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The Concept of Biosimilars: From Characterization to Evolution—A Narrative Review

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Abstract

Biologic agents are currently the fastest emerging segment of drug expenditure. Unlike chemically synthesized small-molecule drugs, biologics are more complex, medicinal products produced by a living organism. They have become part of the standard of care in the treatment of a large variety of diseases, such as growth disorders, autoimmune diseases, cancer, cardiovascular illnesses, hemophilia, and rare genetic conditions, to name a few. Biosimilars, which are copies of biologics that are highly similar, were introduced in the market with an aim to offer efficacy that is not clinically different from the originator or reference product, at lower prices. We aim to clarify the concept of biosimilar, from definitions, history, market entry, challenges faced, and future evolution. For that purpose, we performed a literature search on the sites of the medicines regulatory agencies and PubMed from 1990 to 2014 with the keywords "biosimilars," "market," and "regulatory." In 2006, the first biosimilar, somatropin [rDNA origin], was marketed and led the way for biosimilar drug manufacturing. As a result, manufacturers have entered a diversified competition, facing challenges in manufacturing these complex agents, such as immunogenicity and efficiency. Biosimilars are set to evolve differently in various markets, namely the U.S., Japan, the European Union, and the "pharmerging" economies. ***The Oncologist*** 2018;23:346–352

Implications for Practice: This article highlights the importance of biosimilars, as a cost-cutting strategy, in the delivery of state-of-the-art health care in developing countries, at a fraction of what a reference biological agent would cost.

Introduction

The financial burden of health care and prescription medication has been increasing tremendously all over the world, with an estimated total cost of 1.2 trillion U.S. dollars (USD) by the end of 2016 [1]. Biologic medicines, known simply as biologics, are large and complex molecules, produced from or by microorganisms. This relatively new line of pharmaceutical products represents a significant portion of pharmaceutical product costs, with an estimate of up to 210 billion USD (17.5%) of the total medical spending [1].

For successful entry of a biosimilar market, the following are needed: (a) adequate research and development capacity, (b) specific biomanufacturing platform, (c) supporting activities such as legal expertise and global distribution and commercialization channels, (d) an international network of marketing sales representatives, and (e) strong lobbying with regulatory bodies, opinion leaders, and governments to accelerate the approval of laws and regulations [2].

Biologics have made substantial contributions to improve the effectiveness of treatment of many areas of disease and they are expected to continue to do so in the future. However, these benefits come at increasingly higher costs, which endanger accessibility and the financial sustainability of health care. As a result, the expiration of patents and other intellectual property rights of biologics made it possible for biosimilars to enter the market, which in turn increased competition among manufacturers of biologics, contributing to billions of dollars in savings in the health care sector [3]. In Europe, most biosimilars are marketed with a discount of around 20%–35% versus the price of their reference products [4]. This allows patients to receive therapies that were difficult or impossible to be received. For example, in countries where access to epoetins was especially restricted (e.g., Bulgaria, the Czech Republic, and Romania), cost savings have been estimated at 50%, with an increase in average uptake of more than 250% for a biosimilar [5].

Recently, many reviews have been published on biosimilars [4, 6, 7]. In particular, Santi et al. and Vital et al. focused on the aspects to be considered in biosimilar follicle-stimulating

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hormone (FSH) and rituximab usage, respectively [6, 7]. In this article, we aim to clarify the concept of biosimilars in all therapeutic classes, including definitions, history, market entry, challenges faced, and future evolution.

Materials and Methods

The literature search utilized resources from the websites of several medicine regulatory agencies and in PubMed from 1990 to 2014 with the keywords "biosimilars," "market," and "regulatory."

