Changing Payer Perspectives on Market Access Across the G-5

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Authors

Jill E. Sackman, D.V.M., Ph.D.
Michael J. Kuchenreuther, Ph.D.

NAI is an internationally recognized consulting firm that works globally across the entire spectrum of the healthcare industry providing services to the payer, pharmaceutical, medical device and healthcare delivery sectors. NAI is a pioneer in helping clients to incorporate economic and clinical value as a basis for competitive differentiation across a wide range of therapeutic areas.

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FOREWORD

Companies exploring opportunities in global markets face dynamic demographic and disease trends, changing market demands, and evolving regulatory requirements -- all of which differ from one country to another. This complex environment makes planning for global market entry into both developed and developing countries a moving target.

To make matters worse, reimbursement for existing treatments are under additional scrutiny and are being challenged where benefits are not considered significant. Payers globally continue to demand new types of evidence to aid in decision-making regarding new and existing pharmaceuticals. The escalating cost of drugs is forcing tough decisions, particularly in Europe, where there is an ongoing struggle to ensure drug availability while staying within government-dictated healthcare budgets. Austerity measures and related drug price cuts have put unprecedented pressure on the pharmaceutical industry. Manufacturers are being asked to provide information related not only to safety, appropriate use, and effectiveness but also clinical and economic value. This trend is global and particularly apparent in high cost therapeutic areas (e.g. rheumatoid arthritis, diabetes, and oncology) where large numbers of new and costly therapies are being introduced.

Gaining insight into what payers are looking for has historically taken a back seat to requirements for regulatory approval. Yet today, meeting country-specific access and reimbursement requirements is critical for commercial success. Furthermore, payer perspectives on overall drug benefits can be different from regulatory requirements. For this reason, the market access function needs to take on new roles and serve as a bridge between the commercial and R&D organizations.

This report explores the changes, challenges, and opportunities in the reimbursement environment of the G-5 countries of the European Union. Specific processes for reimbursement and pricing are outlined, as well as the approach for determining "additional medical benefit" for premium pricing. New and impending legislation impacting market access is called out. Specific "watch-outs" and lessons learned for manufacturers are included, as well as case studies that illustrate how the failure to provide data on appropriate comparators or show additional benefit can negatively influence market access decisions.

Rita E. Numerof, Ph.D.
President
Numerof & Associates, Inc.

INTRODUCTION -- AN INDUSTRY IN TRANSITION

Industry Context

It was less than a decade ago that most pharmaceutical manufacturers considered market access the last step in the commercialization process… maybe even something that happened post-launch! However it has become increasingly clear that this approach must change. In light of ongoing economic challenges, countries seek to contain healthcare spending and address concerns about the quality of medical products.

As part of efforts to get healthcare costs under control, payers are driving significant healthcare reimbursement changes. One of the most dramatic developments affecting the global marketplace has been that payers -- public and private -- are demanding more evidence of products' value. Increasingly, payers are establishing evidence-based care paths or therapeutic guidelines and are managing access tightly. These actions position them as a significant customer in product commercialization, and place increasing pressure on companies to rethink their commercial models. Pharmaceutical manufacturers are discovering that incremental product improvement is not persuasive in countries with substantially reduced budgets.

As a result, payer and reimbursement functions are becoming more powerful and decision-making is moving further from healthcare providers. It's no longer sufficient to obtain regulatory approval for a new product and then expect that regulatory data from prospective randomized clinical studies will be enough to convince payers to reimburse at a price premium. Historically, payers have been viewed as administrators, different from "real customers" like physicians and patients. As long as drugs were safe and effective, patients would get their prescriptions filled, and payers would reimburse them. The world is changing.

To adjust to these shifts, pharmaceutical manufacturers will need to make a fundamental shift in their business. To meet increased demands from stakeholders for real value, market access capabilities and processes must be embedded throughout an organization. Ultimately, the key to success will be to define responsibility for market access across functional areas, and throughout the product lifecycle.

Payers as Customers

Increasingly the pharmaceutical industry is coming to terms with the fact that payers and other key stakeholders are *customers* -- not barriers to product success. A number of factors, including information transparency, more crowded therapeutic spaces, and an intense focus on cost, has shifted the bargaining power between pharma and payers.

