# Potential Savings from Accelerating US Approval of Complex Generics

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# Introduction

Complex generics represent an important but underutilized avenue of savings for US patients and healthcare payors. A subset of generic prescription drugs, complex generics are copies of non-biologic medicines that have a complex molecular base, route of delivery, formulation, or dosage form; are a drug-device combination product; or have other particularly complex approval requirements.[1] Despite recent efforts to promote the approval of complex generics, these products are still slow to be approved by the US Food and Drug Administration (FDA).

Understanding that complex generics can provide significant cost savings to the healthcare system and improve patient access, policymakers, payors, patients, and industry experts have expressed interest in ensuring that these products can come to market in a timely and predictable manner. The FDA and industry stakeholders have an immediate opportunity to incorporate policies addressing review and approval of complex generics in the ongoing negotiations around the reauthorization of the Generic Drug User Fee Amendments (GDUFA).

This paper estimates the potential cost savings to the US healthcare system from seven complex generics approved in Europe and/or Canada but not yet approved in the United States. Based on an analysis of US sales of the associated brand products, we estimate that the continued delay in the approval and launch of these complex generics in the United States results in annual lost savings of $1.3 billion (range $600 million–$1.7 billion).

## GDUFA, FDA, AND INSUFFICIENT PROGRESS ON COMPLEX GENERICS

First enacted in 2012, GDUFA was established "to speed the delivery of safe and effective generic drugs to the public and improve upon the predictability of the review process" (*FDA, 2021*). GDUFA terms, which lasted for five years, were negotiated by the FDA and generic drug industry representatives. Under GDUFA, the FDA can "assess user fees to fund critical and measurable enhancements to the performance of FDA's generic drugs program" (*Ibid.*). The resources from generic drug manufacturers allow the FDA to hire additional staff to review abbreviated new drug applications (ANDAs) and carry out other activities related to the review and approval of generic drugs.

In 2017, a second GDUFA (known as GDUFA II) was reauthorized for another five-year term. The FDA and generic industry stakeholders are currently working to reauthorize GDUFA III, for fiscal years 2023–2027.

One commitment the FDA made in 2017 under GDUFA II was to work to accelerate the approval of complex generics.

[1] *Alford (2020) observes that the FDA tends to define complex generics by example and that a given complex product could, and often does, meet multiple definitions of complex. For example, Advair Diskus® involves complex characterization of the active ingredient, challenges related to pharmacokinetics and bioequivalence, and is a drug-device combination with complex interplay.*

Concurrent with the enactment of GDUFA and GDUFA II, the FDA made commitments to Congress to achieve certain performance standards and other related goals. One commitment the FDA made in 2017 under GDUFA II was to work to accelerate the approval of complex generics. To do this, the FDA established the Pre-ANDA Program to "clarify regulatory expectations for prospective applicants early in product development, assist applicants to develop more complete submissions, promote a more efficient and effective ANDA review process, and reduce the number of review cycles required to obtain ANDA approval, particularly for Complex Products" (*FDA, 2017*).

The Pre-ANDA Program includes additional meetings (product development, pre-submission, and mid-review cycle) between ANDA applicants and the FDA to help address regulatory uncertainties and reduce the number of review cycles. Relatedly, FDA has published a number of product-specific guidance documents for complex generics with the intent of fostering their development and approval.

## FDA's Drug Competition Action Plan and Complex Generics

Also in 2017, the FDA announced the Drug Competition Action Plan (DCAP) with specific acknowledgement of the importance of accelerating approval of complex generics. In an October 2017 statement, then–FDA Commissioner Scott Gottlieb announced a series of policies intended to facilitate approval of complex generics that were an outgrowth of the DCAP, explaining:

> This focus [on complex generics] is critical because, first and foremost, these drug products provide important therapies to patients. They are also becoming increasingly significant to the economic health of the generic drug industry. Being able to "genericize" a complex drug can be a high-value opportunity for a generic drug maker that helps underwrite the costs of other generic applications. In other words, because brand-name versions of complex drug products are often higher-priced than many other brand name drugs, any steps we can take to encourage the development of generic competitors to complex drugs will have an outsized impact on access, and prices.

