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Early Benefit Assessment for Pharmaceuticals in Germany: Lessons for Policymakers

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ABSTRACT: Since 2011, Germany's Pharmaceutical Market Restructuring Act has mandated that all newly introduced drugs are subject to an assessment of their benefits in relation to a comparator, typically the current standard treatment. For drugs found to have some additional benefit, the manufacturer and the statutory health insurers negotiate a price. For drugs found to have no additional benefit, their price is set in reference to the price of the comparator. This new system is intended to reduce spending on expensive new drugs that are no more effective than existing treatments, while encouraging pharmaceutical companies to invest in innovative drugs that improve health outcomes. The German experience provides lessons for the United States, where comparative effectiveness research is publicly funded but public insurance programs are limited in their ability to use its findings to make coverage or pricing decisions.

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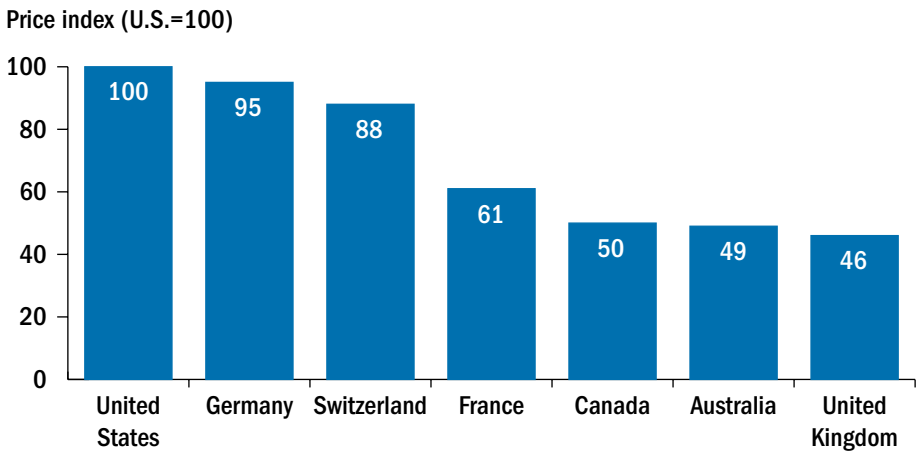
OVERVIEW

In Germany, pharmaceutical manufacturers were until recently free to set prices for prescription medicines approved for coverage under the statutory health insurance system. However, in the face of rapidly increasing prices for brand-name drugs and prescribing behavior shifting towards expensive new drugs, Germany enacted legislation to fundamentally change the way of establishing the value of new drugs and using it as the basis for price negotiations.

Pharmaceutical prices in Germany are high relative to most other wealthy nations, although they are not as high as they are in the United States. One recent analysis found that in 2010 drug prices in Germany were 5 percent lower than in the United States, but roughly double those found in Canada, Australia, and the United Kingdom (Exhibit 1).[1]

Since 2011, the Pharmaceutical Market Restructuring Act has mandated that all newly introduced drugs are subject to an assessment of their benefits in

Exhibit 1. Retail Price Indexes for Sample Drugs, 2010



Source: P. Kanovos, A. Ferrario, S. Vandoros et al., "Higher U.S. Branded Drug Prices and Spending Compared to Other Countries May Stem Partly from Quick Uptake of New Drugs," *Health Affairs,* April 2013 32(4):753–61.

relation to a comparator, typically the current standard treatment. For drugs found to have some additional benefit, the manufacturer and the statutory health insurers negotiate a price. For drugs found to have no additional benefit, their price is set in reference to the price of the comparator. This new system is intended to reduce spending on expensive new drugs that are no more effective than existing treatments, while encouraging pharmaceutical companies to invest in innovative drugs that improve health outcomes.

The German experience provides lessons for the U.S., where comparative effectiveness research is publicly funded but public insurance programs are limited in their ability to use its findings to make coverage or pricing decisions.

