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How to Explain Price Gaps between Me-too Drugs?

A 2001-2009 Panel-data Analysis

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Although dating back to the 1960's, the debate surrounding me-too drugs is still valid today given the continuing proliferation of these drugs on the market. Similar to the originator drug in a given therapeutic class in terms of chemical structure and mechanism of action, some consider these drugs to be therapeutically equivalent due to a 'class effect', whereas others justify their presence on the market in terms of innovative content, even minor. If me-too drugs are effectively close to the originator, then theoretically there should be no difference in price between the first-in-class and follow-on drugs given that one of the regulator's primary objectives is to reward innovation. How do things actually stand?

The aim of this study is to explain price differences between the originator drug and successive follow-on drugs in a given therapeutic class over the period between 2001 and 2009. With an average price gap of 59% per drug group, our results reveal significant price differences between the originator and successive follow-on drugs. In conformity with French drug pricing regulations, one of the main factors determining price gap is therapeutic innovation. Yet, the size of the price gap resulting from even minimal innovation (+ 16% for one degree of innovation, + 43 % for two degrees or more) raises questions. Furthermore, monotonic pricing significantly widens the price gap proving inequitable for patients whose health status justifies stronger doses. In the light of foreign experience, the question of controlling me-too drugs to be included or excluded from the reimbursed drugs basket also deserves being raised.

The proliferation of me-to drugs on the market, also referred to as follow-ons in international literature, has been the subject of numerous debates since the 1960's regarding their interest, therapeutic equivalence and price (Goozner, 2004).

Me-too drugs are new entrants to an existing therapeutic class with very similar chemical structures, mechanisms of action, adverse side effects and therapeutic indications. They are the product of incremental innovation, minor modifications to the chemical structure of the original molecule. These innovations supposedly improve a drug's efficacy, safety or tolerance and claim to significantly improve the treatment of patients (Morgan *et al.* 2005).

Me-too drug advocates and opponents disagree as to the need for their existence. For the former, the incremental innovations[1] from which a drug benefits makes it possible to adapt treatment according to tolerance levels and adverse side-effects (Morgan *et al.*, 2005). Furthermore, advo-

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[1] The use of the term 'innovation' here is no doubt excessive in that it refers to a minor therapeutic improvement as opposed to radical innovation implying the discovery of a new therapeutic class.

E1

Therapeutic equivalence between a me-too drug and the originator drug

Therapeutic equivalence is based on a 'class effect' and supposes that drugs with a similar chemical structure and mechanism of action also have similar clinical effects when administered at equivalent doses for a given indication (McAlister *et al.*, 1999). However, this 'class effect' is occasionally contested and some studies emphasise that same-class drugs may differ in terms of indications, metabolism, adverse side-effects or method of administration giving rise to numerous controversies regarding the equivalence or interchangeability of these molecules (Morgan *et al.*, 2005) .

If one refers to the industrial economics theory (Laffont and Tirole, 1993), it may be in the interest of pharmaceutical laboratories to multiply the wording used to define indications in order to introduce artificial differentiations with existing products on the market in the aim of negotiating higher prices. In practice, distinctions such as 'infectious otitis' and 'acute otitis media' are not considered to be different medical entities by prescribing clinicians whose practices are currently determined by scientific recommendations. In the case of antibiotics, for example, the development of bacterial resistance is more likely to condition the use of antibiotics than the indications that had initially justified their authorization on the drugs market.

Another example in favour of therapeutic equivalence is the fact that numerous hospital pharmacies restrict their drug supply to a limited number of drugs in a same therapeutic class. A study has shown that only 19% of French university hospitals retain Fluvastatine in their supply of statins, and other hospitals replace it with an alternative statin (Gallini *et al.*, 2011). In France, financial incentives to encourage physicians to prescribe generic drugs within the framework of the pay for performance contract (CAPI)[1], is another example. These incentives implicitly convey the message that most of the time generics can be substituted for non-generic drugs in the same therapeutic class. Finally, the reference price groups used in Germany that broadly encompass both generic and patented drugs (jumbo class) show that the regulator considers these drugs to be therapeutically equivalent (Giuliani *et al.*, 1998).

