, it will be necessary for the manufacturer to have responded to this guidance to ensure that the eventual device supplied is appropriate. The costs involved could again mean that the manufacturer might choose not to pursue this indication.

In some hospital environments, the issue of different devices being supplied might be somewhat mitigated by them choosing not to use the devices that come in packs and using their own bulk ones to avoid staff errors in picking a device. However, this has its own issues associated with dose measurement and dose accuracy, as discussed in a recent seminar of the EuPFI on the topic [68].

#### *Primary and secondary container closure system*

Generic medicines are not required to be packaged in the same way as the innovator. Pack sizes, printing, color, and so on, can be different to the innovator. If the pack is less convenient for the user, then acceptability might be affected, especially if it is less portable. Conversely, a generic manufacturer might be able to 'spot a gap' in the market by providing packaging with enhanced functionality and, thus, provide their product with a competitive advantage. Differences in external packaging can lead to errors in product selection. The packaging design and style of generic medicines is usually not a copy of the original product (because of copyright and intellectual property rights) but is usually in accordance with the company-specific livery. Regulatory emphasis is on innovative pack design across a manufacturer's product range, which should ensure accurate identification of the individual products and differentiate between products in a range [69].

Importantly, if there is a risk of several pack types of the same medicine (e.g., a tub of tablets and a blister pack) being in the patient's home at the same time, there could be a risk of both being taken, leading to overdose. Therefore, manufacturers should consider this risk when making decisions about how to package their products.

#### *Constraints on generic manufacturers*

Although the foregoing discussion of various aspects of product development illustrates the potential risks of not considering acceptability as part of the approval of generic formulations (and, hence, the risk that this will not be high on the list of criteria being considered by the formulator), it has to be acknowledged that there are some constraints operating for the generic manufacturer, especially if the wish is to produce a product that is identical to the originator. The appearance, dosage device, and packaging of an innovator product might be protected by intellectual property rights that might outlive the patent protection for the API. There might also be risks associated with generics being passed off as the innovator product, although, for reasons discussed earlier, it is unlikely for generic manufacturers to obtain exactly the same flavors, colors, excipient grades, and so on. Exact copies of the

innovator should not be necessary and, perhaps in many cases, not even desirable if there is an opportunity for the generic to have better acceptability than the originator.

There is also a cost involved in demonstrating that the generic product has acceptability that is at least not significantly worse than the originator, and this cost will need to be recouped by the developer. Therefore, a 'level playing field' in this aspect of the evaluation of all generic products by regulatory authorities is required to ensure that manufacturers are not disadvantaged economically for developing products that are demonstrably acceptable to the patient. A slightly higher generic price for a product with good acceptability would avoid the economic risks associated with poorly acceptable generics, as discussed next.

#### **Economic considerations and implications**

The general assumption, and drive, for generic prescribing in many countries is on the basis of saving costs for equal health gains [70]. From an economics perspective, the implicit approach when two products are therapeutically identical is one of cost-minimization analysis, which has a decision rule of adopting the least costly option. However, as described in the foregoing discussion, bioequivalence (in the PK sense) might not necessarily translate to therapeutic equivalence (in the clinical sense) if there are differences in the characteristics of generic medicines that might impact patient preferences, introduce barriers to administration, or lead to medication errors. These can each reduce adherence, limit effectiveness, and cause harm. Consequently, a cost-minimization framework is not appropriate where such differences exist. Likely differences in health outcomes, however small, dictate that cost-effectiveness (utility) analyses should be used when assessing the value of generic products that are potentially not therapeutically equivalent [71].

Generic medicines are generally exempt from formal health technology assessment and appraisal in most jurisdictions. However, the Scottish Medicines Consortium (SMC) has a broad appraisal remit. In the case of hydrocortisone granules in capsules (Alkindi®), the SMC accepted that bioequivalence with hydrocortisone tablets had been established in clinical studies. The premise of the sponsor's economic analysis was for quality of life benefits and reduction in mortality from reduced risk of comorbidity resulting from the ability of Alkindi® to deliver accurate and consistent dosing in young children [72]. In Germany, this argument was not accepted [73] and, as a result, the statutory health insurance funds agreed on a reimbursement that is not as high as the manufacturer proposed, but higher than for that for the comparator product (tablet formulation or compounded capsule formulation). The SMC accepted both mercaptopurine oral suspension (Xaluprine®) [74] and glycopyrronium bromide (Sialanar®) [75] for use by NHS Scotland without consideration of economic factors.

