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Executive Summary

Of the Expert Report on

Ex-Factory Prices in European Pharmaceutical Markets as Reimbursement Framework of the German Statutory Health Insurance

**Issues and Problems of International Reference Pricing for
Innovative Pharmaceuticals**

Expert Report

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**On Behalf of the
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Objective of the Expert Report

1. In 2010, the German government launched another reform of pharmaceutical care in Germany with the *Arzneimittelmarktneuordnungsgesetz (AMNOG; Act for the Restructuring of the Pharmaceutical Market in Statutory Health Insurance)*. According to the *AMNOG*, **innovative pharmaceutical products** (drug innovations; *AMIs*) are supposed to be subjected to an early benefit assessment upon market introduction. If this assessment reveals a major additional benefit compared to appropriate comparative therapies, the product is considered a single-source drug and will be covered in the form of a reimbursement amount by the German statutory (*GKV*) and private (*PKV*) health insurance. This reimbursement amount must be negotiated by the manufacturers through central discount negotiations with the SHI Head Association (*GKV-SV*) or, if in dispute, fixed by an arbitration board (*Schiedsstelle*). This process should or must be based on the **actual ex-factory prices in other European countries**. This also applies to existing single-source drugs.
2. After the *AMNOG* became effective on January 1, 2011, the first decisions on reimbursement amounts are expected for early 2012. Up until then, any open questions in terms of content and methodology regarding the concept of **International Reference Pricing (IRP)**, which is new for Germany, must be clarified. This expert report is meant to make a substantial contribution in this respect. As a result, it takes the requirements of the *AMNOG* and addresses the **health economics and industrial economics problems** of the planned referencing of European comparison prices in view of the current regulatory practice in the 27 EU countries.
3. From a detailed regulatory-economic and empirical analysis of the regulatory circumstances in Europe, **pragmatic conclusions** for an appropriate assessment of reimbursement amounts in Germany in terms of content and methodology are to be drawn based on international comparison prices. For this purpose, suitable **comparison criteria and methods** will be developed. The guiding insight in this respect is the German government's goal for the *AMNOG* to create "a **reliable framework for innovation, for health care for the insured patients and for job security ...**" (statement of the German Federal Ministry of Health of November 11, 2010).

Part I: Economic Analysis of the Regulatory Framework

1 Pricing-Relevant Structural Characteristics in Pharmaceutical Markets

4. In many cases, high prices and frequent prescriptions of patented drugs are considered the driving force behind increasing pharmaceutical spending. As a result, the research-based pharmaceutical industry becomes a target of health policy wherever affordable pharmaceutical care is to be safeguarded as part of statutory health insurance. The reaction of health policy usually consists of government regulation efforts of the **prices or reimbursement amounts and prescription volumes**. By doing so, a conflict of interest

is easily triggered, if high-quality and progressive pharmaceutical care is desired at the same time.

5. Inadequate regulation of prices and quantities bears the risk of negatively impacting the innovative power of the pharmaceutical industry and to inhibit the diffusion process of novel or innovative pharmaceutical products, i. e., the dissemination of therapeutically superior and the displacement of obsolete or medically questionable products. **Innovation hurdles and diffusion barriers** delay the application of new pharmacotherapies; contribute to the underuse, overuse and misuse of pharmaceuticals; negatively impact the state of health and life expectancy of the population and have a more negative than positive effect on efficiency in the long run.
6. That price regulation in particular has a severe negative impact on the pharmaceutical innovation and diffusion process is due to the fact that the research-based pharmaceutical industry is a globally operating “high-tech industry” of a special kind that is concentrated in just a few locations; it is a **research, production and service industry** in one. This results in a number of characteristics of the competitive process in the pharmaceutical market, which in most cases go unnoticed in the health-political reform debates. However, they are relevant to the extent that the *AMNOG* especially applies to those products that are a particularly desired result of the pharmaceutical process of innovation, but they threaten to negatively impact this process in the face of inadequate intervention.
7. The primary competition for the pharmaceutical market is actually not a price competition but an **innovation competition** for ever new and therapeutically superior medicinal products (therapeutic competition): As the pharmaceutical research industry continuously launches innovative pharmaceuticals on a global scale, the suppliers of established products are permanently affected by losses in market share that jeopardize their existence. This can only be compensated by a continuous stream of their own innovations. It ensures that the innovator’s supply monopoly, which is only granted temporarily by patent protection anyway, can be “challenged” anytime by the launch of therapeutically superior drugs from competing manufacturers, i. e., it can be lost rather quickly.
8. At the same time, the innovation competition is also a **price competition** – to the extent that the inventor’s premium or the internal revenue rate on the capital used for research and development (R&D), which also depend on the overall sold quantity of a product, erode due to the losses in market share of the established products (old originals). Even if the initial launch prices of the *AMIs* remain unchanged, this results in **implicit price reductions**, as soon as these drugs get older and lose market shares in the diffusion process.
9. Provided there is intensive innovation competition, the initial launch price of a new drug is – based on experience – assessed according to the additional therapeutic benefit that can be achieved with the *AMI* and the potential need or prescription volume. This is done with the proviso that not just the running **production and marketing costs** can be

covered but that the accrued **R&D costs** can also be recovered by the time of patent expiration, which, as a result, complies with the concept of functioning price competition.