[1] The CAPI are individual contracts signed between the National Public Health insurance and private practice physicians who become eligible for additional remuneration on condition they satisfy set clinical objectives on three separate fronts: prevention (anti-flu vaccine administered to at least 75% of patients aged over 60, breast cancer screening tests in 80% of patients aged between 50 and 74…), chronic diseases (better application of good practice recommendations for diabetic patients, improved monitoring of patients suffering from hypertension…) and drugs prescriptions (the prescription of generic drugs is encouraged for several drug classes).

cates consider that this form of innovation is essential to pharmaceutical progress and to stimulate research within the therapeutic class concerned. Opponents argue that these molecules bring little or no therapeutic improvements, increase R&D and marketing costs, increase prices (Hollis, 2004), and consider that their sole aim is to counter the arrival of generic entrants on the market (Goozner, 2004; Hollis, 2004). They further argue that the resulting market competition thereby introduced has no actual impact on prices (Morgan *et al.*, 2005).

The majority of authors on the subject consider these drugs to be very close to the originator due to the 'class effect'. This is based on the supposition that drugs with a similar chemical structure and mechanism of action also have similar clinical effects when administered in equivalent doses for a given indication (McAlister *et al.*, 1999). Although the class effect is contested by certain studies and the pharmaceutical industry itself, in an attempt to artificially maintain the idea that each new market entrant is highly differentiated, the therapeutic equivalence of me-too drugs is nevertheless often confirmed in practice (insert 1).

If me-too drugs are therapeutically equivalent and therefore devoid of innovation, and if the regulator's primary objective is to reward therapeutic innovation, then theoretically there should be no difference in successive me-too drug prices (Furberg *et al.*, 1999). If, on the contrary me-too drugs contain real innovation, a difference in price is logical and the price gap between two me-too drugs would in part reflect the weight of innovation (Jena *et al.*, 2009).

In this study, we examine the price gap between the first-in-class drug and follow-on drugs within 31 groups from 2001 to 2009 and analyse explanatory factors.

When a new me-too drug enters the market, its price is fixed within the framework of negotiations between the Healthcare Product Pricing Committee (CEPS) and the manufacturing laboratory according to its degree of therapeutic innovation, measured in terms of therapeutic benefit (ASMR indicator)*, expected sales volume and the price of existing drugs in the therapeutic class. The fixed price may, however, vary during the course of a therapeutic class's life cycle with the arrival of generic equivalents, a new molecule or downward price revisions decided by the regulator. At a given date, the price gap between a new entrant me-too drug and the first-in-class can thus be explained both by the initial price fixing procedure and subsequent events. These events can moreover either have an impact on the price of the first-in-class drug, the price of all follow-on drugs or even the price of all prescription drugs in the class.

Significant price gaps between certain me-too drugs with an average gap of 59% per group

The study concerns 259 drugs divided into 31 groups. Each group is comprised of me-too drugs with similar molecular structures thus ensuring homogeneous groups in terms of therapeutic effect and mechanisms of action. To ensure maximum comparability between the drugs in a same group (insert 2), a selection of comparable therapeutic indications was added to the first stage filtering process by chemical structure. This selection was carried out by a clinical practitioner and validated by the physician overseeing the study and an independent hospital pharmacologist. The study also necessitated creating a database combining information from several sources (Sources and method insert).

In 2009, the average price gap between a me-too drug and the first-in-class within a given group was 59% (graph). This average nevertheless conceals disparities within certain drug groups. In the majority of groups the price gap is fairly narrow and negative for five of the groups studied: the antidiabetic alpha-glucosidase inhibitors, the antihistamines, a group of beta blocking agents, the imipramines and tetracyclines. A few groups on the contrary reveal higher price gaps such as the hypoglycemic sulfonylureas and angiotensin-

* The words or terms followed by an asterisk are defined in the glossary on page 5 of this issue.

converting enzyme inhibitors for high blood pressure and ischemic heart disease. In each of these groups, the average price gap between the first-in-class and me-too drugs is extremely high (437% on average for the antidiabetic sulfonylureas reaching a maximum of 940% difference in daily treatment costs (DTC) between the first-in-class at 5 Eurocents DTC and the most costly me-too drug at 52 Eurocents DTC). These two classes are representative of older therapeutic classes within which new generation molecules have been introduced through time explaining higher prices for more recent entrants.