More generally in the UK, the prescribing of generic medicines is typically driven by pressure from commissioners and providers of medicines in their various guises (general practices, Clinical Commissioning Groups, etc.) to reduce costs. Formal economic evaluations are not conducted, and the consequences of this can lead to inefficiencies in the delivery of healthcare. Consider, for instance, a generic medicine that is significantly less expensive than the originator but, because of difference in appearance, is not adhered to by a proportion of patients. These patients might experience a recurrence of symptoms, impairment of quality of life and so on, depending on the disease being managed. If worsening of symptoms were to lead to hospital attendance, additional testing and so on, then the savings would soon evaporate, and costs could increase overall [20]. Although this might be somewhat theoretical, with little direct evidence, it is nonetheless plausible, especially because the cost of hospitalization and associated care considerably exceeds the likely savings, even if this is a rare occurrence [76].

#### **Concluding remarks**

As we have demonstrated in this paper, a lack of consideration of the acceptability of the generic product could undermine treatment efficacy and safety in certain populations, thereby reducing the potential considerable cost saving that could be achieved by promoting the use of generic medicines. Failure to produce a generic that is acceptable to the patient and their caregiver can lead to not only potential for treatment failure via nonconcordance with therapy, but potentially also significant extra costs. Thus, ensuring substantial cost savings by promoting the use of generic products requires equality in terms of not only quality, safety and efficacy in clinical studies, but also acceptability and, hence, efficacy in use.

Given the current ICH focus on unifying guidance on the development and scrutiny of generics [77], it is timely to state our position on this topic [78] and to seek to influence the growing debate to ensure that acceptability is included alongside other factors being considered for harmonization.

#### **Acknowledgments**

The authors would like to acknowledge the contribution of Tiffany Chong and Patrick O'Sullivan, who helped with the regulatory survey. We would also like to thank Garry Inwards and Karin Boon for insightful discussions concerning regulatory aspects.