10. In the innovation competition, non-research-based pharmaceutical companies or those that only perform galenic research are largely without a function with their **generic drug offerings**, because – for lack of their own R&D activities – they launch mere **imitations** and no substantial follow-up innovations, as are typically created in the imitation process of the therapeutic competition. This also applies to importers whose business model is limited to **parallel imports or reimports** of pharmaceuticals. Instead, the economic significance of generic imitations lies in challenging the monopoly of the innovator after patent expiration and, as a consequence, in providing lower-cost offerings and meeting the *AMI* demand more broadly.
11. The reduction in reimbursement for innovative drugs intended with the *AMNOG* will inevitably be in conflict with the functional conditions of the innovation competition, if sufficient **cost recovery contributions** for ongoing pharmaceutical development can no longer be generated due to increased R&D risks and costs on the one hand and the explicit and implicit price reductions as a consequence of keener generic drug competition on the other hand. As a result, the **“intergenerational contract”** that previously applied to the pharmaceutical sector, based on which revenues from the sale of old originals must contribute to financing the development of the next pharmaceutical generation, would be invalid, if future innovations are to remain affordable.
12. As a consequence, astronomically high **therapy costs** that are no longer socially justifiable could arise in individual therapeutic indications (the beginning of which is already seen for orphan drugs or specific oncological products) if the manufacturers must essentially recover their development costs through accordingly high prices at the launch of the new drugs. As far as the *AMNOG* implies such a risk, it should be stated and assessed, and it should be countered in a suitable manner. Naturally, the numerous **market regulation efforts** as necessary conditions of such a “price spiral” must be put to the test first.

2 Market Regulations as Pricing Determinants for Pharmaceuticals

13. The health care system also requires the most intensive competition in the markets in order to be able to ensure efficient and progressive health care. However, due to their specific design principles and the resulting market failure, the existing health care systems technically do not allow competition across the board. Instead, this must be facilitated by a suitable regulatory framework and designed through regulatory measures. In the pharmaceutical market, too, the government must organize a functioning efficiency-based competition in the form of **“managed competition”**.
14. In fact, the regulations currently being practiced in pharmaceutical care in the EU countries are oriented on this model neither primarily nor without conflict. Instead, they

are used to achieve a **number of operative goals**, such as ensuring health care quality, attainability and accessibility or guaranteeing the economic efficiency and financing of pharmacotherapy. As a result, they run the risk of increasing their effects in a desirable or undesirable manner or to weaken each other, make each other superfluous or excluding each other. However, this must inevitably lead to **functional deficits of the regulatory system**.

15. The regulation efforts for cost containment for pharmaceuticals are frequently associated with severe **intervention with regard to pricing and prescription** both for newly launched pharmaceuticals (new products) and established drugs (old or existing products). Its objective may be the expenditure, expenditure and quality, or just the quality of old or new products, with the spectrum of measures ranging from competitive rules of conduct, compulsory tax payments and regress to anti-competitive market intervention. In terms of the level of intervention, all players in the market – pharmaceutical entrepreneurs as manufacturers as well as wholesalers and pharmacists as distributors, or physicians and patients as users – can be affected.
16. As is internationally customary, regulation efforts are distinguished by whether they are geared toward the pharmaceutical supply (manufacturer) or demand (physicians, patients, wholesalers and pharmacies). Among the **regulation efforts on the supply side**, instruments for reimbursement and pricing rank first based on intensity of the intervention and economic significance, because they directly determine the price and, as a result, have a direct impact on the pharmaceutical manufacturer. In contrast, the **regulation efforts on the demand side** are more subsidiary but a necessary complement for making cost containment policy effective at all by influencing the prescription, consumption and distribution behavior of the aforementioned players.
17. By way of examples from various countries, it is shown how differently reimbursement systems, price regulation and price intervention are designed in the EU and what price or quantity effects they can trigger. This shows that, e. g., **reimbursement systems** in Sweden and France are very subtle yet hardly quantifiable in how they contribute to the international price variations at the manufacturer level. And from the examples of France, Great Britain and Germany, it becomes apparent how their joint postulate of “Money for Value” is applied during **price regulation** and how this could be relevant for decisions during the *AMNOG* procedure.
18. From the compiled synopsis of the spectrum of **regulations on the supply side** for all 27 EU countries, it also becomes apparent why it is not possible to provide a clear or even uniform explanation pattern for pricing and its determinants in the national pharmaceutical markets. As a result, the amounts of pharmaceutical prices (especially *AMI* prices) and their changes cannot be derived from “supply and demand” alone like a textbook case; instead they reflect the sometimes eclectic regulatory practice of the individual countries, which is marked by trial and error.