Since announcing the DCAP, the FDA has taken numerous steps toward facilitating approval of more complex generics, including holding public workshops, opening multiple other public dockets, and issuing draft guidances. While these process-related changes are an improvement, there has not been a significant uptick in complex generic approvals.

## Concerns About Slow Complex Generic Approval in the United States

Despite the efforts outlined above and some complex generics coming to market in the last few years, a significant number of important complex products are off patent but lack generic competition. As a result, consumers and payors are not benefitting from generic cost savings, a concern that a number of policymakers have recognized. In addition, more complex products are expected to come off patent in the next few years.

In January 2020, the chair and ranking member of the House Energy and Commerce (E&C) Committee, along with the chair and ranking members of the E&C subcommittees on health and oversight, wrote to the FDA expressing concerns about delays associated with approving complex generics:

> The length of time leading to the approval of some recently approved complex generics raises questions of whether additional actions may be necessary to encourage the development of these products. . . . A primary purpose of this request is to determine whether additional authority is needed to improve the approval process for complex generics drugs to increase access and reduce costs.

In 2019 Senate testimony, Janet Woodcock, then director of the FDA Center for Drug Evaluation and Research, noted, "Since brand-name versions of complex drug products are often higher-priced than many other brand name drugs, efforts to encourage generic competition for complex products also offers outsized potential to increase patient access and lower drug spending." Following an announcement in late January 2020 that Sandoz would no longer seek approval of generic Advair Diskus®, former FDA Commissioner Scott Gottlieb noted publicly, "We must continue efforts to get generic copies of complex drugs to market. There is a large category of brand drugs that are off patent and off exclusivities and should be subject to brisk generic competition, but are not. This is a big opportunity to improve access, lower costs."

## POTENTIAL SAVINGS FROM COMPLEX GENERICS

It is important to note that the savings from complex generics likely will be lower than the savings that would be achieved from non-complex generics. This is because competition is expected to be more limited for complex generics. Due to the inherent complexity of manufacturing these products, the expected number of generic competitors is generally one, two, or perhaps three.

While exact competitive dynamics will vary from drug to drug, we should not expect generic prices to drop by the typical 85 percent, nor the generic market share to reach the average 90 percent. That said, complex generics can bring meaningful savings to the US healthcare system. Consider one product for which the FDA approved a complex generic in 2019: Advair Diskus®, used to treat asthma and chronic obstructive pulmonary disease. As the FDA noted in the 2019 Office of Generic Drugs Annual Report, the out-of-pocket cost for generic Advair Diskus® was reportedly less than half the out-of-pocket cost of the brand product. According to GlaxoSmithKline, sales of Advair Diskus® in the United States fell from $1.4 billion in 2018 to $641 million in 2019. IQVIA data indicate that generics captured more than half of the Advair Diskus® market share within a year of launching.

### Price Dynamics for Complex Generics

As noted above, the number of complex generic alternatives is not expected to exceed three per product given current challenges in developing and bringing these products to market. But FDA research on the impact of generic competition on drug prices shows that even limited competition is associated with significant price discounts.

