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REVIEW ARTICLE

Biosimilars in Rheumatic Diseases: Regulatory Guidelines, Efficacy and Safety Implications in Saudi Arabia

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Abstract:

Background:

Treatment with biologic drugs has enabled many patients with inflammatory rheumatic disease to achieve disease control. In some areas of the world, limited access to biologic therapies has created a demand for lower cost options such as biosimilars, which are highly similar, but not identical to originator biologics. The safe use of biosimilars requires a scientifically rigorous review process for their approval, and guidelines that aid rheumatologists in their use.

Discussion:

In Saudi Arabia, there are no national or regional guidelines to assist rheumatologists in the proper use of biosimilars in clinical practice, and this may potentially affect the quality of patient care. In this review, we discuss the importance of developing a guidance and the need for healthcare professionals and patients to receive education about biosimilars. We discuss the unique requirements for biosimilar approval, and the differences between biosimilars, originator biologics, and generics. We review important considerations related to biosimilar use, such as switching from originator biologics to biosimilars, switching between different biosimilars, interchangeability, automatic substitution, naming, and pharmacovigilance. We also provide recommendations based on the authors' expert opinions as rheumatologists to help ensure the appropriate use of biosimilars in Saudi Arabia.

Conclusion:

The approval and use of biosimilars must be supported by scientifically sound evidence. Guidelines for the use of biosimilars are needed in Saudi Arabia to aid rheumatologists in making clinical decisions. Additionally, educational resources should be provided to healthcare professionals and patients.

Keywords: Biologics, Biosimilars, Guidelines, Rheumatology, Saudi Arabia, Switch.

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1. INTRODUCTION

The introduction of biologic drugs for the management of patients with inflammatory rheumatic diseases has revolutionized treatment and enabled numerous patients to achieve disease control with an acceptable safety profile [1]. In some areas of the world, limited accessibility to biologics has created a demand for lower cost biotherapeutic options such as biosimilars, to increase access to care [2]. For biosimilars to be used safely and effectively, scientifically rigorous requirements for the review and approval of potential biosimilars are needed [3], as well as guidelines for incorporating biosimilars into clinical practice. Additionally, programs to educate clinicians and patients are necessary [4, 5].

A task force consisting of rheumatologists and other specialists, as well as patients and a regulatory expert, developed expert recommendations on the use of biosimilars in rheumatology [6]. The recommendations include five overarching principles; in summary they are: patients and physicians should make treatment decisions together, decisions about treatment should be appropriate for the particular healthcare environment, a biosimilar approved based on scientific rigor is highly similar to the reference product, healthcare professionals and patients should be educated about biosimilars, and pharmacovigilance of all biologics should be reliable and consistent [6]. Although these principles were widely agreed upon by the experts, the level of published evidence was low [6].

In Saudi Arabia, there are national regulations for biosimilar quality considerations and registration requirements [7, 8]. However, there are no local or regional guidelines for the management of Rheumatoid Arthritis (RA) [4, 9, 10]; thus, there is no guidance on the use of biosimilars in clinical practice. In this review, we discuss the need for additional resources and education for healthcare professionals in Saudi Arabia, to assist in clinical decision-making when prescribing biologic drugs. The objectives are to: (1) explain the differences between originator biologics, biosimilars, intended copies, and generics; (2) discuss important biosimilar topics, such as switching from originator biologics to biosimilars, switching between different biosimilars, interchangeability, automatic substitution, naming, and pharmacovigilance; and (3) offer recommendations to healthcare providers for the safe and appropriate use of biosimilars in clinical practice in Saudi Arabia, based on the authors' expert opinions as rheumatologists.

2. DIFFERENCES BETWEEN BIOSIMILARS, ORIGINATOR BIOLOGICS AND GENERICS

2.1. Biosimilar Definition

The World Health Organization (WHO) defines a biosimilar as a product that has similar quality, safety, and efficacy to an approved biologic product [11]. The Committee for Medicinal Products for Human Use within the European Medicines Agency (EMA) defines a biosimilar as a biologic drug containing the active substance of an approved originator biologic to which similarity has been demonstrated following a thorough comparison of the two products [12]. As indicated by these definitions, a biosimilar is required to be highly similar, but not identical to the reference originator biologic [13].