19. While regulation on the supply side exclusively serves to manage spending, the **measures on the demand side** are primarily geared toward ensuring appropriate pharmaceutical care in terms of quality and availability. However, prescription limits for physicians, patient-oriented economic efficiency incentives and pharmacist-specific dispensation rules are also used in most EU countries for cost containment. As a result, especially the research-based pharmaceutical entrepreneurs are getting into a pincer movement on the supply and demand side in which not just the prices but also the quantities come under pressure as a second revenue component. Furthermore, additional hurdles are arising in the diffusion process.
20. The widespread **aut-idem prescriptions** of physicians in connection with the mostly obligatory or at least urgently recommended dispensation of cost-effective generic and imported drugs at the pharmacy is a focused, very effective promotion of generic and imported drugs. It is supposed to increase the rate of cheap existing products in the generics market, strengthen the generics competition and thereby lower the generic drugs pricing level. Therefore, the original manufacturers have next to no chance to generate significant cost contribution margins for their R&D.
21. As long as physicians are required based on obligatory **prescription guidelines and budgets** to exhibit guarded behavior in prescribing high-priced patented drugs at the expense of the cost payers and patients refuse to make additional payments, novel medicinal products are discriminated against. Such practices form a noticeable diffusion obstacle for the affected products. As a consequence, chances for the original manufacturer to recover his R&D spending before the patent expires are decreasing. In turn, progressive pharmacotherapy is withheld from patients and the dynamics of innovation are additionally slowed down in the long run.
22. **Patients copayments** and – in connection with them – the comparably high **costs of pharmaceutical distribution** and **sales taxes** work in the same direction. In most EU countries, patients share in pharmaceutical spending. In that case, a price-elastic demand must be expected in which higher prices result in slightly lower demanded quantities. This affects especially high-priced products when there are therapeutically comparable standard therapies. This effect is reinforced wherever the pharmacy sales price is comparably far above the sales price of the pharmaceutical entrepreneur as a consequence of high wholesale and pharmacy margins as well as sales taxes. Therefore, internationally blatantly different elasticity conditions, distribution costs and excise taxes as determinants of international price differences must enter the IRP process.
23. Typically, novel active ingredients are patented and provide the pharmaceutical entrepreneur with a **temporary monopoly** for his innovation. This is economically necessary and intended in terms of industrial policy, while the leeway for its **market-strategic behavior** results from the regulatory market division in Europe and elsewhere. Under these circumstances, international price divergences for one and the same product inevitably occur. Their extent will then depend on the specific **regulation concepts and practices** in the respective countries on the one hand and the existing

national **health care structures and market specifics** on the other hand. In addition, there are epidemiological, social and economic determinants, which result from the economic power and income situation of a country as well as the state of health and the health preferences of its population.

24. For six **regulations on the supply side**, which have a direct and effective impact on the formation of the sales price of the manufacturer (price fixing and negotiation, discounts and reimbursements as well as price intervention and IRP), three regulation concepts with two versions each can be identified for the 21 most important EU countries. These concepts increase from top to bottom in terms of the regulatory density and intensity:

Free pricing

- without additional regulation on the supply side (**Denmark, Sweden**) or
- with additional regulation on the supply side, such as discounts, reimbursements and price intervention (**Germany, Great Britain**).

Price negotiation

- with the exception of IRP without additional regulation on the supply side (**Ireland, Austria**) or
- with additional regulations on the supply side, such as discounts, reimbursements, price intervention and IRP (**France, Italy, Hungary**).

Price setting

- with prior price negotiations and additional regulation on the supply side, such as reimbursements and IRP (**Poland, Estonia, Latvia**) or
- without prior price negotiations and with additional regulation on the supply side, such as reimbursements, price intervention and IRP (**Netherlands, Belgium, Finland, Spain, Greece, Portugal, Slovenia, Slovakia, Czech Republic**).

25. If one ranks the above-mentioned countries according to the level of their pharmaceutical prices and connects this with the level of their economic power, this results in three regional country clusters (**Northern Europe** with Denmark, Germany, Netherlands, Ireland, Sweden, France, Belgium, Finland, Great Britain and Austria; **Southern Europe** with Italy, Spain, Greece, Portugal and Slovenia; **Eastern Europe** with Slovakia, the Czech Republic, Poland, Hungary, Estonia and Latvia). If one adds the regulation concepts formed, it becomes intuitively apparent that there is a connection between the countries' positioning on the pricing scale, their regional affiliation and the regulation concept practiced in each case.
26. The two versions of the liberal market concept of **free pricing** are found in only four Northern European countries. But even the majority of the five countries that follow the comparatively moderate regulation concept of **price negotiations** are in Northern Europe. In contrast, the harshest regulation concept – **price fixing** with and without prior price negotiation – is predominantly implemented in Southern and Eastern European countries.
27. Since the sales prices of the pharmaceutical entrepreneurs are all the more under pricing pressure the more stringent a regulation concept is and its instruments are being

applied, harsher regulation actually also coincides with lower prices in the countries and regions in the compiled synopsis. This is a plausible reference to a potential causality between the level of regulation and the level of pricing for pharmaceuticals. For the upcoming *AMNOG* reference pricing, this possibly means that with the prospective recurrence to low prices in the Southern and Eastern European countries of the EU their **regulation concepts** would also be **imported by Germany**.

3 International Reference Pricing for Innovative Pharmaceutical Products in Europe

28. In view of the existing international price differences, high-price countries have so far increasingly attempted to also lower their pharmaceutical prices: preferably with **drug imports from low-price countries** (parallel and re-imports) on the one hand and referencing **low-price countries in international reference pricing** on the other hand. In both cases, an international “race to the bottom” (downward spiral effect or *Keller-treppen-Effekt*) threatens to happen. It could easily lower the sales price of the pharmaceutical entrepreneur in the direction of the marginal costs of drug production and **result in losses**, since the total average costs in the pharmaceutical industry are typically above the marginal costs of production.
29. Therefore, the expert report initially shows that it is economically justified when manufacturers as temporary monopolists nationally segment the markets of their innovative products and set **different prices** in the individual countries based on the ability to pay (economic power) and willingness to pay (preferences). Such price differentiations (*Ramsey* prices) allow **patients in low-price countries** access to innovative pharmaceuticals from which they would be cut off, if the price were leveled off at the average. On the other hand, **patients in high-price countries** also benefit from this, since the overall sales of innovations are larger than with the exclusion of low-price countries and, as a consequence, the average costs and prices will be comparatively lower. Ultimately, the price differentiation would enable the **innovators** to cover their “sunk” fixed costs in R&D with a greater likelihood and therefore maintain their innovative power.
30. However, this is contrasted by the widespread and diverse regulatory practice of **international reference pricing** (IRP) to the extent that countries with noticeably divergent ability to pay and willingness to pay mutually reference their prices and prefer low-price countries as a reference. This creates a regulatory network of connections of countries referencing each other with the tendency to develop “**uniform prices**” across countries for internationally offered pharmaceuticals. A synopsis of the common IRP practices in Europe shows that, with the exception of Germany (before the *AMNOG*), Denmark, Great Britain, Malta and Sweden, all other EU member countries as well as Norway and Switzerland practice IRP. **Germany** is directly referenced by 19 of these countries and indirectly referenced by the five remaining countries. As a result and also with regard to its market significance (Germany has an EU-wide influence potential of about EUR 100 billion), it is considered the most important “**anchor country**” in Europe.