Results and Discussion

Definitions, History, Manufacturing, Market Entry of Biosimilars, and Challenges

Definitions

Biologics are medicines whose active drug substance is made by or derived from a living organism, using processes such as recombinant DNA technology with controlled gene expression with the result being the production of monoclonal antibodies [8–10]. A wide range of products fall under the category of "biologics" [1]. Such products have become part of the standard of care in treatment of a large variety of diseases, such as cancer, cardiovascular illnesses, hemophilia, autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, and rare genetic conditions such as Gaucher's disease and Fabry disease [1, 11]. Biosimilars are prescribed in four important therapeutic areas, namely, erythropoietin (EPO) for anemia in patients on renal dialysis, granulocyte colony-stimulating factor (G-CSF) for lowered white blood cell counts after chemotherapy, HGH, FSH for reproduction, and monoclonal antibodies in rheumatology [6, 12, 13].

Due to their protein nature, biologics are large molecules in terms of molecular weight, which makes them less stable compared with small-molecule drugs. They differ significantly in their production process [14]. The production process of biologics is extremely challenging and complex. Two main components play a major role in the production process: the first is that the vast majority of biologics are heavy molecular weight proteins (4,000–140,000 Daltons), which makes them highly unstable compared with their small-molecule counterparts (160–800 Daltons) [15]; and the second is that biologics are produced and secreted by living cells, whereas small-molecule drugs are produced by a chain of conventional chemical reactions [12].

A biosimilar is a medicinal product with a similar safety, efficacy, and quality as an already authorized biologic product. It is made by or derived from a biological source such as yeast or a bacterium [16]. Thus, the lack of significant differences has to be clinically proven by appropriate development of each biosimilar. Biosimilars contain different inactive ingredients and may have different brand names, appearance, and packaging from the reference medicinal product [11]. Several expressions have been used in the U.S., the European Union (EU), Canada, and other countries to refer to biosimilars, including follow-on biologics, follow-on protein products, biogenerics, and generic biologics [1, 17]. In the U.S., the Biologics Price Competition and Innovation Act defines biosimilar as "a biological product highly similar to the reference product notwithstanding minor differences in clinically inactive components;" and with "no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product" [18]. The production of a biosimilar drug needs a reference to the innovator product for its approval [10].

Also, IMS Health (an informational services company) has established an industry to verify the standard market definition for the biosimilars sector; this enables consistent analysis across countries. According to this definition, biosimilars are considered as biologic products that need approval in a country, which has an abbreviated development process for biological products [13].

History of Biosimilars

The first biosimilar medicine was a human recombinant growth hormone named Omnitrope (somatropin [rDNA origin]; Sandoz, Holzkirchen, Upper Bavaria, Germany) [19]. The reference medicinal product cited for Omnitrope was Pfizer's Genotropin (somatropin [rDNA origin]; Pfizer, Cary, NC), which was originally authorized in the EU in 1988 [19]. In 2001, Sandoz International applied for market authorization in Europe using the "well-established medicinal use" route [20]. In June 2003, the Scientific Committee and the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA; member states: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the U.K.) recommended the market authorization of Omnitrope. The European Commission then rejected it and refused to permit its marketing for the commission, stating that Sandoz should have used the "essential similarity" route and not the "well-established medicinal use" route for the authorization process. Official processes took place, in coordination with the European Court of First Instance, in order to cancel the Commission's decision [12, 21]. On March 31, 2004, an extensive and official framework for biosimilars was adopted in the EU. In July 2004, Sandoz tried for the second time to pursue the market authorization for Omnitrope. EMA presented a second positive opinion in January 2006, leading to Omnitrope's approval on April 12, 2006.

Valtropin (somatropin rDNA origin for injection, USP; BioPartners, Lithuania), another biosimilar, a Biopartner's product and recombinant HGH, was approved shortly after Omnitrope [22]. In a manner similar to the process for other biological medicines, all biosimilars are subject to the same precise scientific assessment by the EMA [12].

The two licensed medications, Omnitrope and Valtropin, were the pioneers in the biosimilar emerging market and paved the way for a large number of biosimilar companies. EMA released guidelines and a registration process, specific for biosimilars approval, between 2005 and 2006 [23].

Up to 2016, the EMA accepted 23 biosimilars in various therapeutic areas, beginning with somatropin in 2006, followed by several erythropoietin analogues and, more recently, antineoplastic agents and FSH biosimilars [3, 24–26]. EMA decisions are valid in all EU countries. Each country in the EU is authorized to negotiate the pricing of the biosimilar independently, but cannot make marketing authorization decisions independently of EMA verdicts.