Factors having the greatest impact on me-too drug price gaps

Innovation explains a major part of price differences

In conformity with French drug pricing regulation, innovation explains a major part of the price differences between me-too drugs. The higher the cumulative therapeutic improvement in a group, the wider the price gap between same-class follow-on drugs tends to become. Increasing cumulative innovation in a therapeutic class tends to be accompanied by a progressive widening of the price gap: from 16% between the me-too drug and the first-in-class in cases where cumulative innovation corresponds to one degree of ASMR* (cumulative innovation equal to 1) to 43% for higher levels. The results observed are consistent with the regulator's principle of fixing a higher price for drugs presenting therapeutic innovation. Having said that, the proportionality between therapeutic improvement and the approved price margin can, on occasions, be questioned as the me-too drugs observed here are not the result of major innovation. A low level of cumulative innovation in a class is thus occasionally rewarded by a high price differential. This is the case for the antidiabetic sulfonylurea class for which cumulative innovation is equal to 1 (the lowest level of innovation) for a price difference of up to 437% compared to the first-in-class. Furthermore, in certain classes, significant price gaps coexist with no therapeutic improvement: for example in the exclusive angiotensin-converting enzyme inhibitors (AEC) for high blood pressure and ischemic heart disease class in which the cumulative therapeutic improvement is null for price differentials of up to 394%.

Monotonic pricing widens the price gap

For prescription drugs available in several doses, two pricing options can be envisaged. The first sets a flat price whatever the dosage and the other a price proportional to dosage (monotonic pricing). The higher price difference for drugs priced according to dosage (+32% in comparison with flat priced drugs whatever the dosage), raises questions about this widespread practice. In effect, the price of 86% of me-too drugs available in several dosages included in this study varies according to dosage, which is difficult to justify in that marginal production costs of a new dosage are in general minimal. This pricing practice, governed by an industrial strategy based on price discrimination, contributes to increase the price gap between me-too drugs and is unfair to patients whose health status justifies stronger dosages (Jönnson, 2001).

Context

This article fits within the framework of research on prescription drug regulation carried out by IRDES. Following a substantial revision of the methodology used to analyse price differences between me-too drugs in a same therapeutic class, it cancels and replaces the Issues in Health Economics n° 151, published in February 2010. It is based on an IRDES working paper entitled 'The determinants of Price Discrepancies between Me-too drugs and the First-in-class drug in the same therapeutic Class' (Sorasith *et al.*, 2012), submitted to the Health Economics journal for publication.

E2

The study's methodological options

The first option involved the creation of comparable groups of drugs. Drug price comparisons required selecting me-too drugs with identical indications. The diversity of the wording used to describe indications had to be interpreted and assembled into more generic groups to constitute homogeneous, clinically pertinent groups based on the main therapeutic indications for a same class of drugs. For example, antidepressants with anxiolytic properties: indications with the words 'generalised anxiety disorder', 'panic attacks', 'social anxiety disorder' and 'post-traumatic stress syndrome' were grouped together under the generic indication 'anxiety disorders'. Possible errors in interpretation were reduced to a minimum as drugs presenting the slightest doubt as to the equivalence of their indications were excluded.

This selection process led to a significant loss in the number of drugs included in the study. The final sample was thus made up of 259 drugs divided into 31 groups of therapeutically equivalent drugs. Some groups contained a very limited number of drugs and were therefore unable to represent all the modalities of the independent variable retained. Thus in certain groups containing a low number of drugs, all the drugs in the group presented the same level of innovation. Yet, determining the weight of cumulative innovation in price discrepancies depends on the model's ability to detect a sufficient number of groups containing a sufficiently large number of drugs with different innovation levels.

A second option was this time related to the available time series. A panel data analysis covering the years 2001 to 2009 imposed itself due to the unavailability of certain data prior to 2001. In addition, as the ASMR did not exist prior to 1992, the cumulative therapeutic innovation variable could not be calculated for older drugs which may have created problems of insufficient statistical power regarding cumulated ASMR at levels higher than 1 because of low numbers.

