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The Impact Of Price Regulation On The Availability Of New Drugs In Germany

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ABSTRACT The 2011 German Pharmaceutical Market Restructuring Act subjected brand-name drugs for nonrare diseases to price regulation based on an assessment of their clinical benefit. Indication-specific assessment outcomes range from major added benefit to less benefit than the appropriate comparator(s) and affect price negotiations beyond the first year on the market. Using data on drugs that entered the market in the period 2012–16, we evaluated benefit assessment findings, subsequent drug exits, and their correlates. We considered 171 drug-indication pairs, corresponding to 138 different drugs. Of these, 66 drug-indication pairs (55 different drugs) were found to have added benefit. Almost all drugs with a positive benefit assessment (98 percent) remained on the market, while drugs without a positive benefit assessment were over ten times more likely to exit (25 percent versus 2 percent). US policy makers considering how to address rapidly increasing drug costs may draw valuable lessons from the German experience.

High prescription drug prices have been a headline issue in the US and other industrialized countries in recent years.^{1,2} In 2007 drug prices in Germany were found to be higher than those in all but two other Organization for Economic Cooperation and Development countries.³ This finding reflected limited price regulation for patent-protected brand-name drugs. For example, until earlier in this decade, manufacturers in Germany could set list prices for drugs freely. Although Germany's statutory health insurers, which insure over 90 percent of the people in the country,^{4,5} have been able to negotiate nondisclosed rebates via a tendering process since 2007, competition via tendering has been largely limited to off-patent drugs. (For details on the history of German pharmaceutical regulation, see online appendix exhibit 1.)⁶ As a result, prices for on-patent brand-name drugs increased steadily.⁴

In 2011, motivated by rising drug prices and

supported by statutory health insurers, the German parliament passed the Pharmaceutical Market Restructuring Act, or Arzneimittelmarkt-Neuordnungsgesetz (AMNOG), which subjected new drugs to price regulation based on a formal benefit assessment.⁷ The process begins after a drug is approved by the European Medicines Agency (the European Union equivalent to the US Food and Drug Administration), permitting the drug to be sold within Germany. During the first year following a new drug's launch, the manufacturer sets the drug's price and must submit a report summarizing the product's benefit to the Federal Joint Committee, the highest decision-making body of the joint self-government of physicians, dentists, hospitals, and health insurers (sickness funds) in Germany.

The Federal Joint Committee forwards the report to the Institute for Quality and Efficiency in Health Care (IQWiG), an independent, nonprofit institute that researches the value of medical

interventions, which must conduct a benefit assessment within three months. The evaluation is designed to take into account clinical evidence, and it follows transparent and standardized procedures that are frequently revised, updated, and published online.⁸

Following the presentation of the IQWiG's benefit assessment and a notice period during which medical societies, physicians, and manufacturers may contribute statements and additional data, the Federal Joint Committee reaches a final decision regarding the level of benefit of the new drug for an indication relative to comparator therapies that are identified by the committee prior to assessment.⁸ The detailed reports of each assessment are published online. A drug-indication pair is assigned to one of six benefit levels: major added benefit; considerable added benefit; minor added benefit; nonquantifiable added benefit; no evidence of added benefit; and less benefit than the appropriate comparator(s). If the benefit assessment falls into any of the first four categories for any patient subgroup (for example, only for patients with a specific advanced non-small-cell lung cancer), the Federal Joint Committee gives a positive benefit rating for the indication as a whole.⁹

After the committee's decision, a manufacturer must decide how to proceed in the German market. If the manufacturer is not satisfied with the committee's evaluation (for example, if the manufacturer received a negative benefit assessment, which puts it in a weak position for price negotiations), it can choose to opt out and withdraw its drug from Germany within four weeks.¹⁰ Opting out at this point prevents a negotiated price from being published in the official German drug price list, which can be referenced by other countries' price-setting bodies.