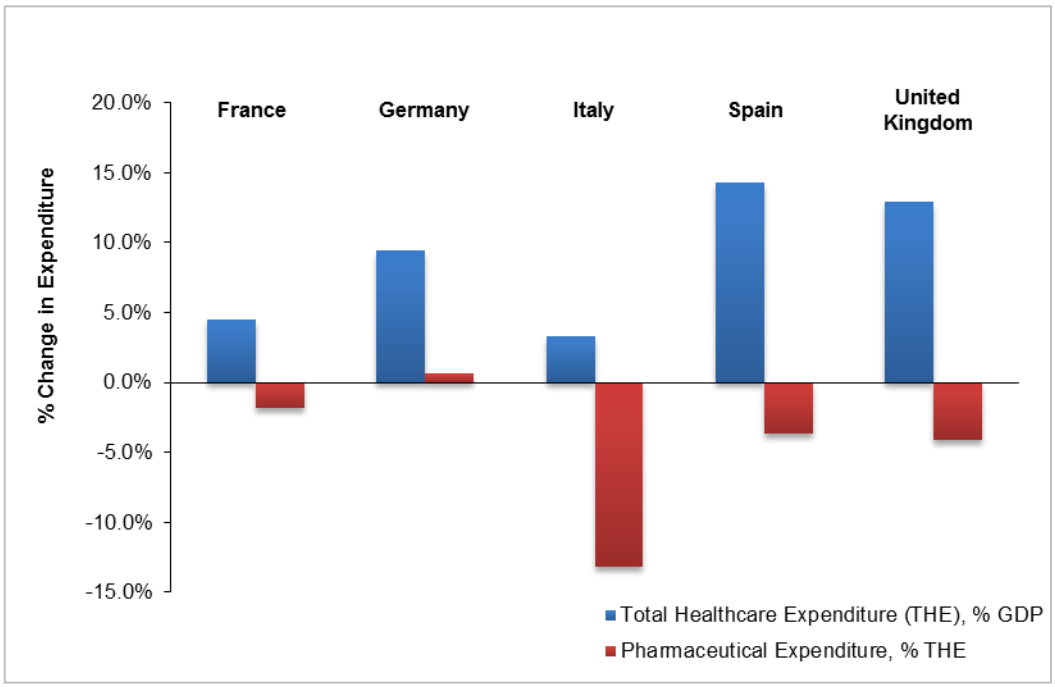
So what are payer customers looking for? We conducted interviews with a number of payers at agencies such as the National Health Services in the U.K. and GKV-Spitzenverband in Germany, and found many consistent themes… starting with data that extends beyond product safety and efficacy in a controlled setting and addresses real world data and health outcomes. Consistently in Europe, payers are requesting data to substantiate products' real world value through performance against comparators and health economic analysis. These data enable payers to make better decisions regarding reimbursement, coverage and cost. It's true that clinical efficacy and safety are still critical for market access, however, payers in the European Union often describe cost-effectiveness and budgetary impact as a close second to therapeutic benefits (based on interviews conducted by NAI for this paper 2013).

To be successful, pharmaceutical manufacturers must provide data payers are looking for, including comparative effectiveness, cost effectiveness, and real world effectiveness. Today there is often a data gap… and in the absence of good data, payers will (and have been) developing their own… from evidence-based care paths, to health outcomes research and real world data looking at head to head comparators. Real world data and health economics are critical in the product value story and must be included from the early stages of R&D through post commercialization.

Building Value in Europe

With growing regulations, record public debt and shrinking budgets (see Figure 1), nowhere is the trend for demonstrated value more visible than in the European Union. In recent years, while healthcare spending has grown, the portion of funds spent on drugs has decreased. But the economic climate has resulted in even greater demands for value from drug makers.

Figure 1. Change in health expenditures vs. change in pharmaceutical expenditure, 2006-2010



Source: OECD

"The trends seem to lead to a gradual replacement of systems based on direct control of prices... [to] alternative pricing systems (for example, systems based on the value provided by the new drug or including a health technology assessment) or reimbursement policies, including complex co-payment systems and external systems of reference prices," says José Fernández-Rañada, Partner at J&A Garrigues, S.L.P., a leading legal and tax services firm in Spain.