## References

- 1 Panteli, D. *et al.* (2016) Pharmaceutical regulation in 15 European countries. Review. *Health Systems in Transition* 18, 1–118
- 2 Appleby, J. (2015) The rise and rise of generic prescribing. *BMJ* 20 (351), XXX–YYY
- 3 Ministère des Solidarités et de la Santé (2019) Arrêté du 12 Novembre 2019 précisant, en application de l'article L. 5125–23 du code de la santé publique, les situations médicales dans lesquelles peut être exclue la substitution à la spécialité prescrite d'une spécialité du même groupe générique. *J. Off. Répub. Fran.* 2019, 5–116
- 4 République Française (2018) LOI no 2018–1203 du 22 Décembre 2018 de financement de la sécurité sociale pour 2019. *J. Off. Répub. Fran.* 2019, 3–191
- 5 Vallet, T. *et al.* (2020) Acceptability in the older population: the importance of an appropriate tablet size. *Pharmaceutics* 12, 746
- 6 Ruiz, F. *et al.* (2019) Sex differences in medicine acceptability: a new factor to be considered in medicine formulation. *Pharmaceutics* 11, 368
- 7 Hales, C.M. *et al.* (2018) Trends in prescription medication use among children and adolescents—United States, 1999–2014. *JAMA* 319 (19), 2009–2020
- 8 Iannelli, V. and Garbi, L. (2019) *30 Most Commonly Prescribed Pediatric Medications*, Verywellhealth
- 9 Samulak, K.M. *et al.* (1996) Randomized, double blind comparison of brand and generic antibiotic suspensions: I. A study of taste in adults. *The Pediatric Infectious Disease Journal* 15, 14–17
- 10 El-Chaar, G.M. *et al.* (1996) Randomized, double blind comparison of brand and generic antibiotic suspensions: II. A study of taste and compliance in children. *The Pediatric Infectious Disease Journal* 15, 18–22
- 11 EMA (2010) *Guideline on the Investigation of Bioequivalence*, EMA
- 12 EMA (2018) *Guideline on Equivalence Studies for the Demonstration of Therapeutic Equivalence for Locally Applied, Locally Acting Products in the Gastrointestinal Tract*, EMA
- 13 EMA (2018) *Draft Guideline on Quality and Equivalence of Topical Products*, EMA
- 14 Andrade, C. (2015) Bioequivalence of generic drugs: a simple explanation for a US Food and Drug Administration requirement. *The Journal of Clinical Psychiatry* 76, 742–744
- 15 Koop, C.E. (1985) Keynote address. In *Improving Medication Compliance: Proceedings of a Symposium* (XXX, eds), pp. 1–4, National Pharmaceutical Council
- 16 WHO (2018) *Toolkit for Research and Development of Paediatric Antiretroviral Drugs and Formulations. Module 5: Acceptability*, WHO
- 17 EMA (2013) *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*, EMA
- 18 Bryson, S.P. (2014) Patient-centred, administration friendly medicines for children - an evaluation of children's preferences and how they impact medication adherence. *Int J Pharm* 469, 257–259
- 19 Ramnal, S.R. *et al.* (2018) Methodologies for assessing the acceptability of oral formulations among children and older adults: a systematic review. *Drug Discov Today* 22 (17), 30477–30474
- 20 Holmes, E. *et al.* (2013) New advice on switching antiepileptic drugs might be a false economy. *BMJ* 2013, 347
- 21 Belissa, E. *et al.* (2019) Acceptability of oral liquid pharmaceutical products in older adults: palatability and swallowability issues. *BMC Geriatrics* 19, 1–9
- 22 Wan, X. *et al.* (2015) Assessing the expectations associated with pharmaceutical pill colour and shape. *Food Quality and Preference* 45, 171–182
- 23 Velasco, C. *et al.* (2016) Crossmodal correspondences between taste and shape, and their implications for product packaging: a review. *Food Quality and Preference* 52, 17–26
- 24 Mieiro, L. *et al.* (2019) Achieving appropriate medication for older adults: A multidimensional perspective. *Maturitas* XX, YYY–ZZZ