In Japan, the first approved biosimilar was Sandoz's growth hormone treatment Somatropin BS (somatotropine; Sandoz, Japan) in June 2009. By 2015, the Pharmaceuticals and Medical Devices Agency of Japan had approved seven biosimilars within the product classes of HGH, G-CSF, erythropoiesis-stimulating agent, insulin, and tumor necrosis factor (TNF)-inhibitor, for use in the country [27].

In the U.S., the U.S. Food and Drug Administration (FDA) approved Zarxio (filgrastim; Sandoz, Holzkirchen, Upper Bavaria, Germany) to be the first biosimilar drug for distribution on March 6, 2015, which comes 5 years after the Affordable Care Act was signed into law in 2010 [21].

Manufacturers of Biosimilars

The South Korean biopharmaceutical company Celltrion manufactured two biosimilars of infliximab, namely Remsima (infliximab; Celtrion Healthcare, Incheon, Korea) and Inflectra (infliximab; Pfizer, Cary, NC), after patents on Remicade (infliximab; Janssen Biotech, Horsham, Horsham Township, Pennsylvania, United States) expired in February 2015. Both medicines have the same dosing regimen, strength, pharmaceutical form, and therapeutic indications (ankylosing spondylitis, Crohn's disease, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, and psoriasis) as those of the reference drug Remicade [28]. Although Remsima and Inflectra have already been licensed in Canada and the EU, they are being preregistered in the U.S. [29–33]. It is expected that the number of biosimilars and their market authorization will expand significantly over the next 5 years as top-selling biologics such as Herceptin (trastuzumab; Roche/Genentech, California), Enbrel (etanercept; Amgen, CA), Humalog (insulin lispro; Lilly, Indiana, USA), MabThera (rituximab; Roche, Basel, Switzerland), Aranep (darbepoetin alfa; Amgen, CA) go off patent.

Generics manufacturers, research and development-based pharma, and biotech companies will be competing to develop biosimilars. Phase II trials sponsored by Teva pharmaceutical industries for a biosimilar version of Roche's rituximab (MabThera/Rituxan (rituximab; Biogen and Genentech USA, Inc.)) are approaching their end. Pfizer agreed with Biocon (India) to manufacture biosimilar insulin. Eli Lilly and AstraZeneca declared their intention to manufacture biosimilars, and Boehringer Ingelheim is creating a dedicated division for the development and commercialization of its own biosimilars. In the meantime, leading innovator biotech companies such as Biogen Idec and Amgen are proposing plans to develop biosimilars, which has mainly called out emerging markets in Asia and South America. For example, electronics manufacturer Samsung and digital technology leader Fujifilm have joined the pharmaceutical industry with a focus on biosimilars. As such, further biotech ventures are planned to be pursued by Samsung "in its effort to attain target revenues of 1.8 billion USD from biopharmaceuticals by 2020" [13]. The entry of these players may not necessarily herald similar actions from more companies in other industries, but brings a fresh inflow of cash to fund development programs and branding models that have already paid off in other industries [34, 35].

Market Entry

The introduction of a biosimilar into the market requires a specially designed pharmacovigilance plan. Clinical, analytical, and nonclinical (animal and/or in vitro) studies are needed to collect data confirming high resemblance and noninferiority between biosimilars and reference biologic products. Data from these studies must confirm that both products have similar and noninferior clinical results. Some countries have different criteria for market authorization of biosimilars. In Canada, for example, equivalence studies are preferred, and that is the target of the clinical development. Otherwise, indications cannot be extrapolated (or extended) to those of the reference biological product [36]. Biosimilars are identified by their "unique designations" added to the generic name; the EMA uses the brand name as part of the approval process. The requirement of clear identification is necessary for safe prescription and administration, as well as for monitoring the safe use of the medicine during the whole life cycle [12, 37, 38].