This trend is borne out by changes in evaluation for reimbursement across the region. For example, in the U.K. and Germany, free pricing for new drugs no longer exists. In the U.K., the current Pharmaceutical Price Regulation Scheme (PPRS) will expire by year end-2013 and be replaced by Value Based Pricing (VBP). VBP is intended for substances launched after January 1, 2014 (as well as some existing medicines subject to industry discussion). The new policy is likely to rely heavily on real word data to determine a drug's true value. Likewise in Germany, the Pharmaceuticals Market Reorganization Act (Arzneimittelmarkt-Neuordnungsgesetz -- AMNOG, December 2010) aims to limit the cost of pharmaceuticals.

Elsewhere, most nations in the EU are also raising the bar on evidence and on the definition of improvement in standard of care (i.e. innovation significant enough to demand premium price), especially in light of the economic turmoil that has characterized the European marketplace in recent years. Focus has increased on health technology assessments (HTAs), tenders, and other ways to limit market access. The rules of access are changing rapidly and value demonstration is increasingly a requirement globally. Adapting to these shifts is critical for success.

REIMBURSEMENT REQUIREMENTS IN THE EUROPEAN G5: FRANCE

Reimbursement Process and Key Players

Healthcare in France is financed by the government national health insurance system. The entire population enrolls in compulsory health insurance. Insurance premiums are deducted automatically from payroll; employers share costs. Supplemental insurance may be purchased from private payers. Only about 4% of hospital costs are paid for through private insurance, but up to 20% of drug costs are paid through supplemental plans. There are public hospitals (65%), non-profit hospitals (15%), and private for-profit hospitals (20%). The French healthcare system allows patients to choose their own physicians and pay them directly. Patients file for reimbursement from the government based on standardized fees set by the social security administration.

Reimbursement for pharmaceuticals is determined primarily at the national level. Following market authorization from the European Medicines Agency (EMA) or from the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), a drug is assessed by the independent health authority, Haute Autorité de Santé (HAS). HAS provides advice to decision-makers on reimbursement and pricing of health technologies (drugs, devices and procedures) and interventions in the field of public health.

The HAS' Transparency Committee is currently accountable for clinical evaluation and drug assessments based on defined "medical benefit" (SMR -- Service Médical Rendu) and on "improvement of medical benefit" compared to the current standard of care (ASMR -- Amélioration du Service Médical Rendu). SMR assessments include five (5) criteria: 1) efficacy and safety; 2) existence or absence of therapeutic alternatives; 3) severity of the disease to be treated; 4) treatment type, specifically preventative, curative or symptomatic; and 5) public health impact. Each criterion is scored from insufficient to major. The ASMR is scored from no improvement to major innovation.

Other information may be included in the Transparency Committee's assessment including epidemiologic data, orphan drug status, or national public health priorities. Currently, health economic studies are rarely used, despite the 2008 establishment of a dedicated Committee for economic evaluation. Following review, the Transparency Committee assessment is submitted to a Department of Health committee known as the CEPS (Comité Économique des Produits de Santé), which makes pricing and reimbursement decisions based on the HAS recommendation.

During the current economic crisis, healthcare expenditures and drug costs in particular have become a topic of intense debate. In 2011, the HAS reported that

in the wake of the Mediator scandal,* drug assessments based on SMR and ASMR will be replaced. Health Minister Marisol Touraine has supported the introduction of health economic evaluation into evaluation of drugs. In 2012, HAS announced a new tool, the Index Thérapeutique Relatif (ITR), which will compare a medicine to an appropriate comparator, indexed from inferior to highly superior.

Concerns raised by the French that the ITR system will become more like the English-style system have been countered by HAS President Jean-Luc Harousseau, who says that this program will differ because they won't use "des années de vie gagnées en bonne condition," or Quality Adjusted Life Years (QALYs).[1] He has also emphasized the importance of real world data in reevaluating products already on the market. ITR evaluation criteria include:

- Clinical relevance of comparators
- Clinical relevance of primary and secondary endpoints
- Validity of studies presented to demonstrate superiority and non-inferiority, (direct or indirect comparisons).