If the manufacturer decides to keep its product in the German market, the AMNOG process proceeds to price negotiations with the statutory health insurer umbrella organization, the National Association of Statutory Health Insurance Funds. Over the course of six months, the parties are expected to come to an agreement regarding the drug's price. If there is no proof of added benefit relative to the preselected comparator drug(s), the new drug can be directly placed into a reference price group, if one is available. Reference pricing—in which prices of drugs in a reference group serve as an upper bound on reimbursement for the statutory health insurers—is the preferred way of regulating drug prices in Germany. However, if a reference price group is not available, negotiations are initiated with an upper price limit of the price at which the annual cost of therapy with the new drug is no higher than the annual cost of therapy with its compar-

ator(s). If the parties cannot agree, an arbitration board is assigned to set a price within three months.¹¹ Private health insurers, which cover the rest of the population (roughly the 10 percent with the highest earnings),^{4,5} adopt the final price and send a representative to observe the negotiations.¹² Following arbitration, a manufacturer can decide again to exit the German market, but the price of the new drug will be published in the official German drug price list. Appendix exhibit 2 summarizes the major steps in the AMNOG process,⁶ including price negotiations¹³ and arbitration,¹⁴ over the fifteen-month period immediately following a drug's market entry and indicates potential market exit points for manufacturers during the process.

Public opinion supported the AMNOG at the time of its passage, as it promised to slow one of the most prominent sources of cost growth in the German health care system.¹⁵ However, the AMNOG process also presents the risk that important new drugs will be withdrawn from the German market as a result of conflicts between payers and manufacturers over reimbursement prices. We therefore sought to understand the circumstances under which manufacturers have withdrawn their products from the German market.

Study Data And Methods

We conducted a retrospective analysis of the association between observable features of new pharmaceutical products and post-AMNOG market exits.

DRUG SELECTION We identified all new drugs brought to market in Germany in the period 2012–16. We excluded drugs that came to market during 2011, as the AMNOG was implemented during that year and a set of special, short-term regulations applied through the end of July 2011. We similarly excluded drugs that came to market after 2016 to allow sufficient time for the observation of benefit assessment and relevant outcomes for all products. Because the AMNOG process can take up to fifteen months, a drug approved in late 2017 might not have completed the process until 2019. We excluded vaccines, drugs for rare diseases, and nontherapeutic products, as the AMNOG process for these products differs from that applied to traditional pharmaceutical products.

DATA SOURCES AND EXTRACTION Data were compiled using five sources with information on the German pharmaceutical market. First, annual German pharmaceutical reports were used to create a complete list of drug introductions in 2012–16.¹⁶ Second, data on opt-out announcements, original manufacturer list prices,

and the prices of appropriate comparable therapies (when available) were collected from the online databases of the National Association of Statutory Health Insurance Funds.¹²

Third, data were collected from the Federal Joint Committee's database,¹⁷ which categorizes drugs into fourteen therapeutic areas and indicates whether the AMNOG process determined that a specific drug-indication pair offered added benefit. A binary indicator of added benefit (versus no added benefit) was recorded. Drug-indication pairs were flagged as having added benefit if they ever received an assessment of major added benefit, considerable added benefit, or minor added benefit. Drug-indication pairs always found to have nonquantifiable added benefit or no added benefit, or for which benefit data were undocumented, were coded as having no added benefit. At the active ingredient level, a drug was flagged as having a positive benefit assessment if any one of its indications was found to have added benefit. For two hormonal drugs (one for oral contraception and one for postmenopausal hormone replacement), no benefit assessment was undertaken. These products were not included in the analysis of products by benefit status.

Fourth, data on the set of drugs that entered arbitration and the set of drugs that exited the German market were collected from the 2017 AMNOG report, which is published by Germany's third-largest statutory health insurer.¹⁰ Fifth and finally, the S&P Capital IQ database was used to assign publicly listed status and revenue data to manufacturers.¹⁸

ANALYTIC PLAN We recorded summary statistics for variables of interest in the form of overall and grouped sample means. We recorded the differences in means of observable characteristics between products with and without a positive benefit assessment. All analyses were performed using Stata/MP, version 15.1.