Finally, one of the study's limitations comes from the fact that exogenous effects related to regulatory reforms means that the characteristics of pharmaceutical firms or the effects of pharmaceutical industry strategies were not captured by the independent variables included in the model. For example, the Transparency Commission charged with evaluating improvements in medical services rendered (ASMR), was revised three times during the course of the period being studied, and it is impossible to assert whether these changes altered the ASMR allocation criteria. Furthermore, certain health system observers consider that at the beginning of the 1990's a pharmaceutical laboratory's nationality or size, and thus the employment opportunities generated in France, were also susceptible of interfering with pricing or reimbursement policies. In its current annual reports, the CEPS claims it no longer practices price differentiation according to a laboratory's nationality in conformity with the European directive stipulating that there should be transparency in the price setting procedures, thereby prohibiting such practices (CEPS, 2010).

For further information: Sorasith *et al.* (2012).

The reference pricing scheme (TFR) applied to a me-too drug or first-in-class further widens the price gap

As soon as a me-too drug falls under the reference pricing scheme (TFR)*, the laboratory is incited to align its price to that of the same-class generic drug. When the first-in-class drug is subject to this reference price (TFR) its price is thus subject to a downward revision which significantly increases the price gap between the originator and follow-on drugs. Thus, when the first-in-class drug is under TFR, the price differentials within the group increase by 75% compared with groups in which the first-in-class is not subject to TFR. Inversely, when the me-too drug is subject to TFR it also leads to a downward price revision but automatically results in narrowing the price gap between the me-too drug and the first-in-class (-36 %).

Certain factors have little or no effect on price differentials

Me-too drug's market share has little impact on price gaps

Me-too drug's market share in terms of volume is used in this study as a proxy for expected or actual sales volumes taken into account in setting the price of low innovation drugs (CEPS, 2010). High sales volumes should theoretically result in a lower negotiated price. Our results, however, indicate the contrary: we observe that drugs benefitting from a higher market share also benefit from higher prices even if the effect is relatively slight: a 1% increase in market share increases the price gap by 1%. The hypothesis according to which laboratories strategically under-estimate their expected sales volumes during price negotiations with the regulator in order to obtain a higher price cannot be totally excluded, even if they expose themselves to the risk of financial penalties within the framework of the negotiated agreement policy as practiced in France (Sorasith et *al.*, 2012).

The arrival of generic entrants has no effect on price differentials

The entry of a me-too generic on the market has no impact on the price gap between the me-too drug and the first-in-class even though regulation stipulate a 12.5% price reduction on all patented me-too drugs eighteen months after the arrival of its generic equivalent. It is possible, however, that the downward price revisions on first-in-class drugs that occurred between 2001 and 2009 invalidated the narrowed price gap thereby masking me-too drug-price reductions in a given class.

The size of certain price gaps raises questions

Globally, the price gaps between me-too drugs revealed in this study are consistent with current regulations. Within a given class of drugs, even minimal innovation increases the price gap between the first-in-class and follow-on drugs. Subjecting a me-too generic to a reference price (TFR) on the contrary significantly reduces price differences within the group whereas subjecting the first-in-class to TFR, thereby lowering its price, significantly increases them. Other results are more difficult to interpret as they are probably the result of a combination of contradictory effects such as market share that tends to widen the price gap.

The size of the price gap associated with innovation, even minimal, (+16% for one degree of innovation, +43% for two or more) is questionable. The first concerns the very definition of innovation. Certain classes of drugs selected here, virtually identical in terms of chemical structure and therapeutic indications, benefit from a high level of cumulative innovation. Can these innovations, that essentially concern a drug's galenic form rather than its chemical structure or therapeutic indications, be considered as real innovations or as improved imitations of the original molecule? Does it have any effect on these drugs' therapeutic equivalence, the hypothesis on which this study is based?

The second question arises as soon as therapeutic equivalence is evoked and the drugs in question are considered interchangeable. The observed price differentials then questions one of the aims of price regulation that supposedly encourages real innovation, thereby discouraging imitation. This observation is not specific to France and is on the contrary shared by other countries although it is impossible for us to compare their respective importance (Jena *et al.*, 2009). The regulator's position in the face of these price gaps differs according to country: the introduction of reference prices for entire therapeutic classes as practiced in Germany or Hungary for example, eliminates cost differences for the public financers. In these