2.2. Manufacturing Biosimilars

Biologic drugs are proteins; therefore, they are large molecules [11, 14]. The production of biologics is complex and generated from living organisms or cells [13, 15]. Due to the manufacturing complexities, and the potential for post-translational modifications (*e.g.*, glycosylation, oxidation, methylation), which are dependent on the producing cells and their growth conditions, it is almost impossible to create a biologic that is identical to the originator [3, 15]. In addition, manufacturers of prospective biosimilars must create the entire process *de novo*, since manufacturing processes are proprietary [15, 16]. Even minor differences in the manufacturing procedure can lead to changes in the structure and thus the biological activity of the final product. This may alter its safety, efficacy, and immunogenicity profile [3].

In contrast, small molecule drugs are chemically synthesized and have relatively simple chemical structures compared to biologics [13, 14]. Manufacturers of generic drugs can produce an identical small molecule to that of the originator, even if the manufacturing process differs [14]. A standard chemical characterization analysis and a bioequivalence study conducted in humans are enough to prove the equivalence of the two products [14].

2.3. Regulatory Requirements for Biosimilar Approval

Due to small differences between the originator biologic and a potential biosimilar that arise during manufacture, the approval requirements for biosimilars are much more extensive than those for generic products [12]. Similarity to

the original product must be demonstrated through an extensive comparison of biological activity, quality, efficacy, and safety [12]. Biotherapeutic products that claim to be similar to an originator but have not provided adequate evidence of comparability are often referred to as intended copies or non-comparable biotherapeutics [13]. Many countries are developing regulatory pathways for the approval of biosimilars [3, 13], often based on guidelines developed by the WHO, EMA, or United States (US) Food and Drug Administration (FDA) [11, 12, 17].

3. REVIEW AND APPROVAL OF BIOSIMILARS IN SAUDI ARABIA

3.1. Regulatory Agency and Guidelines

In Saudi Arabia, the Saudi Food & Drug Authority (SFDA) is responsible for the review and approval of all drugs [18, 19]. Guidelines on the registration of biosimilars were published by the SFDA in 2010 [18], and in 2017 the SFDA published guidelines on quality considerations for biosimilars [8].

The guidances from the EMA and the International Conference on Harmonisation were used as resources in the development of the SFDA biosimilar guidelines [7, 8]. The general guidance document includes information on preclinical and clinical studies, extrapolation, interchangeability, and substitution [7]. The quality guideline provides information on the target product profile, comparability requirements, manufacturing processes, choice of the reference medicinal product, analytical methods, biological activity, and purity [8].

Specific quality requirements for potential biosimilars include the following [8]:

- The reference product can be the originator, or a product approved by the SFDA or a strict regulatory authority.
- Characterization of the biosimilar includes the composition, physical properties, and primary and higher order structures.
- The primary amino acid sequence of the proposed biosimilar must be exactly the same as that of the reference drug.
- Any post-translational changes in the structure of the proposed biosimilar, such as glycosylation or oxidation, must be characterized. Any variations between the proposed biosimilar and the reference product require justification and must be demonstrated to not affect clinical activity, particularly potency or immunogenicity.

3.2. Non-Clinical and Clinical Data Requirements for Potential Biosimilars

The requirements for non-clinical *in vivo* studies and clinical studies will depend on the extent of data provided for the physicochemical, biological, and non-clinical *in vitro* characterization [12]. Since the analytical data requirements for potential biosimilars are extensive, the non-clinical and clinical study requirements are not as strict as for originator biologics, although requirements may vary by product [11]. The SFDA regulations are based on the EMA guidelines, which include the following [3, 7, 20]:

- Comparative-dose pharmacodynamic studies that are highly sensitive may be enough to demonstrate efficacy. Or, at least one clinical trial that is adequately powered to demonstrate equivalence must be conducted.
- Safety must be evaluated in at least one clinical trial that is adequately powered to demonstrate equivalence.
- Immunogenicity must be included as part of the safety evaluation.

It is important to note that the head-to-head clinical studies comparing a potential biosimilar to the reference product are powered to establish equivalence, not superiority or non-inferiority [3].