After validating primary and secondary endpoints and comparator data, "Relative Efficacy" will be assigned. The product will then be classified in 1 of 5 classes:

- **Inferior:** No reimbursement
- **Identical:** No reimbursement/reduced reimbursement (vs. comparator)
- **Slightly superior:** Same price as comparator
- **Moderately superior:** Reimbursement at a negotiated price
- **Very superior:** European price

Planning for Data Generation and Successful Negotiation

Anticipating questions from the industry on this new mechanism for assessing products, HAS set up a formal procedure of 'early appointment' ('rendez-vous précoce') to review and discuss clinical development. To schedule an appointment, a manufacturer should have completed phase II studies and the drug should either address an unmet medical need or provide significant innovation. Additionally, the manufacturer will need to provide a list of questions covering comparators, intervention, choice of end points, follow-up duration, etc. HAS President Harousseau has emphasized the importance of these meetings

* The amphetamine derivative Mediator was marketed by Servier to overweight diabetics but often prescribed to healthy women as an appetite suppressant. Mediator, also prescribed off-label as a weight-loss aid, is allegedly responsible for hundreds of deaths from heart valve damage in France. It was ordered off the market by AFFSAPS in 2009, years after the first cardiovascular risks warnings emerged. The drug was pulled in Spain and Italy years before France. It was never authorized in the U.K. or U.S.

for manufacturers to understand the "rules of the game" with regard to product evaluation.

By law, economic assessments are required for drugs that are perceived as having a significant impact on health costs or will significantly change the management of a disease. This will automatically apply to drugs with a high ITR and those with high prescription volume potential.

Challenges and Opportunities

According to recent Socialist Party research, nearly 40% of the population lacks the resources to receive adequate healthcare. Because of this access challenge, Health Minister Marisol Touraine has made reducing healthcare costs a key item on her agenda.

CEPS, which sets price/volume agreements to cap revenue of a pharmaceutical, is tasked with implementing cost containment policies. To cut costs, CEPS might decide to implement risk-sharing agreements. Orphan drugs with high annual costs may lose their preferential status without sufficient data about the clinical value of the product in its intended population.

Additional cost reduction could also be achieved by reducing the number of products financed outside of the hospital GHS system (Group Homogène de Séjour, part of the Tarification à l'Activité). Currently, expensive pharmaceutical products are paid for directly by the federal Social Security system, rather than through a hospital intermediary as part of the GHS. These medicines appear on the "Liste en sus" and it is possible that some medicines could be removed when generics become available. It is also likely that regional health agencies will play a greater role in efforts to increase healthcare efficiency, ensure consistency in prescriptions and control off-label use.

REIMBURSEMENT REQUIREMENTS IN THE EUROPEAN G5: GERMANY

Reimbursement Process and Key Players

Approximately 72 million (of 82 million inhabitants) in Germany are covered by statutory health insurance (SHI); remaining individuals use private insurance. There are approximately 240 public health insurance companies. Premiums are shared between employees (50.45%) and employers (49.55%). There is no competition between the public plans (all provide nearly the same services); patients may select a "sickness fund" of their choice.

The Federal Joint Committee or G-BA (Gemeinsame Bundesausschuss) is the central decision making body concerning drug access for those with statutory (federal) health insurance. Established in 2004, the G-BA has predecessors dating to the 1920s. The G-BA's accountabilities for drugs include: 1) exclusion of prescription drugs (if there is no perceived additional benefit); 2) setting reference pricing; 3) determining OTC exemption lists; 4) therapeutic advice; 5) guidance on off-label use; 6) and cost effectiveness analysis.

Reimbursement decisions for drugs are driven by the G-BA and SHIs. The G-BA is responsible for identifying new drugs and classifying them into reference price groups. As part of the decision making process, independent experts and physicians may be consulted, the Institute for Quality and Efficiency in Health Care (IQWiG) may be asked to conduct analyses, and the German Institute for Health Technology Assessment (DAHTA) may be engaged for technology assessment. Therapeutic class and comparison to existing treatments serve as the main criteria for price group classification.

Beginning in 2008, IQWiG is required by the G-BA to evaluate the benefit ratio for pharmaceuticals, and since 2006, it has also evaluated the cost-benefit ratio. Evaluation is based on accepted international standards and guidelines for evidence-based medicine and health economics (e.g. benefit dossiers).