- 25 Sjövall, J. *et al.* (1984) Methods for evaluating the taste of paediatric formulations in children: a comparison between the facial hedonic method and the patients' own spontaneous verbal judgement. *European Journal of Pediatrics* 141, 243–247
- 26 Uhari, M. *et al.* (1986) Acceptance of antibiotic mixtures by infants and children. *Eur J Clin Pharmacol* 30, 503–504
- 27 Jahnsen, T. and Thorn, P. (1987) An acceptability study of two pivampicillin mixtures in children in general practice. *Scandinavian Journal of Primary Health Care* 5, 241–243
- 28 Stevens, R. *et al.* (1996) A randomized study of ondansetron syrup in children: evaluation of taste acceptability and tolerance. *Pediatr Hematol Oncol* 13, 199–202
- 29 Cohen, R. *et al.* (2009) Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. *Eur J Pediatr* 168, 851–857
- 30 Wollner, A. *et al.* (2011) [Acceptability, compliance and schedule of administration of oral antibiotics in outpatient children]. *Arch Pediatr* 18, 611–616
- 31 Gauzit, R. and Lakdhari, M. (2012) Generic antibiotic drugs: is effectiveness guaranteed? *Médecine et Maladies Infectieuses* 42, 141–148
- 32 Tattevin, P. *et al.* (2013) Efficacy and quality of antibacterial generic products approved for human use: a systematic review. *Clinical Infectious Diseases* 58, 458–469
- 33 Baguley, D. *et al.* (2012) Prescribing for children - taste and palatability affect adherence to antibiotics: a review. *Arch Dis Child* 97, 293–297
- 34 Kim, M.K. *et al.* (2006) Vomiting of liquid corticosteroids in children with asthma. *Pediatric Emergency Care* 22, 397–401
- 35 Woertz, K. *et al.* (2011) Taste sensing systems (electronic tongues) for pharmaceutical applications. *International Journal of Pharmaceutics* 417, 256–271
- 36 Inoue, Y. *et al.* (2012) Study of the physicochemical properties of tulobuterol dry syrups using taste and smell sensors. *Chemical and Pharmaceutical Bulletin* 60, 442–448
- 37 Tokuyama, E. *et al.* (2009) Famotidine orally disintegrating tablets: bitterness comparison of original and generic products. *Chemical and Pharmaceutical Bulletin* 57, 382–387
- 38 Uchida, T. *et al.* (2013) Evaluation of palatability of 10 commercial amlodipine orally disintegrating tablets by gustatory sensation testing, OD-mate as a new disintegration apparatus and the artificial taste sensor. *Journal of Pharmacy and Pharmacology* 65, 1312–1320
- 39 Bagger-Sjoberg, D. and Bondesson, G. (1989) Taste evaluation and compliance of two paediatric formulations of phenoxymethylpenicillin in children. *Scand J Prim Health Care* 7, 87–92
- 40 Kraus, D.M. *et al.* (2001) Effectiveness and infant acceptance of the Rx medibottle versus the oral syringe. *Pharmacotherapy* 21, 416–423
- 41 FDA (2015) Size, shape, and other physical attributes of generic tablets and capsules guidance for industry. *Fed. Regist.* 2015, 35366–35367
- 42 Ruiz, F. *et al.* (2017) Standardized method to assess medicines' acceptability: focus on paediatric population. *J. Pharm. Pharmacol.* 69, 406–416
- 43 Vallet, T. *et al.* (2018) Standardized evaluation of medicine acceptability in paediatric population: reliability of a model. *J. Pharm. Pharmacol.* 70, 42–50
- 44 Vallet, T. *et al.* (2018) A decision support tool facilitating medicine design for optimal acceptability in the older population. *Pharmaceutical Research* 35, 136

Commented [LM3]: For TS: reference styling required:

1. Please abbreviate journal titles according to housestyle
2. Please use punctuation for journal titles according to house style
3. Please put journal titles in italics.
4. Please remove issue numbers

Commented [LM4]: For AQF: please provide page range or article number.