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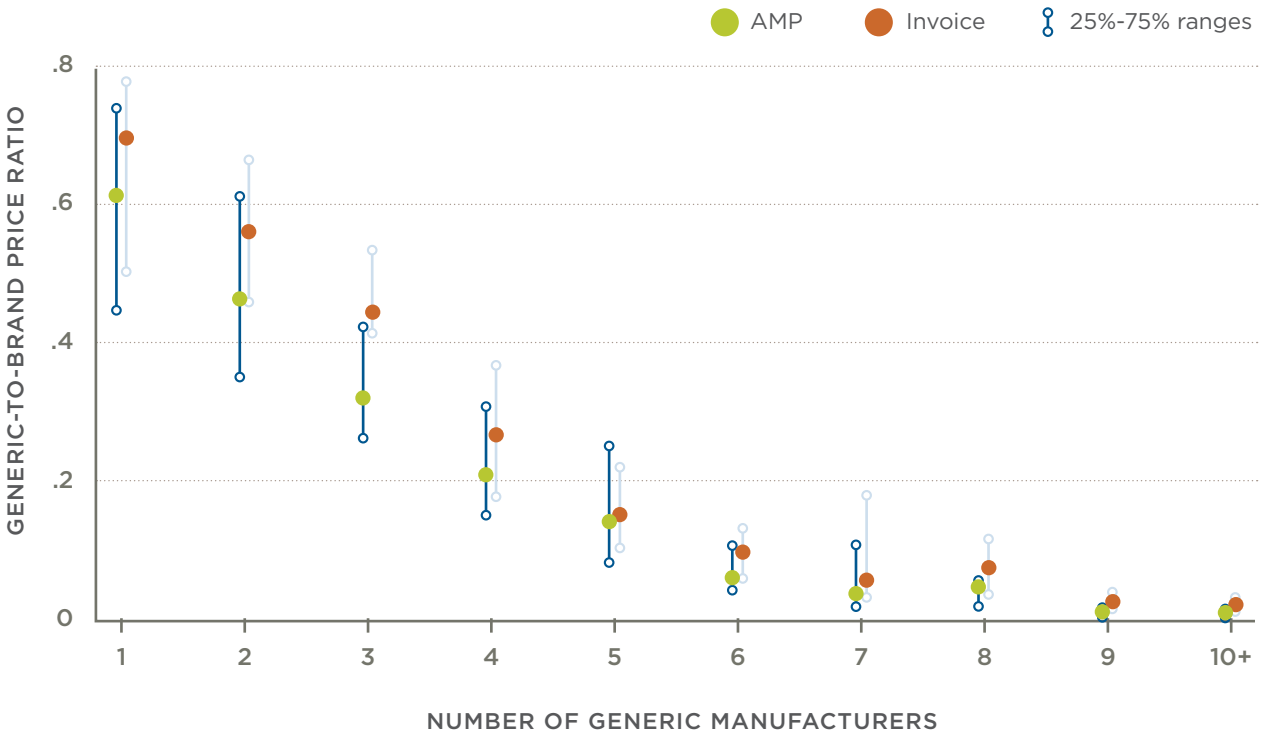
In a recent FDA analysis, the median generic price discount (with price measured as the invoice-based wholesale price) is 30 percent with one generic on the market (*Conrad and Lutter, 2019*). Discounts increase as the number of generic manufacturers increases (see **Figure 1**). For example, the generic price discount is 43.8 percent with two generics on the market, rising to 55 percent with three generics.

### Complex Generic Market Share

As previously stated, non-complex small-molecule generics often capture the overwhelming majority of market share. Generics were 90 percent of all prescriptions filled in the United States in 2019, according to the Association for Accessible Medicines (*2020*). The generic substitution rate (that is, the rate generics are used when they

**FIGURE 1: MEDIAN GENERIC-TO-BRAND PRICE RATIO**




***Source:*** *Reproduced from data from Conrad and Lutter (2019) illustrating the median average manufacturer price, invoice price, generic price discounts, and the 25–75% range of discounts from the analysis of 181 unique products for which a first generic entered in 2015, 2016, or 2017.*

are available) in Medicare Part D in 2017 was 90.8%, according to the Centers for Medicare & Medicaid Services (*Verma, 2020*). Market share for complex generics is estimated to be 40–60 percent because the number of complex generic competitors is likely to be relatively few and barriers to generic entry for complex products remain sizeable.

### Brand Manufacturer Pricing Strategy

In typical small-molecule drug markets with generic competition, the brand product does not reduce its price and instead opts for a smaller market share but consistently high margin. Conversely, among biologic drugs in the United States, net prices for reference biologics have declined as biosimilar competition enters the market. The pricing strategy around a complex brand product after generic entry could follow either path in the United States, or a third option, an authorized generic. In this third scenario, the reference product price would not decline, but the brand manufacturer would introduce a non-branded version of its own product at a competitive discount. From a market and savings perspective, this latter strategy is akin to selling a portion of the brand product at a discount.