Once a potential biosimilar receives approval, the labeling should clearly identify the biosimilar so that pharmacovigilance can be conducted effectively [3]. Pharmacovigilance is necessary to monitor adverse events following exposure to larger numbers of patients for an extended period of time [11].

4. QUESTIONS ABOUT BIOSIMILAR USE

Since biosimilars have been demonstrated to be highly similar but not identical to an approved reference biotherapeutic product with regard to quality, safety, and efficacy [11, 13], questions have arisen among clinicians concerning how best to incorporate these products into clinical practice. The types of questions are provided below.

4.1. Extrapolation

Extrapolation refers to the approval of a biosimilar for an indication of the reference product without directly comparing them in a clinical study [21]. The WHO guidelines allow extrapolation if particular criteria are fulfilled; the FDA and EMA will consider it based on the evidence provided for each case [3, 11]. The SFDA states that it may grant extrapolation if a range of criteria are met [7]. Clinicians have asked how regulators can be sure of the safety and efficacy of a biosimilar without clinical data on the treatment of a particular disease [22, 23], especially since the biosimilar may have received approval based on only one head-to-head study [3].

To consider allowing extrapolation, it is first necessary to have a detailed characterization of the amino acid sequence, tertiary structure, and biological activity of the proposed biosimilar, as well as clinical pharmacology studies confirming biosimilarity [23]. Then, once biosimilarity has been established, following the principle that the structure of a compound determines its function, the biosimilar and the reference product should act in the same manner for all indications of the reference product [23].

4.2. Naming

There is no naming style for biosimilars that has been agreed upon by the international community [13]. A proposal is being considered by the WHO in which all biologics, including originators and biosimilars, will receive a name consisting of the International Non-proprietary Name (INN) plus a unique identifier [13]. The different naming conventions developed by individual countries may cause confusion among physicians and pharmacists, especially if patients travel. The presence of biosimilars necessitates careful organization and tracking in pharmacies, and if this requires an investment in additional technology, the cost to patients may increase.

4.3. Interchangeability and Automatic Substitution

In the US, if the FDA were to determine that a biosimilar and its reference product are interchangeable, then individual states have the option to allow automatic substitution of the biosimilar for the reference product by the pharmacist, without conferring with the prescriber [22, 24]. However, the FDA has not finalized a guidance on the requirements for demonstrating interchangeability, and there is no biosimilar approved to be interchangeable with the originator [22, 25, 26]. In the EU, the decision on whether to assign interchangeability is made by individual countries, not the EMA [27].

The SFDA specifies that pharmacists cannot switch a patient from the originator product to a biosimilar without permission from the treating physician [7]. Additionally, the SFDA states that switching from the originator drug to a biosimilar, or between biosimilars of the same reference drug, is only acceptable after the physician discusses the option with the patient.

Some physicians have concerns about the concept of automatic substitution, or non-medical switching, for several reasons. First, with the current pharmacy structure that is in place throughout Saudi Arabia, and the variations in biosimilar regulations, naming practices, and pharmacovigilance requirements in different countries, it would be a challenge to track adverse events and identify which biosimilar a patient is taking at the time of an adverse event [2, 3]. Additionally, switching data may not be available when a biosimilar is approved, thus there would be no scientific evidence to support this approach. Although the likelihood of experiencing an immunogenic reaction after multiple biosimilar switches is unknown, it is important to consider this possibility because immunogenicity may result in serious adverse events or loss of already established efficacy [15, 28]. Lastly, once multiple biosimilars are available for a single originator, it may be difficult for the purchasing department in a healthcare facility to choose a particular biosimilar each year if patients are continuously switching products.

5. RHEUMATOLOGY BIOSIMILAR APPROVED IN SAUDI ARABIA

The SFDA has approved 8 biologic therapies for use in rheumatology indications (Table 1), including one biosimilar, Remsima [29]. Remsima is a biosimilar of infliximab manufactured by Celltrion and licensed under a local company, Jazeera Pharmaceutical Industries [29, 30].

Table 1. Rheumatology biologic therapies approved in Saudi Arabia [29].