Commented [LM5]: For AQF: please provide editor details if available.

Commented [LM6]: For AQF: please provide volume and page range.

- 45 Toverud, E.-L. *et al.* (2011) Norwegian patients on generic antihypertensive drugs: a qualitative study of their own experiences. *European Journal of Clinical Pharmacology* 67, 33–38
- 46 Riner, B. *et al.* (2017) 'No generics, Doctor!' The perspective of general practitioners in two French regions. *BMC Health Services Research* 17, 707
- 47 Desai, R.J. *et al.* (2018) Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: cohort study. *BMJ* 361, k1180
- 48 Nordenmalm, S. *et al.* (2019) Children's views on taking medicines and participating in clinical trials. *Archives of Disease in Childhood* 104, 900–905
- 49 EMA (2020) *Paediatric Committee (PDCO) Members*, EMA
- 50 European Parliament (2001) *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use*, European Parliament
- 51 EMA (2013) *Position Paper on Potential Medication Errors in the Context Of Benefit–Risk Balance and Risk Minimisation Measures. Focus on Medication Errors Caused by Confusion of a Newly Introduced Medicinal Product with an Authorised/Established One, Containing the Same Active Substance but Different in Some Aspects*, EMA
- 52 EMA (2017) *Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population*, EMA
- 53 FDA (2012) *Guidance for Industry Size of Beads in Drug Products Labeled for Sprinkle*, FDA
- 54 EMA (2018) *Summary of the European Public Assessment Report (EPAR) for Alkindi*, EMA
- 55 EMA (2012) *Summary of the European Public Assessment Report (EPAR) for Xaluprine*, EMA
- 56 EMA (2016) *Summary of the European Public Assessment Report (EPAR) for Sialanar*, EMA
- 57 Evelina London Children's Hospital (2020) *Evelina London Paediatric Formulary*, Evelina London Children's Hospital
- 58 Ontario Pharmacists Association (2020) *But that Medicine Tastes Bad! (Tips for Giving Antibiotics to Kids)*, Ontario Pharmacists Association
- 59 **Neonatal and Paediatric Pharmacists Group (2020) Personal Communication. 20 April.**
- 60 **Medicines and Healthcare products Regulatory Agency. (2019) Survey response. Personal Communication. 19 December.**
- 61 De Craen, A.-J. *et al.* (1996) Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. *BMJ* 313, 1624–1626
- 62 Rogkakou, A. *et al.* (2007) Severe skin reaction due to excipients of an oral iron treatment. *Allergy* 62, 334–335
- 63 Lévesque, H. *et al.* (1991) Reporting adverse drug reactions by proprietary name. *Lancet* 338 (8763), 393
- 64 Millar, J. (2000) Excipient E110: a cause for complaint? *British Journal of General Practice* 50, 664
- 65 EMA (2018) *Quality of Medicines Questions and Answers: Part 2. Administration of Oral Immediate Release Medicinal Products through Enteral Feeding Tubes*, EMA
- 66 National Pharmaceutical Services (2014) *Tablet Splitting, Commonly Asked Questions*, National Pharmaceutical Services
- 67 EMA (2018) *Quality of Medicines Questions and Answers: Part 2. Specific Types of Product - Graduation of Measuring Devices for Liquid Dosage Forms*, EMA
- 68 Walsh, J. *et al.* (2020) European Paediatric Formulation Initiative Workshop Report: Improving the Administration of Oral Liquid Medicines in Paediatrics using Dosing Syringes and Enteral Accessories. *European Journal of Pharmaceutics and Biopharmaceutics* XX, YYY–ZZZ
- 69 Medicines and Healthcare Products Regulatory Agency (2015) *Best Practice Guidance on the Labelling and Packaging of Medicines*, Medicines and Healthcare Products Regulatory Agency
- 70 Duerden, M.G. and Hughes, D.A. (2010) Generic and therapeutic substitutions in the UK: are they a good thing? *Br J Clin Pharmacol* 70, 335–341
- 71 Dakin, H. and Wordsworth, S. (2013) Cost-minimisation analysis versus cost-effectiveness analysis, revisited. *Health Econ* 22, 22–34
- 72 Scottish Medicines Consortium (2018) *Hydrocortisone 0.5mg, 1mg, 2mg and 5mg Granules in Capsules for Opening (Alkindi®)*, Scottish Medicines Consortium
- 73 Apotheke adhoc. [Glaucoma: Injection of virus instead of eye drops?]. <https://www.apotheke-adhoc.de/nachrichten/detail/pharmazie/glaukom-virus-injektion-statt-augentropfenaugenerkrankungen/print.html>. May 20, 2020
- 74 Scottish Medicines Consortium (2012) *Mercaptopurine 20mg/mL Oral Suspension (Xaluprine®)*, Scottish Medicines Consortium
- 75 Scottish Medicines Consortium (2017) *Glycopyrronium 320 Micrograms/mL (Glycopyrronium Bromide 400 Micrograms/mL) Oral Solution (Sialanar®)*, Scottish Medicines Consortium
- 76 Dolinar, R. *et al.* (2019) The non-medical switching of prescription medications. *Postgrad Med* 131, 335–341
- 77 ICH (2018) *Reflection Paper: Further Opportunities for Harmonization of Standards for Generic Drugs*, ICH
- 78 Milmo S. (2019) The European generics and biosimilars sector is working on the creation of a single pathway to accelerate development of and access to medicines. *Pharmaceutical Technology* 43, XXX–YYY
- 79 Demers, D.M. *et al.* (1994) Antimicrobial drug suspensions: a blinded comparison of taste of twelve common pediatric drugs including cefixime, cefpodoxime, cefprozil and loracarbef. *Pediatr. Infect. Dis. J.* 13, 87–89
- 80 Ito, M.K. *et al.* (1999) A matter of taste. *Am. J. Health Syst. Pharm.* 56, 80–81
- 81 Kardas P. *et al.* (2005) [A blinded comparison of palatability of 13 common pediatric antibiotic suspensions]. *Wiad. Lek.* 58, 15–20
- 82 Kim, Y.I. *et al.* (2015) Efficacy and safety of glaucoma patients' switch from a 2% dorzolamide/0.5% timolol fixed-combination brand-name drug to its generic counterpart. *J. Ocul. Pharmacol. Ther.* 31, 335–339
- 83 Matsuo, R. *et al.* (2008) [Bitterness of the mixture of clarithromycin dry syrup and carbocisteine preparation--difference between brand name and generic drugs]. *Yakugaku Zasshi.* 128, 479–485
- 84 Miura, Y. *et al.* (2007) [Sensory evaluation test: odor component analysis and endotoxin content of Krestin and Carbrocin (generic drug) to compare palatability]. *Gan To Kagaku Ryoho.* 34, 1259–1263
- 85 Uestuener, P. *et al.* (2014) Taste acceptability of pulverized brand-name and generic drugs containing amlodipine or candesartan. *Int. J. Pharm.* 468, 196–198
- 86 Figueiras, M.J. *et al.* (2009) Assessing lay beliefs about generic medicines: development of the generic medicines scale. *Psychol. Health Med.* 14, 311–321