Between January 1995 and June 2007, 136 biologics were approved in the U.S. by the FDA, and 105 in the EU, with 67 products receiving approval in both regions [39]. Currently, 907 medicines and vaccines are being developed by U.S. biopharmaceutical research companies to target more than 100 diseases [42]. The first biologics sold in the U.S. include human insulin, erythropoietin, growth hormones, and cytokines [17]. In 2008, biologic sales accounted for 30% of the top 100 pharmaceuticals, and reached 50% of all pharmaceutical sales in 2014. In 2015, 8 of 10 best-selling medications were biologics, and worldwide spending reached 200 billion USD [3].

Although biologics are highly effective, their cost is a burden on the health care sector and end-consumer. Therefore, producing biosimilars to serve as the "biosimilar" versions of biologics would help in saving billions of dollars annually. These savings are projected to reach around 9 to 12 billion USD for the U.S. Medicare program during the next decade [1].

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Worldwide, biosimilars are at different stages of their evolution. The names biosimilars are given and the regulatory frameworks governing them differ from authority to authority. The end result is, however, the same, and the approaches are increasingly harmonized. So far, Europe has by far the best-established framework, with which the U.S. is more or less aligned. Health Canada, the regulatory authority that, among other responsibilities, oversees the regulations on biosimilars, has applied recent changes to their Guidance Document in which the Fact Sheet has been substantially rewritten and contains an overview and description of the regulatory framework for biosimilars [36]. The Fact Sheet also includes a new section on drug and patient access, which includes a statement clarifying that the authorization of a biosimilar is not a declaration of equivalence between the biosimilar and its reference biologic

drug, and is independent of any decision as to interchangeability between these drugs. Interchangeability decisions are considered a matter of provincial and territorial jurisdiction. Health Canada recommends that decisions regarding switching to a biosimilar from its reference biologic drug should be made by treating physicians in consultation with the patients [35].

Although Japan, the U.S., and the EU are considered the most important markets for biosimilars, China, India, and other countries also produce biosimilars but do not have the precise definitions and regulatory pathways for approval. This is mostly due to the fact that copy versions of patented agents are manufactured regardless of the patent rights with little to no regulatory oversight. For example, Reditux (rituximab; Dr. Reddy's, Hyderabad, India), an intended copy of rituximab that has not met any criteria of a real biosimilar to date, has been approved in India since 2007 based on limited evidence comparatively to what is required in the EU or the U.S. [13].

Geographically, the market for biologics and biosimilars comprise three district clusters: the U.S., other advanced economies such as Europe, Japan, and Canada, and the "pharmerging" markets (China, India, Brazil, and Mexico). For now, Europe has taken the lead in the field of biosimilars. The U.S. is the most globally expanding market in biologics and will be an essential player in the long-term biosimilars market potential. The advanced economies have the advantage of an established framework for biosimilars, but to date, the uptake has been slow. Biologics already exist in pharmerging markets, and are experiencing the highest growth rates. Japan has recently established regulations for biosimilars based on EU guidelines [28].

U.S. Market. In April 2015, the FDA released two highly anticipated sets of guidance on biosimilars. The first guidance, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," aims to help companies show that a suggested therapeutic protein product is biosimilar to a reference product. The guidance also defines a risk-based "totality-of-the-evidence" approach currently used by the FDA. This allows the FDA full access to the data submitted to demonstrate biosimilarity in order to assure that the proposed product is biosimilar to the reference product [40]. The second guidance is entitled "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product." It offers an overview of analytical, biological, and physicochemical characterization factors to consider when evaluating a proposed therapeutic protein product being biosimilar to a reference product before submitting a 351(k) application, also known as "biologics license application" [41]. In May 2015, the FDA also released a draft guidance on "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." This guidance document is being distributed for comment purposes only and provides answers to common questions from companies interested in developing biosimilar products. The question and answer presentation addresses questions that may arise in the early stages of product development, such as how to request meetings with the FDA, addressing differences in formulation from the reference product, how to request exclusivity, and other issues [24]. In March 2010, President Obama signed into law the Biosimilar Act as part of a major health care reform. The law underlines the requirements to determine the interchangeability of biosimilarity, in addition to setting forth rules on the exclusivity period for innovator companies [42]. The U.S. is expected to play a pivotal role in the success, or failure, of the biosimilar market in the next decade. This assumption is based on its health care system's growing demand for low-cost, high-value drugs and its competing and leading manufacturers in the pharmaceutical industry such as Pfizer and Merck. Thus, this opportunity will be the cutoff point for the success or failure of biosimilars in the next decade [12, 13]. In parallel, strategically, the potential U.S. savings attainable from biosimilars vary from 2.0 to 2.8 billion USD over the period of 2010–2029 [12].