GERMANY'S STRATEGY FOR ASSESSING THE VALUE OF PHARMACEUTICALS

In January 2011, the Pharmaceutical Market Restructuring Act came into force.[2] Enacted by a conservative and pro-business coalition government, the purpose of the law was threefold:

1. Accelerate access to innovations for patients while paying a fair price for truly innovative drugs.
2. Keep the German market attractive for pharmaceutical manufacturers and researchers from both inside Germany and abroad.
3. Put a lid on the high cost of new brand-name drugs.

Indeed, the high costs of new drugs, long patent duration, and free price-setting by manufacturers, along with health care providers' tendency to prescribe pricier new drugs, offered an open field for cost-containment. And while Germany is a leader in the use of generic drugs, pharmaceutical companies have been putting new products on the market to make up for revenues lost to generics, offsetting some of the savings generated by generics' use (Exhibit 2).

To achieve these objectives, the new law introduced early benefit assessments of new prescription drugs. Under this system, a drug's clinical benefit is assessed in relation to a comparator: manufacturers and health insurers negotiate a price for those drugs found to have an additional benefit, and prices are set in reference to the comparator for drugs found to have no additional benefit. Following clear rules and a tight timeline, the early benefit assessment supports timely and transparent decision-making.

While the Pharmaceutical Market Restructuring legislation primarily targets new medicines, it has also paved the way to expand assessments to pharmaceuticals already on the market, medical devices, and medical treatments and interventions in general. It is important to note that the law exempts orphan drugs from the benefit assessment process: when a drug's sales revenue does not exceed €50 million (US$68 million) in the previous

The German Health Care System

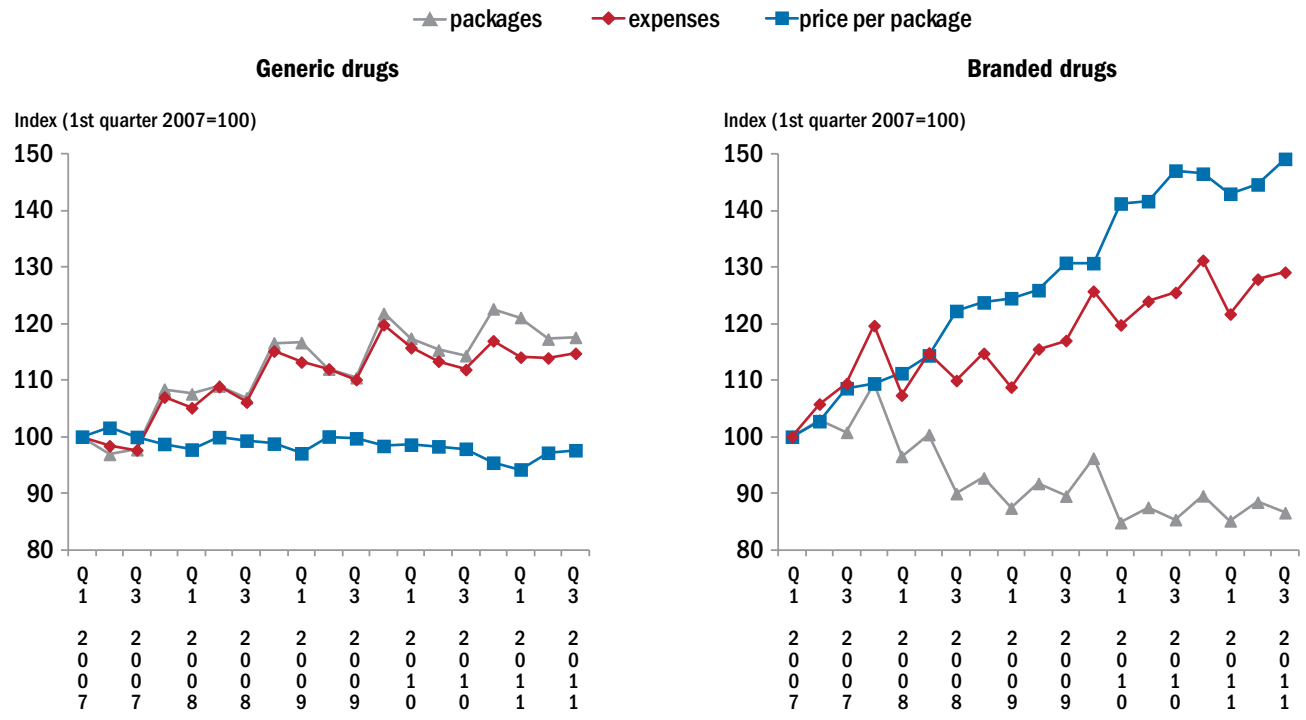
Germany is home to the oldest social security system among the major industrialized countries. Statutory health insurance (SHI) is one of five pillars of protection granted by law to every resident, the others being pension, unemployment, occupational accident, and long-term-care insurance. As of January 2013, residents can choose among 144 "sickness funds" that provide coverage under the statutory health insurance system. Sickness funds operate like private companies and bear the financial risk for the members they serve. By law they cannot reject applicants on the grounds of age, health status, or medical history ("guaranteed issue"). The statutory health insurance system is funded by contributions, divided equally between employers and employees, and to a small extent by general tax funds. The contribution rate, presently 15.5 percent of salary, is set by the German government. A virtual health fund collects and then distributes the money from and to the sickness funds based on their enrolled population's risk.