Scientific Name	Trade Name	Year of Approval*	Mechanism of Action
Abatacept	Orencia	IV: 2010 SC: 2014	Selective T-cell co-stimulation modulator
Adalimumab	Humira	2005	TNF inhibitor
Etanercept	Enbrel	2006	TNF inhibitor
Golimumab	Symponi	2015	TNF inhibitor
Infliximab	Remicade	2011	TNF inhibitor
	Remsima [†]	2016	–
Rituximab	MabThera	2008	Targets CD20 on B cells
Tocilizumab	Actemra	IV: 2014 SC: 2017	IL-6 receptor antagonist

*Provided by the respective manufacturer.
[†]Biosimilar
 IL, interleukin; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor.

Remsima, also known as CT-P13, was one of the first biosimilars developed within the rheumatology therapy area, and it has been evaluated in two large pivotal studies [31]. PLANETAS and PLANETRA were global phase 1 and phase 3 studies, respectively, and were double-blind, randomized, parallel-group, 54-week equivalence studies with 48-week extensions that compared the efficacy, safety, and pharmacokinetics of CT-P13 to reference infliximab [32 - 35]. PLANETAS enrolled 250 patients with ankylosing spondylitis and PLANETRA enrolled 606 patients with inadequately controlled RA [32, 35]. In both studies, CT-P13 and reference infliximab were found to be comparable in terms of efficacy, safety, and pharmacokinetics at 54 weeks. Also, in the extension studies, patients who switched from reference infliximab to CT-P13 experienced comparable efficacy and safety to the patients who had received CT-P13 from the study start [33, 34].

6. GUIDELINES FOR USE OF BIOSIMILARS IN THE MIDDLE EAST AND NORTH AFRICA

Experts from the Middle East and North Africa (MENA) region agree that rheumatology society guidelines on the treatment of RA, such as those from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), are largely applicable to the MENA region; however, the MENA region does have some unique characteristics such as financial limitations and differently structured health systems [9, 36, 37]. A group consisting of rheumatologists, other clinicians, and methodologists from several professional organizations in the MENA region have adapted eight recommendations on both early and established RA from the 2015 ACR guidelines, and these recommendations have been published [37, 38]. Experts have also recommended that educational initiatives and guidance developed specifically for the MENA region include standards on switching to biosimilars, and the use of biologics in general, in order to assist rheumatologists in their management of patients [4, 19].

7. MEDICAL CARE IN SAUDI ARABIA

7.1. Management of Rheumatic Diseases

In Saudi Arabia, there are no country-specific guidelines on the management of RA [4] or other rheumatic diseases. All citizens in Saudi Arabia are eligible to receive treatment with originator biologics; however, the criteria for treatment are not clear [4]. This may result in under- or over-treatment with biologics. The lack of guidelines on the management of RA has resulted in varied treatment patterns within the country and no recognized standard of care [4]. For instance, in a survey of practicing rheumatologists in Saudi Arabia, 78% (42/54) of respondents stated that they use outcome measures to assist them with treatment decisions [4]. Only 41% of respondents reported that they incorporate quality of life and physical function measures in their practice [4].

7.2. Future of Pharmaceuticals and Patient Safety in Saudi Arabia

In late 2016, experts in the areas of regulatory science and healthcare innovation met with government officials and academicians in Saudi Arabia to develop recommendations for improving the quality of medications and patient safety in the country [19]. There was agreement between the experts that decreasing the quality of medication to achieve lower

costs is not acceptable. Recommendations related to biosimilars that resulted from the conference include the following [19]:

- National standards on therapeutic switching of biosimilars are needed, and should be developed through a collaboration between regulatory agencies and the Ministry of Health.
- National regulatory organizations must ensure the integrity of biosimilars throughout the supply chain, as they do for originators.
- Patient medication leaflets should be reviewed by a committee of healthcare professionals and researchers to make sure the information is at the appropriate literacy level, before providing them to the public.
- A clear method for reporting quality concerns with biosimilars (particularly with switching) should be instituted.
- A national research center should conduct observational studies to evaluate the quality of biosimilars.
- Regulatory agencies in Saudi Arabia should conduct bioequivalence studies so that they do not need to rely on the studies conducted by the manufacturers.