European Market. The EU has the most solid legislative foundation and pathway for biosimilars, making it currently the most advanced market. Nonetheless, the number of companies producing and launching biosimilars remains small.

Every country in the EU has its own laws and regulations related to biosimilars. This implies that parameters of penetration will vary from one country to another in areas such as local pricing, reimbursement policies, stakeholder impact, and attitudes toward a biosimilar's adoption and use. Other parameters include the type and duration of treatment, devices associated with medications, and the patients and health care professionals who might have conservative attitudes toward biosimilars. Currently, the two countries constituting half of the biosimilars market in the EU are Germany and France. This is mostly due to their well-established payer systems and a strong generic market. At present, Spain and the U.K. are starting to increase their market share, but their market penetration is still low. It seems they are focused on generics more than biosimilars, despite the presence of strong payers [13]. The latest available market research data suggest that G-CSF has registered the highest rate of penetration (25%), whereas HGH has the lowest rate (4%); the difference is mainly correlated with the patient's choice [43]. As for EPO, market penetration seems to be influenced by the payer-pharma contracts [13]. Finally, potential savings of €50–€100 billion and biosimilars price reductions by 20%–40% are expected in Europe by 2020. Also, the patents of most of the monoclonal antibodies are set to expire by 2020, which might intensely modify the oncology landscape by opening the door for biosimilars [24].

Emerging Markets. Although Europe, the U.S., and Japan have the highest number of biosimilar molecules in development [44], the pharmaceutical industry is expanding into developing countries at a rapid pace. This is because the growth pattern in developed markets continues to flatten. In addition, globalization is causing pharmaceutical industries to cut through traditional boundaries and push into developing countries—the so-called emerging markets [45]. Emerging markets constitute 70% of the world's population, account for a 31% share of global gross domestic product, and are predicted to account for approximately 30% of global pharmaceutical spending [46, 47]. Pharmerging markets currently account for 33% of the global growth in drug demand at the expense of the U.S. and EU. In 2015, they accounted for 28% of the market worldwide spending [3, 34].

A survey in India found that physicians were willing to prescribe a first-line critical therapy if it was offered at a 60%–70%

discount, whereas in China, getting on the essential drugs list means usage by many hospitals at a 25%–50% price cut [48].

India saw the launch of its first biosimilar in 2003 when it launched biosimilar rituximab at half the price of the biologic product. Today, 25 Indian companies are marketing close to 50 biosimilar products [49, 50].

Also, India has been at the center of controversy recently as a result of some of its renowned generics and biosimilar companies producing and marketing biosimilars of still-patented original products without any reliable comparative trials or licensing. These factors, among other regulatory guidelines, will shape the actual market contributions of such products in the future. The pharmerging markets have developed their own regulations and laws related to biosimilars according to the European framework but with lower general requirements, fewer clinical trial requirements, and less regulatory control [13]. The less stringent regulations have consequently led to a decrease in developmental costs, which is reflected in the final sale prices of the drugs. These regulations also have had an encouraging effect on the local smaller manufacturers to enter the market and compete accordingly.

Emerging markets including the BRICS (Brazil, Russia, India, China, and South Africa) and MIST (Mexico, Indonesia, South Korea, and Turkey) provide the best future opportunity for manufacturers of biosimilars [49, 51]. With millions of people in these developing countries, and unmet medical needs, the uptake of biosimilars is expected to be tremendous.