Coverage is generous and includes ambulatory care, hospital care, and prescription drugs, and a range of other health care services such as check-ups, cancer screening, psychotherapy, and physiotherapy. Copayments exist for prescription drugs, dental visits, vision aids, and elective services.

Outpatient providers are private practitioners working in solo or small-group practices as independent, self-employed entrepreneurs and are predominantly paid on a fee-for-service basis. Hospital ownership is split among municipal or state (regional) hospitals, not-for-profit and for-profit hospitals. The public hospitals, including university and teaching hospitals, attend to 50 percent of all patients.

Key features of the German health care system are choice and regulated competition within a self-governed system, not a state-run health care system. Compared with some Americans, Germans enjoy enormous freedom to choose and change their providers and health plans.

Exhibit 2. Prescription Drug Spending, Volume, and Prices in Germany, 2007–2011



Source: NVI (INSIGHT Health); Pharmacy retail prices.

12 months, the manufacturer does not have to prove the drug delivers an additional medical benefit over a comparator. While such cases are rare, they are growing in number.

Early Benefit Assessment: Process, Key Players, Timeline

The Pharmaceutical Market Restructuring Act of 2011 sets out new rules, roles, and an ambitious timetable for all stakeholders involved.[3,4] One key player is the Federal Joint Committee, a nonstate self-governance body including payer, provider, and patient representatives[5] that has far-reaching, quasi-legislative powers and is responsible for making coverage decisions within the statutory insurance system.

Once a new drug enters the market, its manufacturer sets the price, which is then valid for one year.[6] Manufacturers seeking longer-term reimbursement under Germany's sickness funds are required to submit a dossier to the Federal Joint Committee providing evidence from clinical studies regarding their drug's effectiveness, quality, and safety. Dossiers must be submitted within one year of a drug's introduction to the market. The Federal Joint Committee then commissions an independent health technology assessment institute, known as IQWiG, to assess the added value of the drug—as a new active substance, for a new therapeutic indication, or with added benefit for a specific patient population—compared with a comparator.[7] The comparator, normally the current standard treatment, can be another drug (often a generic), a nondrug treatment, or other current standard interventions. IQWiG reports its findings to the Federal Joint Committee, which then makes its decision on the drug's added value within six months of its introduction. If no additional benefit is found, the drug's price is set in reference to its comparator. If the drug is found to offer additional benefit, manufacturers and statutory health insurers negotiate a price, which goes into effect one year following market introduction.

Establishing additional benefit, or added value, is a complex process. The reform law and related regulation require assessments to take into account patient-relevant goals ranging from survival to quality of life. Some of these are quantifiable, while others are not. Since the definition of the goals, as well as the weighing of benefits, require value judgments, it is not surprising that the assessment process is vulnerable to challenge from manufacturers, but also from providers and payers.

What Is Added Benefit?

The companion regulation to the pharmaceutical reform law sets out six levels to measure the extent of benefit or even harm from a new drug, ranging from "major added benefit" to "lower benefit" (Exhibit 3).