## ANALYSIS OF LOST SAVINGS FROM DELAYED COMPLEX GENERIC APPROVALS

In this section, we present an analysis of the savings that the US healthcare system could realize from seven complex generics that are approved in Europe and/or Canada but not yet approved in the United States. The products in this analysis are: Abraxane® (paclitaxel), Forteo® (teriparatide), Invega Sustenna® (paliperidone), Restasis® (cyclosporine), Risperdal Consta® (risperidone), Sandostatin LAR® (octreotide), and Venofer® (iron sucrose). Each of these products have ANDAs pending at the FDA while generics have been approved by the European Medicines Agency (EMA) and/or Health Canada.

Neither the EMA nor Health Canada have explicit approval processes for complex generics, products known in those markets as non-biological complex drugs (NBCD) follow-ons. EMA has developed an agency working group to improve discussions and formal guidance related to complex products, and in Canada the approval process for these products is case by case, although industry has encouraged the agency to develop a clearer pathway (*Lunawat and Bhat, 2020*). According to Klein et al. (*2019*), through 2018 a "total of 85 NBCD follow-on products [have been] approved in the EU, of which half since 2013."

### Assumptions

To estimate expected drug savings from generic competition for the seven complex products listed above, we consider a range of potential market dynamics. Generic price discounts are assumed to be 30–44 percent, and generic market share 40–60 percent. The price of the brand product is assumed to either remain constant (typical in traditional generic markets) or decline by 20 percent (in a manner similar to what is observed with the introduction of biosimilars or with the launch of an authorized generic). Using these assumptions, expected savings from complex generics range from 12 percent to 34 percent of annual brand sales and center near 25 percent. Savings estimates are annual and assume other impediments to generic launch, such as litigation, settlements, and supply constraints, are resolved and non-binding.

### Data

**Table 1** presents the seven products as well as the brand manufacturer, indications, first generic approval date in Canada or Europe, and 2019 US brand sales as reported by manufacturers. US sales in 2019 for these seven products totaled approximately $5 billion.

**TABLE 1. COMPLEX GENERICS APPROVED IN CANADA OR EUROPE BUT NOT THE UNITED STATES**

| DRUG NAME (GENERIC NAME) | MANUFACTURER | CONDITIONS TREATED | FIRST APPROVED C = CANADA, EU = EUROPE | US SALES (2019, $ MILLION) |
|---|---|---|---|---|
| **Abraxane® (paclitaxel)** | Bristol Myers Squibb | Breast, lung, and pancreatic cancers | Mar. 2019 (EU) | $122 |
| **Forteo® (teriparatide)** | Eli Lilly | Osteoporosis | Aug. 2019 (C)<br>Oct. 2016 (EU) | $646 |
| **Invega Sustenna® (paliperidone)** | Janssen/Johnson & Johnson | Schizophrenia, schizoaffective disorder | May 2019 (C)<br>Jul. 2019 (EU) | $1,685* |
| **Restasis® (cyclosporine)** | Allergan/AbbVie | Suppressed tear production | Mar. 2017 (C) | $1,138 |
| **Risperdal Consta® (risperidone)** | Janssen/Johnson & Johnson | Schizophrenia, bipolar I disorder | Oct. 2020 (EU) | $314 |
| **Sandostatin LAR® (octreotide)** | Novartis | Symptoms of certain metastatic carcinoid tumors | Aug. 2020 (C)<br>Apr. 2019 (EU) | $881 |
| **Venofer® (iron sucrose)** | American Regent/ Daiichi Sankyo | Iron deficiency caused by chronic kidney disease | Jun. 2018 (EU) | $299 |

** Sales for Invega Sustenna® are estimated to be 80 percent of 2019 US sales reported by J&J for Invega Sustenna® and Invega Trinza®.*

### Results

By our estimate, generic competition in the United States for the seven complex products in this analysis would yield annual savings between $600 million and $1.7 billion, with a median savings estimate of $1.3 billion. These significant savings could have been realized already if the currently pending ANDAs for these complex generics had been approved earlier by the FDA.

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## Conclusion

Complex generics represent an untapped savings opportunity for the US healthcare system, including patients, Medicare, Medicaid, and commercial payors. The FDA and other stakeholders have made efforts to facilitate a more robust complex generic marketplace, but these have thus far resulted in process improvements more than outcome gains. With more complex products on the verge of losing exclusivity and patent protection, it is important for policymakers to achieve demonstrable progress in increasing access to complex generics in the US market.

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