LIMITATIONS The primary limitation of this analysis was the binary nature of the added benefit variable, which prevented differentiating between drugs that had added benefit for only one patient subgroup or indication and drugs that had added benefit for all patient subgroups or indications, or between incremental and significant added benefits.

A secondary limitation was that the relatively short period of observation (five years) following the implementation of the AMNOG meant that it was not possible to observe long-term

EXHIBIT 1

Distribution of the sample of drug-indication pairs entering the German market, by therapeutic area and result of the AMNOG process, 2012–16

| Therapeutic area of drug | All (N = 171) | | Added benefit (n = 66) | | Entered arbitration (n = 20) | | Exited market (n = 28) | |
|--|---------------|----|------------------------|----|------------------------------|----|------------------------|----|
| | No. | % | No. | % | No. | % | No. | % |
| Cardiovascular diseases | 10 | 6 | 5 | 8 | 0 | 0 | 0 | 0 |
| Diseases of blood and blood-forming organs | 4 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diseases of the digestive system | 3 | 2 | 0 | 0 | 1 | 5 | 1 | 4 |
| Diseases of the genitourinary system | 6 | 4 | 1 | 2 | 1 | 5 | 2 | 7 |
| Diseases of the musculoskeletal system | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diseases of the nervous system | 9 | 5 | 1 | 2 | 4 | 20 | 3 | 11 |
| Diseases of the respiratory system | 12 | 7 | 6 | 9 | 0 | 0 | 0 | 0 |
| Eye diseases | 8 | 5 | 1 | 2 | 0 | 0 | 1 | 4 |
| Infectious diseases | 21 | 12 | 14 | 21 | 1 | 5 | 0 | 0 |
| Metabolic disorders | 25 | 15 | 5 | 8 | 9 | 45 | 13 | 46 |
| Oncologic diseases | 52 | 30 | 31 | 47 | 3 | 15 | 5 | 18 |
| Others | 8 | 5 | 1 | 2 | 0 | 0 | 1 | 4 |
| Psychiatric diseases | 6 | 4 | 0 | 0 | 1 | 5 | 2 | 7 |
| Skin diseases | 5 | 3 | 1 | 2 | 0 | 0 | 0 | 0 |

SOURCE Authors' analysis. **NOTES** All data are presented at the drug-indication pair level for the 138 assessed drugs, which were associated with a total of 171 drug-indication pairs. Summary statistics for the categories "Added benefit," "Entered arbitration," and "Exited market" present details for nonexhaustive, non-mutually exclusive subsamples of these products. The drugs include two products for which no benefit assessment was completed (both are among the five new drug-indication pairs for diseases of the genitourinary system). "Benefit" refers to drugs that were found to have added benefit. The arbitration process is explained in the text. "Exited market" refers to drugs that exited the German market. AMNOG is Arzneimittelmarkt-Neuordnungsgesetz, the Pharmaceutical Market Restructuring Act, as explained in the text.

impacts of the law on the introduction of new drugs in Germany.

Study Results

Over the observation period, 171 new drug-indication pairs that met the sample inclusion criteria entered the German market (exhibit 1). The largest shares of entrants were drugs for oncologic diseases (30 percent), drugs for metabolic disorders (15 percent), and drugs for infectious diseases (12 percent). Of the 171 drug-indication pairs, 169—corresponding to 138 different drugs—completed the AMNOG process.

Seventeen (12 percent) of the 138 drugs that completed the process entered arbitration (exhibit 2), and 22 (16 percent)—corresponding to twenty-eight drug-indication pairs—exited the market (exhibits 2 and 3). These drug-indication pairs consisted of drugs for metabolic disorders (thirteen drugs), oncologic diseases (five), nervous system diseases (three), genitourinary system diseases (two), psychiatric diseases (two), digestive system diseases (one), eye diseases (one), and other conditions (one) (data not shown). Drugs in the following therapeutic areas did not experience any market exits: cardiovascular diseases, diseases of the blood and blood-forming organs, musculoskeletal diseases, respiratory diseases, infectious diseases, and skin diseases.