Uses

As mentioned above, biosimilars can be used in a large variety of diseases, such as cancer, cardiovascular illnesses, hemophilia, autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, and rare genetic conditions such as Gaucher's disease and Fabry disease [1, 52]. Due to its cost being lower than the original biological, biosimilars are more accessible to a wider group of people and countries; for example, in countries where access to epoetins was especially restricted (e.g., Bulgaria, the Czech Republic, and Romania) [5]. This is of extreme importance to allow high-quality health care to extend to developing countries and sensitive populations.

Challenges

New entrants in the biosimilars market face several challenges and encounter many barriers such as manufacturing, market access, and sales and marketing competition. The latter is defined as "a combination of pooled knowledge and technical capacities that allow a business to be competitive in the marketplace" [53]. An initial high-quality manufacturing and production process is the backbone of any reliable biosimilar product maker hoping to penetrate any regulated market. Manufacturers are under constant pressure to prove their final product is similar to the original drug in preclinical and clinical studies, in addition to showing that they can reliably maintain reproducibility at a large scale within the same site or at different production sites [14, 17].

Commercializing a biosimilar can be as challenging as the manufacturing process itself. One of the key obstacles to overcome in biosimilar commercialization is the set limitations placed on pharmacies by regulatory authorities. In addition to the commercialization regulations, pricing and reimbursement policies are a major factor influencing biosimilar companies' decisions to enter a market or not. Although biosimilars are supposed to be a cheaper alternative to innovative biologics, biosimilars are only anticipated to be 10%–20% cheaper due to the complexity of their development and production [54]. This has led biosimilar companies to avoid marketing in countries with low pricing policies and poor reimbursement rates so as to preserve their projected target sale prices [17, 25]. A U.S. study has estimated that the cost of the biosimilars trials would range from 10 to 40 million USD and that the required investment in manufacturing processes ranges from 250 to 450 million USD [55].

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The assessment of the cost-effectiveness of a biosimilar depends on its relative effectiveness. If an appropriately designed clinical study demonstrates equivalent effectiveness between the biosimilar and the comparator, then the least expensive medication is chosen, and this is likely to be the biosimilar [56]. An example will be the use of a biosimilar erythropoiesis-stimulating agent, in which the biosimilar was compared with erythropoietin and was found to have similar efficacy, but the cost of the biosimilar was significantly cheaper [57]. The same can be said for infliximab in Central and Eastern Europe [58].

Another challenge is that biologics as well as biosimilars can sometimes trigger unfavorable immunogenic reactions due to their protein antigenic nature [59]. The level of immunogenicity varies between products, and may increase when biologics are frequently administered over a long period of time [3]. Many factors affect the immunogenicity of biologics and their biosimilars including their structural characteristics (structure, primary sequence, novel epitopes, glycosylation, oxidation, and deamination); the patient's age, gender, genetic make-up and immune status; the dose, route and frequency of administration; and the product formulation. Compound instability is positively correlated with higher immunogenic potential [1, 60, 61]. The reactions encountered can be severe and represent a medical emergency [3, 38].

Conclusion

First introduced to the market in 2006, biosimilars are considered a great alternative to innovative biologic products that can save the preceding health care systems billions of dollars. Omnitrope and Valtropin, both recombinant HGH, were the first biosimilars approved in the market and were pioneers in the biosimilars global market. Many challenges still face the biosimilars industry in terms of manufacturing, pricing and market access, immunogenicity, cost-effectiveness, and efficiency. Nonetheless, the biosimilars market is becoming one of the

most competitive markets and is expected to grow substantially in the next decade. Their market can be divided into four major clusters: Japan, the U.S., the EU, and the pharmerging economies. Each one of these markets has its own regulations and laws related to biosimilars, with the EU being the current leader in the regulatory and approval pathway legislative aspect. Thus, the future of the biosimilars market will be shaped as the other major clusters refine and adjust their regulatory processes that define their placement in the health care system. In parallel, the benefits of developing biosimilar drugs that are 25%–35% cheaper allow developing countries to access high-quality care.

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Disclosures

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