**Commented [LM7]:** For AQF: please note that personal communications should be moved to the main text in the form 'e.g. 'J. Smith, pers. commun. 2020'. Please either replace or remove these references and indicate clearly the edits required. Please also confirm that you have permission to cite these personal communications.

**Commented [LM8]:** For AQF: please provide volume and page range.

**Commented [LM9]:** For AQF: it was not possible to verify this reference. Please check that the web address is correct. Please provide an alternative reference if this is no longer available.

**Commented [LM10]:** For AQF: please provide page range.

Table 1. Title

Refs	Medication	Population	Method	Key findings
<b>Cohort study</b>				
[47]	Branded products and authorized generics (same active ingredients, appearance, and excipients as from branded product) or generic drug products (same active ingredients as branded product but might differ in appearance and excipients) for one of study drugs: alendronate tablets, amlodipine tablets, amlodipine benazepril capsules, calcitonin salmon nasal spray, escitalopram tablets, glipizide extended-release tablets, quinapril tablets, and sertraline tablets	94 909 patients switched to authorized generic or generic drug products and 116 017 product	Switchbacks to branded drug to product in year after their switch to authorized generic or generic drug products	Switching from branded to authorized generic drug products associated with lower switchback rates compared with switching from branded to generic drug products
<b>Device evaluation</b>				
[40]	Acetaminophen (Temptra syrup) delivered by Medibottle or with oral syringe	Rx 30 healthy infants, aged 2–14 months, receiving routine vaccinations	Effectiveness based on percentage of infants receiving intended dose. Infant acceptance scored using validated medication acceptance scale (MAS) (MAS)	Significantly more infants received 100% of intended dose with Rx medibottle (93.3%) than with oral syringe (56.7%, $P=0.0074$ ). Infants had significantly higher mean MAS score when using Rx medibottle ( $8.3\pm 1.8$ versus $7.3\pm 1.7$ , $P=0.002$ ). Significantly higher percentage had ideal MAS scores of 9 or above with Rx medibottle (73%) compared with oral syringe (17%, $P=0.0001$ )
<b>Drug evaluation</b>				
[39]	Two penicillin suspensions	Children 3–10 years with otitis media	Child's spontaneous judgment and parent's judgment of acceptability	No differences in taste scores between two suspensions
[21]	Oral liquid pharmaceutical products	Older patients	Explorations performed using CAST (ClinSearch Acceptability Score Test®)	Oral liquid pharmaceutical products are suboptimal alternative to solid oral dosage forms in patients with swallowing disorders. Palatability remains crucial in older populations, especially women
[29]	Three antibiotic syrups, suspensions, and oral solutions most often prescribed to children in France: amoxicillin–clavulanic acid (princeps and generics), amoxicillin (princeps and generics) and cefpodoxime proxetil (princeps as no generics available)	953 children from 0.5 months to 14 years whom a pediatrician had prescribed an antibiotic in form of syrup, suspension, or oral solution	Taste assessment based on representations of five facial expressions	Differences in palatability and acceptability between amoxicillin–clavulanic acid reference products and some generics. Such differences did not appear between amoxicillin reference products and amoxicillin generics
[79] <sup>a</sup>	12 antimicrobial suspensions (Lorabid, Keflex, Suprax, Cefzil, Augmentin, Vantin, Ceclor, Sulfatrim, Pediazole, Dynapen, V-Cillin-K, and Veetids) and two penicillin VK suspensions	Pediatric	Smell, texture, taste, aftertaste, and overall acceptance	No difference overall detected between the two penicillin VK suspensions evaluated
[10]	Brand and generic antibiotic suspensions of erythromycin sulfisoxazole, and sulfamethoxazole approved in USA	Children 3–14 years with clinical indication	Patient's verbal response and facial hedonic scale to rate taste, aftertaste, and parent's rating of ease of administering medication	For erythromycin-sulfisoxazole, no significant differences between generic products and innovator in terms of taste and compliance. For trimethoprim-sulfamethoxazole, innovator tasted better than generic product, but with no difference in compliance

**Commented [LM11]:** For AQF: please note that this table has been modified to make it as succinct as possible (e.g., reference titles moved to reference list). Please check each entry as some appear to have information missing.

**Commented [LM12]:** For AQF: please provide a brief title to accompany Table 1.



- [36] Tulobuterol Dry Syrup in original form and two generic forms 25 healthy well-trained human volunteers with average age of 23 years Gustatory sensation tests, taste and smell sensors, and physicochemical measurements Differences in preparations caused by variations in manufacturing and specifications, such as types of additive and their content and coating property methods used
- [80]<sup>b</sup> Two bile acid sequestrants mixtures: Prevalite (generic) and Questran Light (innovator) Ten tasters from pharmacy administrative personnel at health system Informal taste test: five-point scale for taste, texture, and smell Tasters preferred Questran Light over Prevalite for taste, smell, and overall quality
- [27] Two pivampicillin mixtures Children 1–7 years with infection Child's evaluation of parent's evaluation of taste or peppermint taste administration Better acceptability and easier administration with banana than cocoa-
- [81]<sup>c</sup> 13 antibiotic suspensions 25 volunteers Appearance, smell, texture, taste, and aftertaste compared with amoxicillin (Amotaks) as reference drug In overall score, different preparations of same substance obtained similar scores, statistically nondifferent, with one exception for clarithromycin, in which Klacid was characterized by better palatability
- [34] Two prednisolone liquid preparations Children 2–10 years with acute asthma exacerbation Five-point facial hedonic scale (>5 years of age) Better taste score for Orapred than for generic prednisolone
- [82]<sup>d</sup> Two eye drops: brand-name and generic of dorzolamide/0.5% timolol fixed-combination (DTFC) 112 patients with mean age of ≈ 63 years Questionnaire on discomfort and symptoms for use of eye drops Higher incidences of bitter taste and blurring with Cosopt (brand-name), and of headache with Batidor (generic), but no significant differences ( $P > 0.05$ ) noted. No significant difference in discomfort score between the two drugs
- [83]<sup>f</sup> Mixture of clarithromycin dry syrup and carbocisteine preparation: brand name and generic Six healthy male volunteers Human gustatory sensation tests Extent of bitterness of mixture of clarithromycin dry syrup and carbocisteine preparation varied significantly among generic formulations
- [84]<sup>f</sup> Krestin and Carbocrin (generic drugs) No information Sensory evaluation test. Questions were asked about odor, taste, feeling on tongue, and overall evaluation, to find out which was easier to swallow Krestin was significantly superior to Carbocrin, showing clear difference in palatability between the two products
- [6] Two original formulations of memantine: tablets and oral solution Older patients Evaluations scored with acceptability reference framework (CAST and rodent Taste Aversion (BATA) model tested aversiveness) with original oral solution of memantine driven by palatability. According to CAST, coated tablet, which created a physical barrier between memantine hydrochloride and taste buds, was well accepted in older population, which was not the case for the oral solution. BATA model objectively confirmed aversiveness of this formulation. Exploring sex differences, consistent findings from both human studies and animal models highlighted a higher sensitivity of females to unpalatable oral formulation as proposed cause for suboptimal acceptability
- [9] Generic products of cephalexin, erythromycin ethyl succinate sulfisoxazole, penicillin V, and trimethoprim sulfamethoxazole approved in USA 42 adult volunteers Subjects tasted one class of brand and generic antibiotics and rated them according to smell, texture, taste, and aftertaste At least one generic preparation of cephalexin, erythromycin ethyl succinate/sulfisoxazole and penicillin V potassium was rated equal in taste to respective brand-name products. Erythromycin estolate and trimethoprim sulfamethoxazole brand-name suspensions rated significantly higher than other products tested. For cephalexin, penicillin V, and erythromycin ethyl succinate/sulfisoxazole, taste of generic products rated equal to that of innovators. For trimethoprim sulfamethoxazole and erythromycin estolate, taste of innovators rated higher than that of generic products