31. What impact the previously free pricing and full reimbursement of patented drug prices in Germany really has on the sales prices of the pharmaceutical entrepreneurs in the referencing EU countries is quantitatively almost impossible to assess. Too diverse are the IRP concepts pursued by them and too nontransparent and changeable are their practices. In contrast to generic drugs, the manufacturers are also in a position to **proceed strategically during the launch of innovations**. In the interest of the highest possible launch price in markets with the highest possible sales, they endeavor to offer their new products initially in the large reference countries without IRP where pricing is relatively liberal, where relatively high launch prices can be realized and where a certain market significance can be attained quickly. This was previously the case in **Germany** and still applies to Denmark and Sweden. On the other hand, it may be necessary from a market-strategic standpoint to delay the market launch of innovations or forgo it altogether in those countries that practice particularly rigid price regulation or are predominantly referenced by such countries that orient themselves on lowest-price countries – such as **Estonia, Greece, Italy, Latvia, Poland** or **Slovakia**. This would also explain why the launch of new drugs in many of these countries is noticeably delayed and patients must wait for novel pharmacotherapy particularly long as compared to **Germany**.
32. Under these conditions, the current IRP in the EU should have two impacts: First, the launch prices for a new drug in the referencing countries need **not to deviate far from the price in the anchor country**; and second, especially smaller yet frequently referenced countries with little economic power (and correspondingly rigid price regulation in most cases to ensure affordable prices) must expect that foreign manufacturers **launch their innovations only with a time delay or not at all** in their market. However, both results are in contradiction to the *Ramsey* postulate of accepting prices for innovative pharmaceuticals in the interest of the greatest possible welfare in the EU community of states that differ in terms of the ability to pay and willingness to pay of the individual member countries, thereby preventing poorer countries from suffering supply deficits or being excluded from health care altogether.
33. If **Germany** turns to international reference pricing in the future for innovative new and existing products in accordance with the *AMNOG*, **it will inevitably lose its previous anchor function** in pricing in the European IRP system. It has already been attempted by means of simulations to assess the quantitative effects of price reductions in individual countries to the IRP system overall. Due to the wealth of diversity and strategic susceptibility of the IRP system as well as the statistical-methodological measurement problems, the results inevitably only provide an initial empirical clue. At least, they can be used to show that a 10% decrease in the sales prices of the pharmaceutical entrepreneurs in Germany could lead to annual revenue losses in the billions for the European pharmaceutical industry.
34. However, these are only effects of the first and second rounds, which means that additional down-ward spiral effects remain unconsidered. Yet they will become relevant for Germany in the future. Once Germany is no longer an anchor country, the remaining

anchor countries of Great Britain, Denmark and Sweden with their lower price level compared to Germany will move into the focus of negotiations with the SHI Head Association (*GKV-SV*) for the **existing single-source drugs**. Furthermore, due to the involvement of Germany in the existing IRP system, there is a threat of an additional re-referencing that would exert a downward pressure on prices. In turn, it is unclear for the **new single-source drugs** how and in what sequence they will be launched in other European countries in the future, i. e., which countries will be available for referencing in Germany at all with what actual sales prices at the time of negotiations. As a result, the outcome of this “referencing roulette” depends entirely on the modalities of negotiation, especially the groups of countries and calculation procedures used as well as the future marketing strategies of the manufacturers who react to this.

4 Conclusion: Appropriate Reference Pricing Requires Comparable Reference Countries

35. The regulatory-economic analysis shows that the legislature ventures into difficult and not easily surveyable terrain with the *AMNOG*. After all, an institutional change in the EU lies ahead in the highly sensitive pharmaceutical patent market with regard to the pricing modalities in Germany and triggered by the IRP system. This leads not only to a **loss of Germany’s anchor function** but will also have long-term repercussions on the entire European pharmaceutical pricing structure due to its prominent market significance. As far as we can imagine based on the present analysis, the following consequences must be expected:

- Based on the status quo, the manufacturers of “**existing single-source drugs**” will have to expect revenue losses, which they will suffer not just in Germany but wherever these products have been launched and are subject to the IRP mechanism in Europe and beyond on a worldwide scale.
- In principle, this also applies to “**new single-source drugs**” if the numerous countries that reference Germany do not bill list prices but the reimbursement amounts that were reduced through central discount negotiations. How large these revenue losses will be depends crucially on how the manufacturers behave strategically in calculating their prices and in launching their innovative products.
- Such strategies bear the risk that novel products (*AMIs*) will in the future **no longer be launched in Germany first** – as they were in the past – but in the remaining anchor countries, if launch prices that are above the reimbursement amount to be expected in Germany can be realized there.
- The consequence would be **delays in the launch** of innovative pharmaceuticals, not just in Germany but also in those reference countries that formally or informally go by the lowest prices and demand these via the referencing mechanism at the expense of patients who depend on progressive medical therapies.