8. RECOMMENDATIONS, BASED ON EXPERT OPINION, ON THE USE OF BIOSIMILARS IN SAUDI ARABIA

Since no guidelines on the use of biosimilars in clinical practice exist in Saudi Arabia [4], and because the greatest concern must be patient safety, we have provided several recommendations to help ensure that biosimilars are used appropriately in Saudi Arabia (Table 2).

Table 2. Recommendations for use of biosimilars in Saudi Arabia.

1.	The introduction of biosimilars in Saudi Arabia should be based on clinical evidence as well as cost considerations.
2.	Switching between originator biologics and biosimilars or between different biosimilar products should be a clinical decision made by the treating physician, in collaboration with the patient, on an individual patient basis. Automatic substitution at the pharmacy level is not appropriate.
3.	Biosimilar names and labels should be distinguishable from originator biologics and should provide adequate information to ensure appropriate prescribing and dispensing and to track adverse events.
4.	Once biosimilars are approved for use, pharmacovigilance must be conducted to monitor their efficacy and long-term safety through post-marketing surveillance, clinical studies, and registry studies.
5.	Clinical practice guidelines that incorporate use of biosimilars should be developed for rheumatologists in Saudi Arabia.
6.	A local or regional rheumatology society should conduct educational activities to teach stakeholders about biosimilars.

8.1. Introduction of Biosimilars in Saudi Arabia

When deciding to introduce biosimilars into a country, the most important consideration is patient safety, not the potential cost savings [5]. Therefore, the safety and efficacy of proposed biosimilars must be supported by scientifically sound evidence. Differences in approval processes across countries are inevitable; however, to protect patients' safety, it is important to ensure the regulatory review is based on internationally accepted scientific principles. This may also increase the efficiency of the application process and lead to a more expeditious review and approval of biosimilars.

Once the evidence demonstrates that a biosimilar is comparable to an originator, then the decrease in cost is an acceptable reason to prescribe it, if the patient consents [2, 39]. The EULAR treatment guidelines for RA note that cost-effective therapies should be the preferred option as long as they are as safe and effective as the more expensive ones [39]. Pharmacoeconomic analyses of rheumatology biosimilars have been conducted in Europe. One cost analysis evaluated the impact of switching to a rituximab biosimilar, CT-P10, in 28 countries in Europe [40]. The authors estimated the savings over one year to be €24.2 million for the RA indication [40]. Another analysis estimated the potential for cost savings with the introduction of the infliximab biosimilar CT-P13 in six countries in central and Eastern Europe [41]. The authors estimated that over three years, use of CT-P13 for the management of patients with RA could save €15.3 to €20.8 million [41].

Although CT-P13, also known as Remsima, is available in Saudi Arabia, no data are available on the potential for cost savings with Remsima or other biosimilars. A pharmacoeconomic analysis should be conducted to inform regulators, physicians, and patients of the possible budget impact of biosimilar use. Physicians tend to be more accepting of biosimilars if they know their patients will benefit from the reduced cost, and both direct and indirect costs must be considered [2, 39]. Cost savings that result from the introduction of biosimilars should remain within the healthcare budget for the continued benefit of patients.

Once rheumatologists decide to prescribe a biosimilar, the question arises as to which patients should receive it. It is not yet known which patients would be eligible to receive a biosimilar if the originator is also available at the same institution. Physicians may choose to start biosimilars in patients who are biologic-naïve and have failed therapy with disease-modifying antirheumatic drugs. Available evidence suggests that the use of a biosimilar, including patient screening, drug administration, and monitoring, does not differ from the use of the corresponding reference product. .

8.2. Switching

The decision to switch between originator biologics and biosimilars or between different biosimilars should be made only by the physician, in collaboration with the patient, based on scientific evidence [6, 7, 39]. According to the ACR, only the treating physician should be allowed to switch a patient to the biosimilar [42]. Switching a stable patient from the reference drug to a biosimilar for cost-saving reasons (non-medical switch) should not be conducted without prior approval from the prescribing physician and the knowledge of the patient [7, 42]. Patients agree that the decision to prescribe a biosimilar should not be based on cost alone [5].