In total, 55 drugs (representing 66 drug-indication pairs) received a positive benefit assessment, and 83 drugs (representing 103 drug-indication pairs) received a negative benefit assessment (exhibit 3).

Exhibit 2 presents additional information on features of assessed drugs by benefit status and overall. Drugs without a positive benefit assessment were over ten times more likely to leave the German market than drugs with a positive benefit assessment (25 percent versus 2 percent). Drugs without a positive benefit assessment were only slightly more likely to go to arbitration than those with a positive benefit assessment (14 percent versus 9 percent). However, among all drugs that entered the arbitration process, those without a positive benefit assessment were far more likely to exit the market after that point (83 percent versus 0 percent) (data not shown). Drugs with a positive benefit assessment had a greater number of average indications (1.4 versus 1.1). Although data were not available for all products, drugs with a positive benefit assessment also had a higher ratio of the drug's launch price to the appropriate comparable therapy price (5.1 versus 1.4); were manufactured by larger manufacturers, as measured by revenues (annual revenues in the year before drug launch of

\$33.9 billion versus \$21.6 billion); and were from a greater share of publicly listed manufacturers (91 percent versus 80 percent).

Discussion

In the early years of a new legislative framework in Germany in which newly approved brand-name drugs were required to justify their price to an independent body during their first year on the market, only a minority of drugs—primarily for metabolic disorders—subsequently exited the German market. Our analysis shows that a positive benefit assessment was a strong predictor of remaining on the market, while a negative benefit assessment was a strong predictor of subsequent market exit. This underscores the importance of a transparent benefit assessment process with clearly defined requirements and procedures.

Although manufacturers that received a negative benefit assessment for their drugs had the opportunity to initiate arbitration to secure a higher reimbursement price, few did so. Those that did were unlikely to reach a favorable outcome through this process.

Several factors may explain these findings. First, the widely perceived legitimacy of the benefit assessment process could have led manufacturers to believe that there was a low likelihood of major changes to a product's reimbursement prospects as a result of arbitration. Because little is known in advance about the outcome of the arbitration process, engaging in arbitration leads to guaranteed costs for the manufacturer with a low expected likelihood of a positive

EXHIBIT 2

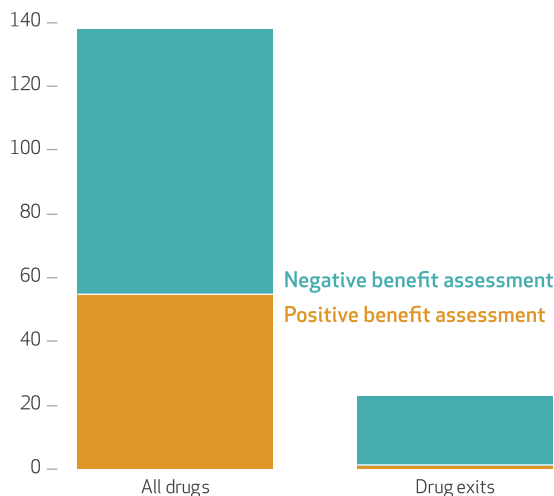
Factors related to the AMNOG process, overall and by benefit assessment, 2012-16

| | All | Positive benefit assessment | Negative benefit assessment |
|--|---------|-----------------------------|-----------------------------|
| Mean manufacturer revenue in year before drug launch (billions \$US) | \$26.57 | \$33.92 | \$21.55 |
| Publicly listed manufacturer | 84% | 91% | 80% |
| Number of indications | 1.2 | 1.4 | 1.1 |
| Price ratio ^a | 3.1 | 5.1 | 1.4 |
| Opted out of the German market ^b | 7% | 2% | 10% |
| Initiated arbitration | 12% | 9% | 14% |
| Exited German market after opt-out period ^c | 9% | 0% | 16% |
| Left German market for any reason ^d | 16% | 2% | 25% |

SOURCE Authors' analysis. **NOTES** Of the 138 assessed drugs, 55 had a positive benefit assessment and 83 had a negative benefit assessment. AMNOG is Arzneimittelmarkt-Neuordnungsgesetz, the Pharmaceutical Market Restructuring Act, as explained in the text. ^aRatio of original manufacturer price to appropriate comparable therapy price. ^bAfter a decision by the Federal Joint Committee, as explained in the text. ^cAfter arbitration, as explained in the text. ^dIncludes drugs that opted out or and those that exited the market.