- [25] Three oral suspensions of bacampicillin. Two penicillin 103 children with upper respiratory tract infections, judgment and hedonic scale of B formulations were ranked in between assumed to be pleasant to taste and formulation U 3–12-years old, with signs facial expressions assumed to have unacceptable taste on basis of clinical of bacterial infection for which treatment with penicillin was indicated
- [28] Two flavors of ondansetron syrup Children 3–12 years undergoing chemotherapy Panel of five faces; asked Preference for strawberry formulation
- [37] Nine formulations of famotidine orally disintegrating tablets (ODTs): the original manufacturer's formulation and eight generic versions 11 well-trained volunteers Human gustatory sensation tests, comparison of release profiles, and taste sensor measurements Bitterness intensities of generic products A, E, and F showed significantly stronger bitterness compared with original product; no significant differences in sweetness scores between original and generic products, which were significantly less sweet than original product. Among the eight generic products tested, variance in sweetness intensity not large; large variances in intensity of bitterness, with some generic products being significantly more bitter than original product. Some generic products showed similar bitterness level as original product
- [38] Ten formulations of amlodipine ODTs: original Six healthy female subjects, 26±9-years old Human gustatory sensation testing (bitterness intensity, disintegration time in mouth, palatability in mouth and after splitting out), disintegration/dissolution testing, and evaluation of bitterness intensity using taste sensor Factors most affecting palatability of amlodipine ODTs were disintegration and taste
- [85]<sup>f</sup> Brand-name and most prescribed generic medicines containing either amlodipine, a popular calcium-channel blocker with a bitter taste, or candesartan, a recognized angiotensin type 2 receptor antagonist Healthy healthcare workers: 19 nurses and 12 physicians 25–49-years old Smiley-face scale depicting four degrees of pleasure Pulverized brand-names and generics containing either amlodipine or candesartan did not differ with respect to taste acceptability
- [26] Containing amlodipine, a popular calcium-channel blocker 76 patients, 0.2–8.1-years old Time required by nurse to give drug to child was recorded; score of acceptance was given by nurse Significant time difference between erythromycin Brand 1 and 2; no significant difference between two penicillin products
- [35] With bitter taste, or candesartan, a recognized - angiotensin type 2 receptor antagonist Electronic tongue measurements Results clearly showed that formulations could be distinguished according to their excipients and manufacturer
- [30] Receptor antagonist 1482 patients <6 years Taste assessment based on representations of five facial expressions Confirmed disparity in terms of acceptability among the different antibiotics prescribed for children even for same drug, warranting evaluation for marketing of future generic pediatric oral drug suspensions
- Guidance**
- [41] Generic tablets and capsules – – Differences in physical characteristics (e.g., size and shape of tablet or capsule) can affect patient compliance and acceptability of medication regimens or could lead to medication errors
- Review**
- [33] Antibiotics Pediatric Reviewing clinical evidence around palatability of antibiotics Certain drugs (e.g., flucloxacillin) are so unpalatable that they should not be prescribed as syrups without prior 'taste testing' in an individual child, whereas others (e.g., oral cephalosporins) are well accepted, although are more expensive with a broader antimicrobial spectrum than might be strictly necessary