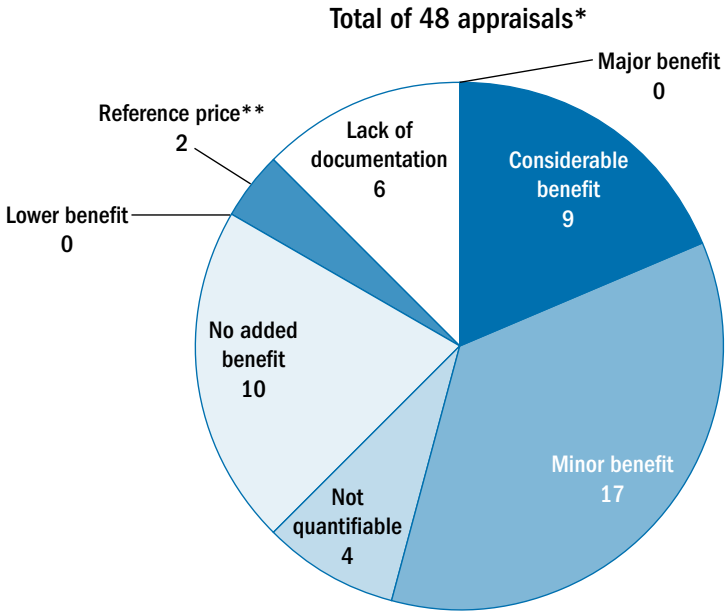
For those drugs found to bring added benefit, there are three levels:

1. *Major added benefit* is defined as sustained and substantial improvement not previously achieved by the current standard therapy. Such improvement could be disease remission, a major increase in survival time, a sustained absence of serious disease symptoms, or an extensive avoidance of serious side effects.
2. *Considerable added benefit* is defined as marked improvement over the comparator, expressed by a perceptible alleviation of the condition, a moderate increase in survival time, some alleviation of serious symptoms, and avoidance of serious adverse effects.
3. *Minor added benefit* is defined as moderate improvement, for example showing a reduction in nonserious symptoms and/or avoidance of side effects.

Most of the methodological and legal debates about drug assessments revolve around these three categories. The other three categories of decision are: 4) *added benefit present but not quantifiable,* 5) *no added benefit has been proven,* and 6) *lower benefit than the comparator.*

In the 48 benefit assessments completed by mid-September 2013, 30 drugs showed some added benefit. In the remaining cases, some of the dossiers submitted by manufacturers had applied an inadequate comparator, several either did not have a relevant study to back claims of benefit or lacked data on harms, and some were

Exhibit 3. Findings from Early Assessments of Pharmaceuticals: Highest Added Benefit Category per Substance



* As of September 12, 2013.
** The two manufacturers in the "reference price" category requested their new drug be assigned a reference price right away, without going through an assessment.
Source: Federal Joint Committee, press kit of September 12, 2013, upon release of the Arzneiverordnungs-Report 2013. Schwabe/Paffrath (eds.). Arzneimittelverordnungs-Report 2013. Aktuelle Daten, Kosten, Trends und Kommentare. 2013 (in German). The AMNOG report has been issued annually since 1985 by a team of independent pharmacologists, economists, and physicians.

incomplete in other ways.[8] In such cases, manufacturers are free to resubmit more comprehensive or updated dossiers.

Such problems with incomplete or inadequate evidence in the dossiers are likely beginners' mistakes, which may be overcome as drug manufacturers gain better understanding of the requirements. To this end, the Federal Joint Committee offers a priori consultations with the industry to give advice on preparation and submission of dossiers as well as on appropriate comparators and endpoints.[9] The Federal Joint Committee has also hosted several expert meetings to discuss and resolve challenges and unintended consequences of the new law.