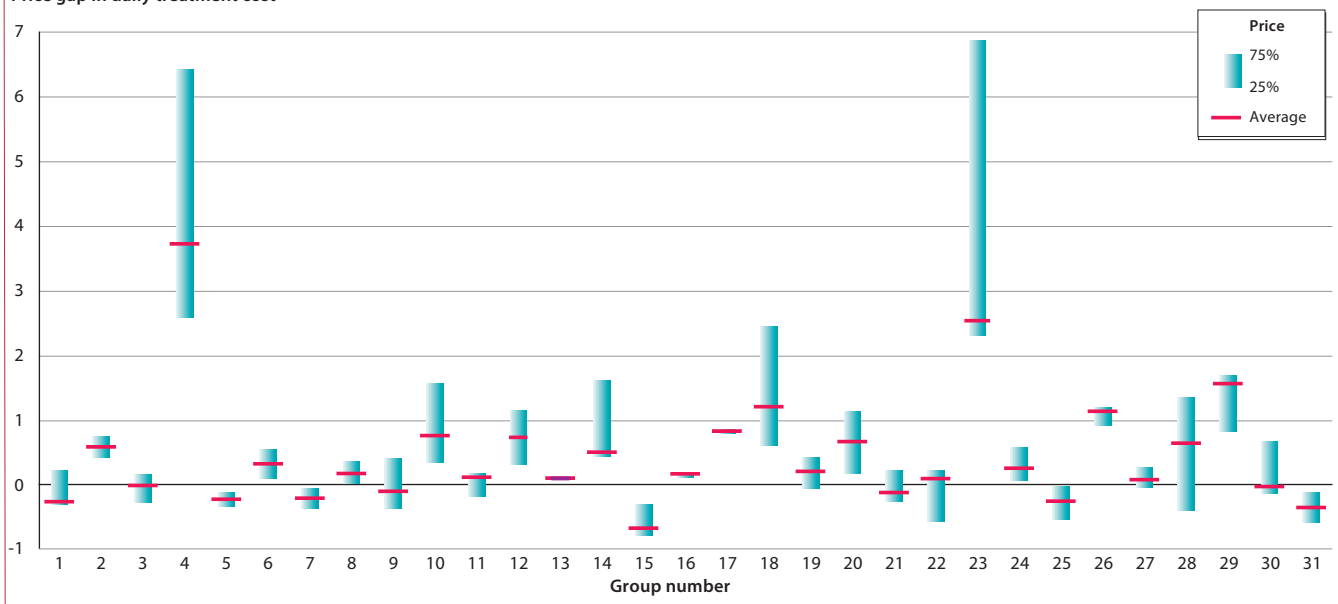
Sources et method

To carry out the study, several sources of information were brought together in a single database: the drug characteristics (date of entry on the market and therapeutic improvement index [ASMR] taken from the Thesorimed database), prices over the period 2001-2009 (Sempex), posology in order to calculate daily treatment costs (IMS Health permanent survey on medical prescriptions), market share (National Health Insurance Medic'am) and generic/originator*status (AFSSAPS List of Generic Drugs). The drugs retained in the database are orally administered, available on prescription, reimbursed by the National Public Health Insurance and belong to therapeutic classes including me-too drugs. Only drugs composed of a single active principle were retained. As several filters were applied to the data base, our final sample comprised 259 drugs distributed between 31 same-class drug groups.

The econometric model is based on a random effects model in which the random effect occurs at group level rather than individual level (the drug) in order to better take into account a drug's hierarchical structure within a group in the analysis of price gap variability (Raudenbush and Bryk, 2002). Price discrepancy variance is thus decomposed to distinguish between variability due to the individual characteristics of the drug and the characteristics of the group. This model has the advantage of obtaining more precise parameters and permits the introduction of group-specific variables to explain price gap variability between the groups. For further information on the methodology, see the corresponding working paper (Sorasith *et al.*, 2012).