- Lower reference prices in other countries and strategic delays in the marketing process reduce the manufacturers' revenues in the market segment of single-source drugs. Such **revenue losses** must either be caught prospectively through higher offer prices during the launch of the future innovations or they go at the expense of the dynamics of innovation and therefore future patient pharmaceutical care with innovative products.
36. Overall, it must be expected that due to Germany's new role in the IRP system lower prices will form for innovative drugs that are nonetheless still high and tend to be largely uniform. However, this result is bought with a **decrease in the financing basis** for future R&D projects, **delayed availability** of innovative pharmaceuticals, especially in smaller countries with stringent pricing regulations, and with **additional welfare losses** for those countries that suffer supply deficits or receive no pharmaceutical care with innovative medicinal products due to insufficient price differentiation.
37. As a result, it must be deliberated how the reference pricing in Germany can be designed in such a manner that undesired impacts can be at least minimized, if not avoided. The key for this is a **stringent selection of reference countries** on the one hand, which are comparable to each other according to theoretically valid and empirically secured criteria, as well as a **practicable procedure for conducting price comparisons** and **adjusting comparison prices** for the effects of particularly price-distorting national regulations on the other hand.
38. From a regulatory-economic standpoint, only such countries can be considered for referencing that are comparable in terms of their economic, social and epidemiological structure and that have approximately the same **ability to pay** and **willingness to pay** for their pharmaceutical care. And for the comparison procedure itself, not just operational **norm-setting** and **standardization** of the legally stipulated "actual sales prices" is required as a comparative figure but also their **weighting** with prescription quantities as well as the **correction** of irregular price determinants based on a valid empirical analysis.

Part II: Empirical Analysis

5 Ability to Pay and Willingness to Pay as Criteria for Country Selection

39. Only with the prerequisite of largely homogeneous circumstances in the individual countries will international price comparisons lead to meaningful results. What is needed in particular is a catalog of criteria that facilitates an adequate selection of countries or a meaningful price comparison from an economic standpoint. Prices for innovative pharmaceuticals can be based on a **variety of influential factors** in a public health care system, i. e., the societal (added) value of the innovation, patient benefit, the ranking of medicinal products within the health care system, the existing burden of

disease or in principle the **ability to pay** and **willingness to pay** of individual countries or their population.

40. Indicators that are easy to determine, largely indisputable and lend themselves to measuring the ability to pay and willingness to pay are the **gross domestic product (GDP)** per capita in euro as an indicator for ability to pay on the one hand and **health care expenditure (HCE)** and **pharmaceutical expenditure (PhE)** – each per capita in Euro – as measurements for the willingness to pay. For the empirical determination of a **group of countries** (country basket) from the countries that are comparable to Germany, an econometric link of the two criteria of ability to pay and willingness to pay is generated. The willingness to pay is alternatively measured based on health care expenditure and pharmaceutical expenditure per capita. The statistical criterion for including a country into the country basket is a maximum of **one standard deviation** of its GDP and spending amounts compared to Germany's values, graphically resulting in a rectangular area as a "selection range" with Germany at the center.
41. According to the criteria of GDP and health care spending, the following countries turn out to be comparable to **Germany** (country basket 1; see chart below):

Belgium, Denmark, Finland, France, Greece, Great Britain, Ireland, Italy, Netherlands, Austria, Sweden and Spain.

Together with Germany, these 12 countries are among the so-called EU 15 countries, which formed the European Union before the Eastern expansion in 2004. As EU 15 countries, only **Luxembourg** and **Portugal** drop out of the given selection range. If pharmaceutical spending is used as a criterion of willingness to pay instead of health care spending, also **Denmark** and **Great Britain** are not in the country basket: They belong to the EU 15 countries but not to the European Monetary Union (EMU) and have been subject to considerable exchange rate fluctuations during the last years (country basket 2).

42. To correct statistical outliers and to contain strong fluctuations of GDP and health care and pharmaceutical spending, we also perform a logarithmic analysis. This results in a group of countries for both versions of willingness to pay that includes the **EU 15 countries without Luxembourg** but with **Slovenia** as an additional basket country (country baskets 3 and 4). However, **Slovenia** remains unconsidered thereafter, because it is a borderline case at the edge of the selection range and has no representative pharmaceutical market with just two million inhabitants. **Greece**, too, is excluded from the further examination: While it could in principle be used as a comparison country according to its econometric results, the current compulsory measures for consolidation of its public budgets as a result of the debt crisis distort this country's situation in such a way that its inclusion in any pharmaceutical price comparison does not appear meaningful.

43. As a result, the group of countries for the subsequent econometric analysis of the determinants of international price differences for innovative pharmaceuticals in the EU consists of a total of 13 countries:

Belgium, Denmark, Germany, Finland, France, Great Britain, Ireland, Italy, Netherlands, Austria, Portugal, Sweden and Spain.

However, three of these countries (Denmark, Great Britain and Sweden) do not belong to the EMU, so that they face additional problems based on the conversion of the pharmaceutical prices in their national currency into Euros. Neither the use of smoothed exchange rates nor of purchase power parities helps avoid price distortions in such a special market segment as innovative pharmaceuticals. If one would agree to price comparisons without countries outside the Euro area, such problems naturally could not occur.