Early Benefit Assessment Promotes Innovation

Of the 48 substances that passed the benefit assessment as of mid-September 2013, none came out in the highest added benefit category. But more than half were found to have at least some added benefit for some patient groups, and nine showed considerable proof of real innovation. For example, Ticagrelor (also known by the brand name Brilique), manufactured by AstraZeneca, was found to have considerable added benefit compared with use of Clopidogrel as standard treatment (Exhibit 4). The drug is administered to patients suffering from acute coronary syndrome. AstraZeneca was the first manufacturer to submit a dossier under the new regulation in early 2011, and the first to complete price negotiations with the Federal Association of Statutory Health Insurance Funds in early 2012. The result was declared a success by both parties, providing evidence that the new system can help establish fair prices for real innovations.[10]

Adverse Effects

An unintended consequence of the Pharmaceutical Market Restructuring Act is that some pharmaceutical companies announced they would not submit dossiers for early benefit assessment and instead bring their new drugs to the market outside Germany. Manufacturers are very sensitive to drug prices in Germany because it has historically had a high-price market and German reimbursement levels are used as a reference for pricing in many other countries. Low prices in a usually very

Exhibit 4. Early Assessment Findings on Ticagrelor for Patients with Acute Coronary Syndrome

Patient Group	Endpoint with Statistically Significant Effect	Probability of Benefit or Harm	Extent of Benefit or Harm	Overall Conclusion
Unstable Angina / NSTEMI (vs. Clopidogrel)	Overall mortality	Proof	Considerable ↑	Proof of considerable added benefit
	Cardiovascular mortality	Proof	Considerable ↑	
	Dyspnea	Proof	Considerable ↑	
	Myocardial infarction	Proof	Considerable ↑	
	Withdrawal because of adverse events	Proof	Minor ↓	
STEMI (drug treatment)	–	–	–	No added benefit (no data)
STEMI (PCI) (vs. Prasugrel)	–	–	–	No added benefit (no statistically significant event)
STEMI (CABG)	–	–	–	No added benefit (no data)

↑ Advantage of Ticagrelor.
↓ Disadvantage of Ticagrelor.
Source: IQWiG.

profitable market may induce even lower prices in other countries.

In one case Linagliptin (Trajenta), an anti-diabetes drug, was grouped in a reference price group as a result of Germany's assessment process. Two manufacturers, Boehringer-Ingelheim and Lilly, chose to withdraw this product from the German market, hoping to achieve a better entry price elsewhere.[11] In another case, GSK withdrew Retigabin (Trobalt), an anti-epilepticum, from Germany after failing to reach agreement in price negotiations. In both cases, generic drugs for which the companies had not provided comparative effectiveness data were determined through the assessment process to be appropriate comparators.

Yet in another case, the Federal Joint Committee decided against both an IQWiG recommendation and a decision made by the Scottish Medicine Consortium earlier in 2013. Ivacaftor (Kalydeco), a drug produced by the U.S. company Vertex Pharmaceuticals for treatment of children with cystic fibrosis, had been rejected for reimbursement by the Scottish authority because of limited evidence and high cost. In Germany, Ivacaftor qualified as having an additional benefit because it is an orphan drug with a small intended user base.[12] This demonstrates the independence and adaptability of the Federal Joint Committee's decision-making process.

As the committee chairman Josef Hecken has pointed out, Germany approves of new drugs at a higher rate than do other European countries: 64 percent of drugs assessed thus far were found to have some added benefit for at least some patient groups or indications, whereas in other countries only about half of drugs assessed are found to have added benefit.[13] Despite concerns voiced by the industry, Germany appears to be more innovation-friendly in its benefit assessments.

It remains to be seen, however, whether the early benefit assessment legislation will live up to its objectives of identifying true innovations and paying a fair price for them while keeping pharmaceutical expenses at bay in the long run. Data published in September 2013 suggest that the effects of the new process will only unfold with time and have to be seen in context with other powerful drug price control mechanisms, such as reference pricing and mandatory list price discounts for branded medicines.[14]

DISCUSSION

With so many entities and experts involved in the early benefit assessment process, meeting timelines and controlling costs have become challenges. The system must respond to new drugs as soon as they hit the market, with each dossier initiating yet another process that follows a strict schedule and absorbs substantial resources. Keeping up with the speed and volume of new pharmaceutical development could turn out be the litmus test of the new system.