[31]	Generic antibiotic drugs	-	-	Specific problem of taste and treatment acceptability for pediatric oral antibiotic drugs. It appears necessary to review regulations for marketing authorization of generic antibiotic drugs
[32]	Generic medicines	-	Search on Medline and Embase for original research articles on to innovator in terms of purity ( $N=2$ ), <i>in vitro</i> activity ( $N=3$ ), <i>in vivo</i> efficacy in antibacterial generic products experimental models ( $N=4$ ), clinical efficacy ( $N=2$ ), taste ( $N=2$ ), or published in English or French before July 2013	Of 37 studies, 14 (37.8%) suggested that some generic products are inferior compliance and acceptability in children ( $N=1$ ).
Survey				
[46]	Generic medicines	316	General practitioners Survey from Martinique and Guadeloupe	Main disadvantages reported: 'Patients may be confused by changes in presentation' (47% of questioned practitioners); 'Presentation and dosage form differ between laboratories for the same molecule' (44% of questioned practitioners). Practitioners caught between requirements of health insurance regimes and opposition of numerous users and suggested that patient information provided by health authorities should be improved and that drug composition and packaging should be made uniform. One of simplest solutions to make generics more acceptable to both prescribers and patients could be uniformization of their presentation by delivering exact copies (same active and inactive ingredients) or same generic product to same patient for given originator product
[45]	Generic antihypertensive drugs	22	patients from pharmacies in Oslo who had taken brand antihypertensive products as well as substituted generic products	Focus-group discussions Most reported low drug adherence before and after generic substitution. Differences in name, color, form, or taste caused confusion
<b>Tool development</b>				
[86] <sup>a</sup>	Generic medicines	228	Portuguese pilot study (Stage I); 819 Portuguese main study (Stage II)	Development of generic medicines scale (GMS): Stage I, item generation and pilot study; Stage II, two-factor structure concerning beliefs about generic medicines, comprising two core themes: efficacy and similarity to brand medicines

<sup>a</sup>Not discussed (abstract only; full article not found).

<sup>b</sup>Not discussed (informal taste test).

<sup>c</sup>Not discussed (abstract only; full article in Polish).

<sup>d</sup>Not discussed (ocular formulations in adults).

<sup>e</sup>Not discussed (abstract only, full article in Japanese).

<sup>f</sup>Not discussed (proxy measure).

<sup>g</sup>Not discussed (no focus on drugs).

**Table 2. Do some formal or informal discussions take place regarding the acceptability of generic versus originator medicines?**

Answer	Country	Comment
Yes	Croatia	If generic differs from reference in any characteristics, it would be explained and justified in a medicinal product dossier. The dossier is then assessed by competent authorities during the marketing authorization procedure
	The Netherlands	For pediatric products, age-appropriateness of the formulation will be considered in the assessment of the product (as well as when comparing with the original)
In some cases	Denmark	Generic application does not require evaluation of acceptability; only one application where palatability was tested in adults
	Estonia	Deviations from the originator will be discussed during the assessment of the marketing authorization application
	Greece	Not much detail in email
	Ireland	Considers appropriateness of various forms of medication for certain patient groups. However, they do not have a formal standard operating procedure for this
	Latvia	Issues will usually be discussed in EU member state delegate meetings
	Slovakia	Some discussion regarding acceptability took place ~10 years ago when generic prescription was legalized
	Slovenia	Not really answered in the email. The Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) decides on the acceptability of medicinal products on the basis of a positive risk/benefit ratio, derived from the scientific Assessment Report prepared by the experts on the submitted documentation of the given medicinal product. This also applies for generic medicinal products. In the European Mutual Recognition Procedure (MRP) and Decentralized Procedure (DCP), marketing authorizations are granted on the basis of Assessment Reports prepared by the Reference Member State (RMS)
	UK	Assessment of pediatric medicines would take into account current regulatory guidance, most notably the EMA guideline <i>Pharmaceutical Development of Medicines for Pediatric Use</i> [12]. For adults, there is currently no requirement for generic versions of solid dosage forms to be the same size or shape as the originator. Nonetheless, these aspects might be considered during assessment where required
No	Belgium	
	Iceland	
	Spain	
	Sweden	There is a formal review system after approval of a generic product, which evaluates the suitability of the product to be substituted at the pharmacy level based on certain criteria