Comparability of EU countries to Germany

Country	Population in m	Country Basket 1	Country Basket 2	Country Basket 3	Country Basket 4
		linear analysis HCE	linear analysis PhE	logarith. analysis HCE	logarith. analysis PhE
Austria (AT)	8,36	✓	✓	✓	✓
Belgium (BE)	7,61	✓	✓	✓	✓
Denmark (DK)	5,51	✓	—	✓	✓
Finland (FI)	5,33	✓	✓	✓	✓
France (FR)	64,37	✓	✓	✓	✓
Greece (GR)	11,26	✓	✓	✓	✓
Great Britain (GB)	61,60	✓	—	✓	✓
Ireland (IE)	4,45	✓	✓	✓	✓
Italy (IT)	60,05	✓	✓	✓	✓
Luxembourg (LU)	0,49	—	—	—	—
The Netherlands (NL)	16,49	✓	✓	✓	✓
Portugal (PT)	10,63	—	—	✓	✓
Slovenia (SI)	2,03	—	—	✓	✓
Spain (ES)	45,83	✓	✓	✓	✓
Sweden (SE)	9,26	✓	✓	✓	✓

Legend: HCE – econometric link of gross domestic product and health care expenditure (both per capita); PhE – econometric link of gross domestic product and pharmaceutical expenditure (both per capita); green – countries comparable to Germany, red – non-comparable countries; dark green – member of Euro area; light green – not member of Euro area; dark red – country not comparable (in general or within group): data not within selection range; light red – country not comparable: special characteristics (population figure, regulations, etc.).

6 Approaches and Methods of International Price Comparisons

44. As **data basis for the empirical survey**, we use pricing information by *IMS Health* (2011). This is supplemented by country information from the *OECD Health Data* (2011) and *Eurostat* (2011). Overall, the dataset includes 575 observations for the 13 countries

under review, including Germany. Applying so-called **standard units (SU)** allows us to compare various dosage forms to each other and serve as quantitative units for the innovative medicinal products. The available **sales prices of the pharma-ceutical entrepreneurs** (ex-factory prices – EFP) refer to the list price in the respective countries. In total, the data comprises 39 innovations launched in Germany from 2008 to 2010. As explanatory variables, we use the **gross domestic product (GDP)** per capita in Euro, the per-capita **health care expenditure (HCE)** in Euro and the **harmonized index of consumer prices for pharmaceutical products (HICP)**. Additional explanatory variables include the regulatory forms of **administrative or government price setting** and **IRP systems** in the individual countries, a dummy variable for **delayed market launch** of an innovative drug in Germany and the different **ATC classes of classification level 1**, into which the innovative medicinal products fall respectively.

45. The following information is derived from the descriptive statistics of the dataset: The **mean value of the ex-factory prices** is roughly EUR 300; this is mainly due to the relatively high prices of the novel products in some ATC groups. The average **per-capita gross domestic product** for the countries under review is a little more than EUR 29,000; the **per-capita health care spending** is more than EUR 3,300. With a value of 100.1, the **price index for pharmaceutical products** is close to the basic value of 100.0 of the year 2005. The HICP applied especially takes into account different developments in pricing structures in the countries under review.
46. If one takes a look at the relative deviations of the average values compared to Germany, one gets the following pattern: The foreign **EFP** are 14.3% below the German ones, the foreign **GDP** exceeds the German one by 10%, and the **HCE** is about 2% lower abroad than domestically. In contrast, the countries under review show an **HICP** value that is more than 11% lower than in Germany. In 60% of the analyzed drugs in the respective countries, pricing is based on an **IRP system**; 30% of the countries also use the instruments of administrative or government **price setting**. In about one-third of all cases, the reviewed innovative medicinal product was not offered in Germany first. In these cases, an **earlier market launch** took place especially in Denmark, Finland, Great Britain, Netherlands and Sweden.

7 Determinants of International Price Differences for Innovative Pharmaceuticals: Results

47. For the comparably homogeneous group of the 13 countries analyzed here, we find very **heterogeneous effects of the captured influence factors** on the price level and the price differences to Germany. If one were to consider additional countries, heterogeneity would increase significantly and therefore **decrease the comparability of prices for innovations**. Instead, our results suggest to further quantitatively narrow the underlying comparison criteria for ability and willingness and to expand the criteria by the product availability. As a consequence, the number of the potential reference countries for Germany would decrease even further.

48. As the data from 2008 to 2010 show, the **product availability** between the 13 countries under review varies considerably. Apart from Germany, innovations are practically fully available, especially in Denmark, Sweden, and Austria. On the other hand, in 2010 only eleven and nine of the 39 offered innovative pharmaceuticals were available in Italy and Portugal respectively. This **significantly limits the comparability** between the countries under review – especially to Germany. Even in a country like Belgium, which appears to be comparable to Germany in terms of the criteria of willingness and ability to pay, only 15 of the considered innovative products launched in Germany are available for the year 2010.
49. Furthermore, we find **significant price differences** for the countries under review compared to Germany. This particularly applies for the analyzed **innovations in the individual ATC classes**. If we take a look at the relative price deviations to Germany, it is easy to see that **domestic prices for innovative drugs are comparably high on average**. However, it should also be emphasized that, with the exception of Spain, **positive deviations to Germany** can be found in all other countries, i. e., individual drugs have in part considerably higher prices in different ATC classes there – and in various ATC classes drugs are not available at all. Positive price deviations are pre-valent primarily in Denmark and Sweden, both being countries characterized by a relatively low regulatory density. Even in countries such as Italy, Belgium, or Portugal – all with a small number of launched innovations and stringent price regulation – there is no uniform picture with regard to the 31 ATC classes: In these countries, the price for products in specific ATC classes also lies above the one in Germany. In view of the diverging price levels and price differences, the innovative pharmaceuticals should therefore be absolutely **differentiated according to ATC classes** for the IRP. However, for a more comprehensive understanding of the international price differences, additional explanatory factors are also needed.
50. With regard to the **price level**, it can be noted that both a **higher ability to pay (per-capita GDP)** and a **higher willingness to pay (per-capita HCE)** go hand in hand with **higher prices for innovative products**. Likewise, an increase in the general price index for pharmaceutical products (HICP) leads to higher prices for innovations. According to our calculations, a 1% increase of one of the explanatory variables (GDP, HCE or HICP) results in an increase of the manufacturer's price of a magnitude between 0.25 and 0.39%. Other interesting time invariant explanatory factors cannot be considered in this model, since they would be eliminated when differences are formed.
51. In the estimates, the **ability to pay represents an important explanatory factor of the price level and the price differences** between the countries under review. A greater ability to pay implies higher prices for innovations and allows greater positive price differences to Germany. An increase of the per-capita GDP abroad relative to Germany increases existing positive price differences and decreases existing negative differences. Growing prosperity relative to Germany therefore also implies relatively increasing prices for innovative medicinal products compared to Germany: Countries with a