In response to rising drug costs and an aging population, the evaluation process was set by law, known as AMNOG (Arzneimittelmarkt-Neuordnungsgesetz), on a new basis and went into effect in 2011. Under AMNOG, pharmaceutical companies are required to subject all new products to an early evaluation of "additional benefit" by the G-BA post-launch.

"For the most part, IQWiG is asked to conduct analyses, and the German Institute for Health Technology Assessment (DAHTA) may be engaged for technology assessment and comparison to existing treatments," explains former head of the Pharmaceutical Department Statutory Health Insurance Fund Wolfgang Kaesbach. If additional benefit over the assigned appropriate

comparative therapy cannot be proven, the drug is assigned to a reference price group with comparable active ingredients. If no reference price group exists, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) negotiates a reimbursement price which does not increase annual therapy costs over the existing comparative therapy.

Criteria for additional medical benefit include improving health, extending survival, shortening the burden of illness and reducing side-effects or improving quality of life. A drug with additional medical benefit must differ from standard therapy and must exceed the benefit from standard therapy.

If additional benefit is demonstrated, the National Association of Statutory Health Insurance Funds negotiates a price increase over the existing comparative therapy. This amount then applies to all persons with statutory insurance, as well as to those with private insurance. If these negotiations fail, an arbitration board will set the price based on the comparator's price, the price of the product in 15 EU Member States and the prices of other comparable products authorized for the same indication and for marketing in Germany.

AMNOG requires an assessment of additional drug benefit to be carried out from January 2011 onwards. Until the AMNOG evaluation is complete, the price set by the pharmaceutical company applies to the new pharmaceutical (for one year). The G-BA may request an assessment for drugs in the market prior to January 2011 to evaluate additional product benefits (they have already done this for gliptin drugs and six other groups of therapeutically comparable drugs). Furthermore, products launched before this date that are used as a comparator for another drug are also subject to this evaluation process. Drugs which are of little economic significance (less than 1 million € turnover/year with statutory health insurance) are exempt from evaluation.

Planning for Data Generation and Successful Negotiation -- AMNOG Process

Under AMNOG, pricing and reimbursement is determined through a two-part process. Evaluation of additional benefit requires companies to submit a dossier to the G-BA at the time of the market launch containing information on:

- Authorized application areas
- Medical benefit
- Additional medical benefit compared to the appropriate comparative therapy, as chosen by the G-BA
    - Comparator must be approved for relevant indication(s)
    - Comparator must currently be reimbursed (but may be non-medicinal)
    - Comparator must be an adequate therapy according to medical standards

  - If multiple alternatives exist, the comparator must be the most economic therapy
- Number of patients and patient groups for which a therapeutically significant additional benefit applies
- Therapy costs for the SHIs

Thus, says Alexander Natz, Secretary General of the European Confederation of Pharma Entrepreneurs, "it's very important to know exactly what the right comparator is as early as possible." The G-BA will examine additional benefit of the new drug as presented in the dossier. The G-BA can commission IQWiG or other scientific bodies with this "early additional benefit evaluation," or it may carry it out itself. The early additional benefit evaluation is published three months (at the latest) after product launch.

The G-BA decides in the three months following publication how to define the additional benefit of the new drug. Prior to this, manufacturers may submit a written and oral statement which the G-BA considers in making its decision.

Reimbursement negotiations for drugs with "additional medical benefit" occur between the National Association of Statutory Health Insurance Funds and the manufacturer. Pricing takes the form of a supplement or deduction from the costs of the comparative therapy based on the proven additional benefit potential.[2]

Challenges and Opportunities

The AMNOG process takes 12 months (plus three month in case the arbitration board is involved). "Pharmaceutical enterprises are well advised to calculate an additional 12 months of preparation at least," Kaesbach recommends. Germany is clearly demanding different comparators and patient-relevant outcomes in different clinical trial populations than have been required previously for drug reimbursement. It is important to note that comparators required for regulatory approval may be different than those required for market access and optimal reimbursement.

The G-BA's selection of the most economical comparators is likely to be a challenge for market access in Germany. Out of the ten products assessed in 2011, four received poor innovation scores: Esbriet (pirfenidone), Livazo (pitavastatin), Yellox (bromfenac) and Trajenta (linagliptin), and a majority of manufacturers have struggled -- and sometimes declined -- to provide comparative data.[3] Deviating from G-BA's selected comparator without sufficient justification has resulted in negative pricing determinations. In September 2011, Boehringer Ingelheim and Eli Lilly decided not to launch their once-daily diabetes drug Trajenta following the G-BA's negative opinion, largely due to the manufacturer's selection of the wrong comparator.