To help support the assessments, it has been argued that stakeholder groups that benefit from

them, such as private health plans using Federal Joint Committee resolutions as a reference for their own reimbursement rules, should share financial responsibility for their costs.[15] Furthermore, Germany's Federal Joint Committee should strengthen European and international coordination in order to align strategies and share tools, data, and findings with similar benefit assessment agencies, such as NICE, SMI, HAS, or PBAC. Research, innovation, patents, drug authorizations, and product diversification are happening at a rapid pace and on a global scale.

Without an international framework, and without strong links to the nation's health strategy, the new benefit assessment system is at risk of becoming gridlocked.[16] Two years into implementation, the assessment review process faces several challenges.

For example, if most of the drugs submitted pass the test of proving some additional benefit, is it worthwhile dedicating considerable financial and human resources to the process? And how many more resources will be absorbed as the Federal Joint Com-mittee prepares to put standard treatments, new hospital treatments, and medical devices through the benefit assessment proceedings? Is there a better way of telling truly innovative therapies from "me too" products? Some manufacturers are attempting to introduce new drugs via the orphan drug exemption clause by refining therapies for smaller and smaller groups of patients ("slicing"). How will the Federal Joint Committee respond to this kind of gaming of the system?

There are also questions about the review process. For example, how well does the new system serve its purpose if single technological advancements are tested in isolation from population health considerations and overall health policy objectives? What patient-relevant goals should be considered, and how should such benefits be weighed against negative side effects? And how vulnerable is the current process when manufacturers can threaten to withdraw a drug from the German market rather than submitting it to the assessment process?

Relevance to U.S. Health Reform Efforts

Like Germany, the United States has experienced rising prescription drug spending in recent years. With much higher health spending than other nations, as well as tens of millions of people without health insurance, it faces perhaps even greater pressure to control health care costs and improve access to care.

In recent years, German policymakers have sought to use comparative effectiveness analyses to link prices to value, sending market signals meant to encourage innovations that truly benefit patients. As discussed above, this approach to pharmaceutical pricing faces significant challenges, including the administrative burden of generating and analyzing the evidence and controversy surrounding how to measure and compare benefits. The market effects of the new pricing scheme are also unknown, with some potential for unintended consequences. However, these challenges should be weighed against the potential for reducing wasteful spending and promoting innovations that will improve patient care.

With the creation in 2010 of the Patient-Centered Outcomes Research Institute, the United States has sought to strengthen comparative effectiveness research to better inform patients' and physicians' treatment decisions.[17] However, it does not have a public, transparent process for incorporating such research findings into coverage and pricing decisions. Public insurance programs are not allowed to base coverage decisions on cost-effectiveness criteria, and drug prices paid by private insurers are typically determined through proprietary negotiations with pharmaceutical companies. The German experience with early benefit assessment and value-based pricing offers U.S. policymakers an example of an alternative path to consider.

Notes

1 P. Kanavos, A. Ferrario, S. Vandoros et al., "Higher U.S. Branded Drug Prices and Spending Compared to Other Countries May Stem Partly from Quick Uptake of New Drugs," *Health Affairs,* April 2013 32(4):753–61.

2 In Germany the law is known as Arzneimittelneuordnungs-gesetz, or AMNOG. For a detailed account of the AMNOG legislation and companion regulation, and a step-by-step description of benefit assessment proceedings and timeline, visit the English-language website of the Federal Joint Committee at www.english.g-ba.de/benefitassessment/information/. Accessed online February 26, 2013.

3 Ibid., www.english.g-ba.de/benefitassessment/information/.

4 www.vfa.de/en/latest-topics/animation-amnog-early-benefit-assessment.html.

5 It is important to note that while patient representatives take an active part in the Committee's work, discussions, and hearings and have the right to file a motion, they do not have the right to vote on legally binding coverage decisions.

6 M. Ujeyl, C. Schlegel, S. Walter et al., "New Drugs: Evidence Relating to Their Therapeutic Value After Introduction to the Market," *Deutsches Ärzteblatt International,* Feb. 2012 109(7):117–23.

7 The Institute for Quality and Efficiency in Health Care (know by the German acronym IQWiG) was established alongside the Federal Joint Committee in 2004 to provide it with evidence-based evaluations of the benefits and cost-effectiveness of health services. IQWiG reviews available evidence and consults with experts and stakeholders, and then issues recommendations based on its findings. IQWiG functions only in an advisory role, however, with the Federal Joint Committee making final decisions regarding coverage and pricing.