8.3. Naming and Labeling

Biosimilar names and labels must be easily identifiable, to ensure appropriate prescribing and dispensing, and to track adverse events [3]. Once multiple biosimilars are available, the risk of name confusion increases, as does the likelihood of prescription errors. The WHO recommends that all biosimilars have a unique brand name, and if an INN has been assigned, it should be visible as well [11]. Another consideration is to have the manufacturer name clearly visible on the packaging to help identify the product. Additionally, the label of a biosimilar should reflect the clinical data generated to support its approval, and the packaging should state that the SFDA does not allow automatic substitution.

8.4. Pharmacovigilance and Post-Approval Studies

Once biosimilars are approved for use, pharmacovigilance is critical to monitor their efficacy and long-term safety, including their potential for immunogenicity [43]. Multidisciplinary teams that include healthcare professionals, patients, and regulators must collaborate to monitor the safety of biosimilars through timely submission and review of post-marketing adverse event reports [19]. Sometimes, countries experience difficulties with pharmacovigilance, such as: (1) cultural differences in medical practice, (2) few resources for regulatory activities, and (3) limited expertise and interest among clinicians for conducting pharmacovigilance [44].

Pharmacovigilance should consist of post-marketing surveillance and reporting of adverse events, as well as post-approval clinical and registry studies. Post-approval clinical studies help clinicians gain additional understanding of the safety and efficacy of biosimilars in Saudi patients, and registries provide a method to collect extensive real-world data on biosimilar use and safety. These post-approval studies may detect safety signals that were not found earlier.

8.5. Clinical Practice Guidelines and Education

Before biosimilars are used in clinical practice, national or regional guidelines for the management of rheumatic diseases are needed, as well as educational programs for rheumatologists on the topic of standard of care. Guidelines are necessary in Saudi Arabia because of practice differences between rheumatologists in Saudi Arabia and clinicians in other areas of the world. One option is to develop clinical practice guidelines based on those established by EULAR [9]. In addition, to improving care, following evidence-based treatment recommendations may help decrease the cost of care; cost factors were taken into consideration throughout the development of the EULAR guidelines [39].

Rheumatologists and other healthcare professionals should receive education on the treatment guidelines and also on the particular manufacture and approval requirements for biosimilars, because their choice of therapy for an individual patient must be based on a thorough understanding of all treatment options. All healthcare providers, including family medicine physicians, nurses, pharmacists, medication suppliers, health educators, and payers, whether they work in a hospital or clinic, should receive education on biosimilars. All of these individuals have a role in preventing medication errors and educating patients.

8.6. Patient Education

Patients, particularly those less educated or elderly, may have little knowledge of biosimilars. Patients and caregivers should be provided with reliable information at the appropriate literacy level, so they can better understand

the treatment options [5, 19]. The rheumatologist should discuss medication choices with the patient in a detailed manner, and then other healthcare professionals, including primary care physicians, pharmacists, and nurses, should follow up to answer questions. These providers can also create patient education materials based on the biosimilar prescribing information.

CONCLUSION

To ensure patient safety, the approval and use of biosimilars must be supported by scientifically sound evidence. Clinical guidelines that incorporate the use of biosimilars in practice should be developed for rheumatologists in Saudi Arabia to assist them in their clinical decision-making. Additionally, educational resources should be provided to healthcare professionals and patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Hussein Halabi has received speaker's fees/grants from Pfizer, Abbvie, Roche, BMS, Janssen, Actelion, GSK, and Novartis. Ramiz Al Swailem has consulted/received honoraria from BMS, Pfizer, Abbvie, Hoffman-La Roche, and Hekma. Hanan Al Rayes has received honoraria from Roche, Pfizer, BMS, and Lilly, and is the Head of the Saudi Society for Rheumatology. Zeyad Al Zahrani, Waleed Husain, and Hanan Al Osaimi declare that they have no conflict of interest. Yasser El Dershaby and Haytham Mohamed Ahmed are employees of Pfizer. Mohamed Mounir was an employee of Pfizer at the time the article was written. Mohammed A. Omair has received speaker's fees/grants from Pfizer, Abbvie, Roche, BMS, Janssen, Actelion, GSK, and Hekma.

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All authors contributed to the design of the manuscript and were involved in developing, reviewing, and revising the manuscript. All authors approved the final version that was submitted for publication and agree to be accountable for all aspects of the work.

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