There are also demands for manufacturers to add more patient outcome measures as trial endpoints. To this end, pharmaceutical companies are already pursuing partnerships with companies that can offer patient data to power outcome endpoints.

When we asked Kaesbach what data he values most from pharmaceutical companies, he responded that it should include "reliable data and evidence on mortality, morbidity and quality of life." He specifically emphasized quality of life and noted that he was always amazed when pharmaceutical companies demonstrated that their drug extends life, they stop to look at the quality of life associated with longer survival. Quality of life is critical in evaluating additional medical benefit.

Kaesbach made other points about the kind of value drug companies need to demonstrate. "Pharmacoeconomics does not play an important role within the AMNOG process" he added. "We don't like any modeling in the future; no one can truly say what will happen and it is some kind of looking in a glass ball." He commented that if a drug company can demonstrate that their drug is effective in terms of relevant outcomes for patient and that the evidence they have to support it is good, they will reach a reasonable price. Kaesbach also said that pharmaceutical companies shouldn't be surprised by AMNOG… the foundation for comparators and medical benefit was laid in 2004 legislation in Germany.

One other way the AMNOG legislation has impacted companies -- even beyond Germany -- results from the use of German prices as reference prices. Nineteen other countries use German prices as references. Thus, "the German price is crucial when it comes to market access," says Natz. He also emphasizes that many expect the AMNOG law to be an export, and other countries to model their reimbursement models after AMNOG.

REIMBURSEMENT REQUIREMENTS IN THE EUROPEAN G5: ITALY

Reimbursement Process and Key Players

The National Healthcare System (Servizio Sanitario Nazionale/SSN) provides universal healthcare coverage to the Italian population, but over time, regional governments have assumed more responsibility for managing the system on a provincial level. Still, pricing and reimbursement of products is mainly decided on the national level, creating a system most similar to that of Spain. In 2004, the Italian Medicines Agency (Agenzia Italiana del Farmaco/AIFA) was established as the main national authority responsible for the regulation of pharmaceuticals in Italy.

As seen in other EU countries, AIFA relies on a number of technical-scientific consultative committees for guidance, mainly the Technical Scientific Committee (Commissione Tecnico-Scientifica/CTS) and the Committee for Pricing and Reimbursement (Comitato Prezzi e Rimborso/CPR). CTS provides guidance to AIFA around reimbursement and drug classification by analyzing manufacturers' dossiers, focusing specifically on costs, benefits, available alternatives, and specific indications. In addition, the innovativeness of the new drug in comparison with the standard of care and other existing treatment options is a major determinant. Based on these criteria, new products are assigned into 1 of 3 classes:

- **Class A:** Essential drugs for the treatment of serious and chronic diseases; full reimbursement
- **Class H:** Drugs requiring specialist supervision; eligible for full reimbursement only when used in the hospital setting
- **Class C:** Drugs for less serious diseases with no added therapeutic value; no reimbursement

Similar to Spain, the pricing procedure in Italy is strictly linked to reimbursement evaluation. Once CTS advises on reimbursement classification, manufacturers are then allowed to enter into pricing negotiations with regulatory authorities. Here, the CPR will consider the listed price of this particular product in other EU countries, the prices of similar products within the same pharmaco-therapeutic group and similar criteria used by CTS to decide on reimbursement.

Once the drug has been priced, it's up to the regional governments to set formularies. In recent years, there has been considerable debate about this system and its implications for manufacturers and patients. In a speech at the U.S. Embassy in Rome just before the Italian elections in February 2013, Eli Lilly President for Europe, Canada and Australia Andrew Hotchkiss described one

shortcoming of the system as "useless duplication at a regional level of decisions taken at the AIFA level."

In some cases, the government has been able to change their processes in response to criticism. In 2010, responding to criticisms that innovative drugs weren't making it to patients quickly after approval because the regional authorities were taking varying amounts of time to add them to formularies, AIFA and the provinces formed an agreement that all innovative drugs would be included in hospital formularies within 30 days. Still, regional disparities persist.