significantly higher price level move away from the German price level while countries with a lower price level move toward the German level.

52. In contrast, there are **far fewer pronounced effects on the price level and price differences** between the foreign countries and Germany with regard to the **willingness to pay**. The health care expenditure are probably more strongly associated with quantity and structural effects and also fluctuate with quality, so that effects on prices are less distinct. Differences in level of per-capita health care expenditure do not play a significant role, especially in terms of price differences. In many cases, the differences in the health care expenditure of specific countries compared to Germany may also be related to specific developments, especially in the outpatient or inpatient sector.
53. On the other hand, **international reference pricing (IRP) has a significantly negative effect on the price differences** between Germany and the other countries: As a result, IRP has a dampening effect on the prices of the referencing country. In our estimate, this effect amounts to 5 to 7% on average. For positive price differences, IRP would therefore lower the higher foreign prices by 5 to 7% compared to Germany. This emphasizes the function as a price anchor that Germany has had so far in terms of innovative medicinal products. **Reference pricing** abroad, therefore, has the expected effect, i. e., pressure on higher international prices in comparison to Germany is exerted toward the lower price level. On the other hand, administrative or government **price fixing** have no significant impact on the relative price deviation in our analysis, probably due to non-sufficient representativeness of the diverse supply and demand side price regulation measures.
54. Demographic influence factors, such as the **old-age dependency ratio**, **neither show any impact** in our estimates for the sales price of the pharmaceutical manufacturer nor for the corresponding price differences. Their influence may appear to be stronger on the level of the pharmaceutical expenditure, while the effects on prices remain without significance. Therefore, this explanatory factor was not considered any further.
55. Differences in the price level and especially the pricing structure of pharmaceutical products, which are represented in the estimate through the **harmonized index of consumer prices for pharmaceutical products (HICP)**, remain without significant influence on the price differences between other countries and Germany in most of the analyses performed here. Only the inclusion of other explanatory factors has the effect that a relative increase of the foreign price level compared to Germany results in a relatively larger deviation in the existing positive price differences.
56. The inclusion of the **ATC classification** shows significant but very **heterogeneous effects**: For some ATC classes, there are positive effects whereas others display negative coefficients. Whether the price differences increase or decrease depends on to which ATC class an innovation is assigned. In detail, the analysis shows that **price differences** between other countries and Germany also **depend on which ATC classes products belong to**. In general, the ATC classification includes five levels. On the first level, which

is used here, there are 14 main groups depending on the organ (e. g. the heart) or the system (e. g. vascular system) on which the product has its main effect. As a result, existing price differences between other countries and Germany are also always a result of the specific therapeutic application and should therefore be considered.

57. Overall, the estimates show that even in the relatively homogeneous group of the 13 EU countries under review there exists a number of specific explanatory variables for the price level and the international price differences of innovative medicinal products. Price comparisons and IRP therefore require in-depth economic analysis and empirical testing in order to avoid considerable distortions in the international price comparison. Concerning the suitability of specific countries for IRP in case of innovations, it follows from our results that only a **few countries are available as potential reference countries**, since product availability varies strongly even for the candidates selected according to the criteria of ability to pay and willingness to pay. Under this aspect, the results of the empirical analysis argue in favor of a **more restrictive selection of the reference countries**.

Part III: Policy Recommendations

8 Selection Criteria for Determining International Reference Prices

58. The empirical analysis shows that there are **positive price differences** between Germany and the 12 comparison countries for most of the 39 products under review. However, **product availability** of these innovations also varies very strongly from country to country: While a total of 39 innovative pharmaceuticals were available in Germany in 2010, which were offered here from 2008 to 2010, there were only nine and eleven products, e. g., in Portugal and Italy respectively. The determined positive price gap between Germany and the comparison countries can also not be found across all therapeutic categories. Only Spain has consistently lower drug prices than Germany, while they are in part even considerably higher than domestically in all other countries according to ATC class.
59. Furthermore, the analysis confirms the empirical relevance of a series of variables that were already developed as **determining factors for the international price levels and price differences** in the economic analysis of the first part of our expertise. The Ability to pay (represented by per-capita GDP) has emerged as the central explanatory variable: In all of our analyses, it had a significantly positive influence on both the price level and the price differences.
60. Additional important explanatory variables are the different **price regulations** in the specific countries, in particular the **participation of a certain country in an European IRP system**. According to our estimates, international reference pricing results in the decrease of an existing positive price difference and an expansion of an existing negative price difference. If, in a starting situation, the prices for innovations in Germany are

higher than abroad, an IRP system abroad will – as expected – result in international prices moving further away from the German prices. In contrast, if the international price is above the German price in the starting situation, the IRP system also leads to the expected reaction, thus, the international price decreases toward the German price level. As a result, the IRP has a **dampening effect on the prices of the referencing country**. According to our estimates, it is about 5 to 7%. Therefore, for positive price differences, the existence of an IRP system would reduce the higher international prices by up to 7% compared to Germany.