EXHIBIT 3

Numbers of assessed drugs and drug exits from the German market, by benefit assessment outcome, 2012–16



SOURCE Authors' analysis. NOTE There were 138 assessed drugs.

outcome.

Additionally, German law requires that a new drug's annual negotiated cost be no higher than the cost of the comparator in cases in which there is no proof of added benefit even when that comparator is a generic drug. This likely explains the high number of exits observed among oral diabetic therapies, a drug class in which numerous highly effective generic products exist, relative to oncology drugs, a field in which comparators (if they exist) are likely to be very expensive.¹⁹

Future studies should consider the reasons for a finding of no evidence of added benefit and how the causes of this finding (for example, failure to present any evidence versus failure to present admissible evidence based on an appropriate comparator) may have changed over time.

Policy Implications

Under the AMNOG process, pharmaceutical manufacturers can sell their brand-name products in the German market immediately after market authorization by the European Medicines Agency, as has historically been true. Since prices are fully reimbursed during the first year, there are minimal barriers for beneficiaries of the statutory health insurers or privately insured patients in gaining access to medicines. Experience with the new system thus far has demonstrated that most exits occurred either six months after market entry (before price negotiations started) or fifteen months after market entry (following the decision of the arbitration board). Our data support claims made by statu-

tory health insurers that the comparators of drugs that exit the market can easily be substituted for the exiting drugs since, in most cases, the assessment did not show evidence of any additional benefit.

Manufacturers have tried to undermine the AMNOG process by pointing to drug market exits and arguing that people who began treatment with new therapies during the first year of availability may face medical issues when switching.²⁰ The association of innovative pharmaceutical manufacturers, known as Verband Forschender Arzneimittelhersteller e.V., points out that for this reason, regional health insurers have plans in place to import drugs for their clients (at the prices for them in other countries) following drug exits,²⁰ even though it is likely that prices for these products in other countries may be higher than the costs of the alternatives available in Germany. However, there are many drug classes in which products are demonstrated to have comparable clinical effects, and in these cases, switching can be safely accomplished by patients and their physicians.

US policy makers considering how to address rapidly increasing drug costs may draw valuable lessons from the introduction of the AMNOG system in Germany. Most notably, in the early years of Germany's reform there was just one market exit—in the form of opting out—among the fifty-five drugs that were assessed as ever having any added benefit for an indication beyond that offered by existing comparable therapies. This product, the oncology drug regorafenib (Stivarga), was later reassessed by the Federal Joint Committee, which failed to confirm its prior positive benefit assessment.²¹

Thus, it does not appear to be the case that the introduction of a benefit assessment (and subsequent price negotiations) led to decreased access to the types of novel therapies that provide important clinical value. This finding provides early support for the potential to use new mechanisms for controlling drug spending in other contexts.

In the US, where drug benefit assessments are not routinely used in Medicare and Medicaid drug coverage decisions, incorporating more formal and transparent comparative effectiveness analysis could be promising.^{22,23} The AMNOG benefit assessment model also allows for the incorporation of response heterogeneity among patients and by indication. Adoption of such a model could help payers support coverage decisions and build drug formularies.

Conclusion

For all but one of the new drugs that exited the German market before or after AMNOG-directed

price negotiations, the Federal Joint Committee did not find any evidence of added benefit relative to selected comparators—and in the case of that drug, a revised benefit assessment later determined that there was no added benefit. Among those drugs that were always found to have added benefit for an indication among at least one group of patients, no market exits were observed, and price negotiations were satisfac-

tory for manufacturers insofar as they resulted in the ongoing availability of novel drugs with the potential to provide previously undelivered clinical value.

The early years of the German AMNOG experience may thus offer important lessons for other countries seeking to reduce drug spending without compromising patients' access to novel therapies and their benefits. ■

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