8 IQWiG presentations, unpublished, 2012.

9 With so many moving parts and research and evidence evolving, the verdicts of the Federal Joint Committee are not final. The new system allows for temporary permissions as well as for the resubmission of substances that were insufficiently documented or at an early stage when first assessed.

10 Erster AMNOG-Preis ausgehandelt. Ärzte Zeitung, May 31, 2012. Accessed online August 8, 2012. Also see www.g-ba.de.

11 Kein Linagliptin für Deutschland. Ärzte Zeitung, 04-26-2012. Accessed online August 8, 2012/February 26, 2013. In fact, Linagliptin was submitted for reassessment in July 2012. However, the IQWiG appraisal as well as EMA findings that were referred to in the G-BA verdict of February 21, 2013, showed no added value of this drug in diabetes II blood sugar control versus the standard therapy in three different treatment scenarios (monotherapy and combination therapies). Meanwhile, in December 2012, Boehringer-Ingelheim has filed Linagliptin for a third assessment, this time for a new indication. The new verdict, of May 2013, found no new evidence for added value of Linagliptin in blood sugar control. Accessed online September 21, 2013.

12 "G-BA Defends Position of Germany as Innovation-Friendly Market as Kalydeco Receives Mixed Verdict," IHS Global Insight, February 11, 2013, www.ihs.com/products/global-insight/industry-economic-report.aspx?ID=1065976094. Accessed online February 26, 2013.

13 J. Hecken, "Current Tasks and Challenges of the Federal Joint Committee," Presentation at Spreestadt-Forum on Health Care, Berlin, December 17, 2012 (in German).

14 Arzneiverordnungs-Report 2013. Sind die Arzneimittelausgaben weiter im Abwärtstrend oder ist ein neuerlicher Kostenanstieg zu verzeichnen? Was sind die wichtigsten Auswirkungen des AMNOG? Welche Arzneimittel bieten Einsparpotenziale? (Press conference kit, September 12, 2013, in German). Also see IMS Health: IMS Marktbericht: Entwicklung des deutschen Pharmamarkts im Juli 2013 (in German).

15 Since aging and morbidity trends are affecting private health plan insurees just as much as statutory insurance members, drug spending hikes have hit private plans even harder than the sickness funds. Pharmaceutical expenses grew at a rate of 8.59 % for private plans compared with 5.18 % cost increase for sickness funds in 2007–2008, www.pkv.de/publikationen/pkv_publik/archiv/pkv-publik-nr-8-2010/vernuenftige-loesung/.

16 K. Chalkidou and G. Anderson, "Comparative Effectiveness Research: International Experiences and Implications for the United States," Presentation at AcademyHealth, July 2009; and J. Hecken, "Current Tasks and Challenges of the Federal Joint Committee," Presentation at Spreestadt-Forum on Health Care, Berlin, Dec. 17, 2012 (in German).

17 For further information, see: www.pcori.org.

About This Study

We analyzed legislation, the Federal Joint Committee's web content and presentations, media articles and market intelligence reports, and interviews with key players involved in the benefit assessment and early negotiation process. We also examined the methodological and ethical challenges of comparative effectiveness research when determining the appropriate comparator, including how the added value of a new drug or technology is defined and measured in terms of mortality, measurable health outcomes, patient experience, and quality of life for people with severe or terminal conditions. For the purpose of this brief, the term benefit refers to the measurable clinical benefit of authorized pharmaceuticals in the existing market. By contrast, added benefit, additional benefit, and value are used here to describe the above-mentioned broader spectrum of drug-induced improved health outcomes or patient-centered goals.

About the Authors

Sophia Schlette, M.P.H., currently freelancing as a health systems knowledge management advisor, was the international coordinator at the Federal Joint Committee (G-BA) until June 2012. Earlier, Schlette served as international health policy advisor and knowledge manager in various think tanks and an integrated delivery system (Kaiser Permanente). She earned a Master of Public Health degree from Harvard University and a diploma in political sciences from Freie Universität Berlin.

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