61. Based on the available data, especially those innovative pharmaceuticals that were **not first launched in Germany**, i. e., had a later launch compared to the other countries, can also be identified. The delayed launch of a new drug in Germany has a significantly negative influence on the price differences. As a result, the launch delay has a dampening effect. In contrast to an IRP effect – which changes prices abroad – the launch factor influences the prices of innovative pharmaceuticals in Germany *ceteris paribus*.
62. As the last group, we analyzed different **ATC classes** that reflect the existing heterogeneity between the individual classes for innovative medicinal products. In the empirical analysis, we find very heterogeneous effects on the price differences for these ATC classes. For **some ATC classes, there are positive price deviations to Germany, for others there are negative effects**. As a result, price differences between other countries and Germany also depend on the affiliation of an innovative pharmaceutical to a specific ATC class.
63. Overall, our results suggest a narrow interpretation of the underlying comparison criteria of the **ability to pay and willingness to pay** in terms of an appropriate comparability to Germany. Furthermore, factors providing e. g. information on the **availability of innovative pharmaceuticals**, that take into account the **launch delay** and that represent the **ATC classification** of an innovative pharmaceutical in particular should also be considered. Finally, our results show that the prevalent **IRP system** also represents a key determinant of price differences between Germany and comparable countries.

9. International Reference Prices as a Guideline for Reimbursement in Germany

64. The difficulties for the negotiations intended by the AMNOG regarding reimbursement amounts or prices of innovative medicinal products with a major additional benefit are in part based on a **conflict of interest** that is difficult to resolve: While the health funds demand innovative and high-quality pharmaceutical care at the lowest prices (cost containment paradigm), the pharmaceutical industry expects to be compensated for production and marketing costs as well as irretrievably lost R&D expenses (sunk costs) for its innovative pharmaceuticals (cost coverage paradigm).

65. It follows from the explanatory memorandum that the AMNOG was not planned as mere "cost containment legislation" but that the German federal government also intended to pursue the goal of creating "... **a reliable framework for innovation, for health care for the insured patients and for job security ...**". With the AMNOG, the legislature obviously intended a comprehensive "reorganization of the pharmaceutical market" and wanted to create "structural and long-term changes " and especially also "to strengthen competition in the pharmaceutical market" beyond "cost savings with a short-term effect" (statement of the German Federal Ministry of Health of November 11, 2010, p. 2 ff.).
66. If **industrial-economic goals** are also to be considered in the AMNOG, institutional measures are also required, such as the Master Agreement pursuant to Section 130b (9) of the German Social Code Book V (SGB V), which prevents the cost containment paradigm from systematically prevailing at the expense of the cost coverage paradigm. This would inevitably result in the consequence that investments in R&D would be less and less worthwhile, that the innovative dynamic of the research-based pharmaceutical companies would decrease, and that R&D efforts would only focus on the large, revenue-prone therapeutic areas. Furthermore, this would query the quick and complete availability of innovative medicinal products in Germany. In addition, there is the potential evasive reaction of the manufacturers to no longer supply certain countries or to not supply them at the previous prices. Under the conditions of a market economy, the strategic behavior of innovators cannot be prevented, even with a large number of potential reference countries.
67. The consequences of such a slowed down and selective innovation and marketing process for novel pharmaceuticals with a major additional benefit as compared to previous therapy standards are borne by the **patients – including especially those suffering from orphan diseases that cannot yet be cured with medication or from novel disorders**: Many of them will have to wait even longer in the future, and many will have to wait in vain for effective pharmacotherapies. Under this aspect, the Master Agreement can prevent a superior position of the health funds in the discount negotiations and safeguard a fair balance of cost containment and cost coverage interests in order to attain an **appropriate assessment of reimbursement** in Germany based on international reference prices.
68. For this purpose, the expert report will develop suitable **reliable comparison criteria and processes** that can be taken into account regarding the international price comparison in the negotiations between the contractual parties. However, by determining a country group for Germany for an IRP system, no definitive determination of countries for reference pricing after the AMNOG is intended. Certainly, the additional benefit ascertained by the Federal Joint Committee (G-BA) compared to the appropriate comparative therapy is the relevant criterion for negotiating a reimbursement amount. Instead, the determination of a country group is more about identifying adequate criteria for the **pre-selection of possible reference countries**. Based on this pre-

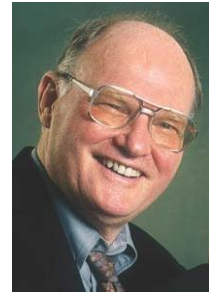
selection, an adequate country selection shall also include other criteria (such as drug availability, regulatory practices or market specifics).

69. Therefore, the politically decided AMNOG procedure must be designed in such a manner as to minimize, if not avoid, **undesirable consequences**. In this respect, a stringent **selection of reference countries**, that are comparable based on both theoretically valid and empirically proved criteria, would be goal-oriented. Also, practicable **procedures for the implementation of price comparisons**, such as **adjusting comparison prices for the effects of particularly price-distorting national regulations**, are required as well. For the comparison procedure itself, not just operational norm-setting and standardization of the legally stipulated "actual sales prices" is required as a benchmark. In addition, their weighting with prescription quantities, a suitable currency conversion based on exchange rates or purchasing power parities as well as adjustment of discounts and irregular price determinants is needed.

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