G

Price gap in daily treatment cost (DTC) in 2009 in relation to the first-in-class, per group



Group number and title *(number of drugs)*			
1 antiadrenergic agents, centrally acting	6	17 2nd generation cephalosporines without urological indications	3
2 Anticholinergic agents	3	18 Corticoids for systemic use, glucocorticoids non associated	6
3 Antidepressants with simultaneous anxiolytic effect	10	19 Vasodilators used in cardiac diseases, organic nitrates	5
4 Antidiabetics, urea derivatives	28	20 Fibrates	12
5 Antidiabetics, alphaglucosidase inhibitors	3	21 ACE* inhibitors exclusive for high blood pressure (HBP)	7
6 Antidiabetics, thiazolidinediones	3	22 ACE* inhibitors exclusive for heart failure and HBP	14
7 Systemic antihistamines, piperazine derivatives	3	23 ACE* inhibitors exclusive for ischemic heart disease and HBP	7
8 Other Systemic antihistamines	10	24 Polyvalent ACE* inhibitors	15
9 Antimigraine drugs	17	25 Imipramines	5
10 Anxiolytic drugs	18	26 Selective calcium channel blockers with predominant vascular effects	32
11 Other antimigraine drugs	4	27 Drugs used in benign prostrate hypertrophy	9
12 Oral selective Beta 2 adrenoreceptor agonists	3	28 Strong opioids	10
13 Beta blocking agents, selective for heart failure	2	29 Simple oxicams	7
14 Beta blocking agents, non-selective, polyvalent	6	30 Statins	29
15 Quasi polyvalent beta-blocking agent	6	31 Tetracyclines	3
16 1st generation cephalosporines	4	* ACE: conversion enzyme inhibitors	

Reading guide: The graph makes it possible to observe the distribution and average price gaps for each of the 31 therapeutic classes (or groups). Each group is given a boxplot position providing two types of information: its position in relation to the origin and its range. The greater the distance from the origin, the higher the average price gap between the different drugs in the group and the first-in-class. Furthermore, a wider ranging boxplot reflects greater price gap dispersion within the group. Groups 4 and 23, for example, with wide boxes at a considerable distance from the origin are both distinguished by high price disparities within the group and high average price gaps between new entrants and the first-in-class.

Sources: Sempex (price) and EPPM d'IMS Health (posology). **Calculations:** Irdes.

For data downloads: www.irdes.fr/Donnees/Qes178_CommentExpliquerEcartsPrixMedicamentsSimilaires.xls

Definitions

Therapeutic improvement index (ASMR) used in the price-fixing procedure for reimbursable drugs is measured according to five levels: from I, 'major improvement' to IV, 'minor improvement' with level V signifying 'no therapeutic improvement'. For the most innovative drugs the 'price fixing' procedure aligns the price of the drug to its current price in four European countries (Germany, the United Kingdom, Italy and Spain). For low innovation drugs, the price is fixed according to ASMR level, expected sales volumes and the price of existing drugs in the therapeutic class (CEPS, 2010). In addition, a drug presenting no therapeutic improvement will not be admitted for reimbursement unless its daily treatment cost is lower than comparable drugs in the class.

A drug's galenic form refers to its specific combination of active ingredients and excipients to create a final medicinal product. It refers to the drug's final form as it will be used by the patient: tablets, capsules, sachets, oral liquid formulations or injectable suspensions, etc.

The originator drug (or first-in-class), as opposed to the generic drug refers to the marketed brand-name drug protected by a twenty-year drug patent.

The Responsible Payment Tariff (TFR), a reference tariff introduced by the 2003 Law on Social Security Funding (LFSS) and fixed by the Healthcare Product Pricing Committee (CEPS), constitutes the maximum reimbursement level for a given drug (generic or originator) in a given generic group. When a generic group is subject to TFR, the price of the corresponding originator drug tends to be aligned with the reference price.

countries, the regulator considers national health reimbursements for higher priced imitation drugs, or drugs containing limited therapeutic improvements as totally unjustified. The pharmaceutical firm however remains free to fix a higher price for the part of innovation which will be borne in this case by the patient. In other countries such as France, these price differences are borne by the financer who thus accepts to reward even minor therapeutic improvements (Godman *et al.*, 2010).

This study finally leads us to question the entry of new me-too drugs on the reimbursable drugs market. With the proliferation of me-too drugs, other countries such as New Zealand have imposed drastic restrictions: new me-too drugs are only admitted for reimbursement if they are systematically cheaper than the reimbursed equivalents. In France, the question of whether there should be more active management regarding the inflow and outflow of drugs in the reimbursed drugs basket has not yet been broached but certain observers demand price level convergence between me-too drugs and generics in the same therapeutic class. ♦

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