Challenges and Opportunities

To address economic concerns in Italy, austerity measures have been taken to control government expenditures on healthcare. Manufacturers have already felt the impact from some of these changes as constant price cuts have eroded pharmaceutical sales. The elections held earlier this year were largely a referendum on previous Prime Minister Mario Monti's austerity measures, and their outcome has largely represented stalemate, so what's next as far as austerity goes is less certain.

The council of ministers in Italy approved a proposal from Minister of Health Renato Balduzzi in late 2012 that includes a wide range of measures relating to the pharmaceutical industry. According to this decree, regions and provinces will be required to update hospital formularies every six months to include new or innovative medicines that are granted positive reimbursement status by AIFA. Additionally, later this year, AIFA will conduct significant revisions to the national reimbursement list with the intention to remove products that are therapeutically outdated or seen as having an unjustifiably high price in proportion to their therapeutic benefit.

Some reports indicate that these reforms are not happening as intended. Italian Senator and doctor Lucio Barani has complained that "It is like having assembled a nice car and not having the gasoline to drive it." Still, it's early days and the government's recent deadlock solved only at the end of April make it hard to predict what the government will do to ensure its reforms go through as laid out in the Baldazzi decree.

REIMBURSEMENT REQUIREMENTS IN THE EUROPEAN G5: SPAIN

Reimbursement Process and Key Players

Spain has a population of over 45 million people and contains 17 autonomous regions. Spain's National Health Service (Sistema Nacional de Salud/SNS) represents a decentralized, publically-funded system that offers Spanish citizens universal public healthcare coverage. With the exception of pharmaceuticals, where some co-payment exists, healthcare services are provided free of charge. Oncology drugs are free of charge to patients, as most are administered in the hospital environment. Over the last three decades, Spain has experienced a massive decentralization of health services. Prior to 1978, all responsibilities in this area corresponded to the central government. Since this time, most of the decision-making power has been transferred to autonomous regions throughout the country, now responsible for their own health planning and programming and maintaining direct control over health management.

While most aspects of healthcare are run independently by each autonomous region, the national government does retain ultimate authority over pharmaceutical regulation and policy. The Ministry of Health (Ministerio de Sanidad, Servicios Sociales e Igualdad -- MSSSI) and the Spanish Agency of Medicines and Medical Devices (AEMPS) concentrate on strategic issues including pharmacovigilance, product approvals, cost-containment, drug pricing and reimbursement. When marketing authorization is granted by the EMA or the AEMPS, the MSC decides whether to include the new pharmaceutical on the national reimbursement list. Decisions to grant reimbursement are based on HTAs that focus on the following criteria: 1) disease severity; 2) therapeutic value and drug efficacy; 3) rationalization of public drug expenditures; 4) alternatives for the indications targeted by the drug; and 5) drug novelty. Since 1998, pharmaceutical companies have been free to set the prices of drugs that the MSC refuses to include on the reimbursement list, however, given that non-inclusion can severely limit a drug's sales potential, few manufacturers have been willing to launch a product without MSC coverage.

Price negotiations between the manufacturer and the national government are critical. Director Agency for Health Technology Assessment at the Instituto de Salud Carlos III Antonio Sarría-Santamera explains: "The price is fixed by the national government and it decides which drugs will be provided through pharmacies and which drugs will be provided at the hospital." During the reimbursement decision-making process, pricing is determined by the Inter-Ministerial Pricing Commission (CIPM). Manufacturers are encouraged to submit as much documentation as necessary to support a positive decision. The price application is required, and includes the desired price as well as the following information:

- Cost per day compared with equivalent products in Spain
- Prices in the country of origin and in other EU countries
- Estimated product sales in Spain
- Detailed production and R&D cost

Given the decentralized structure of the Spanish healthcare system, while the MSSSI is responsible for making national pricing and reimbursement decisions, manufacturers must understand that product use is determined by the regions or by individual hospitals. Every hospital in Spain has a committee that defines the criteria for including drugs in the hospital's formulary and decides which meet their criteria. Moreover, there are both regional-level and hospital-level budgets that can influence a product's use.

In Spain, HTA agencies also play a critical role in disseminating information to hospitals to guide decisions concerning product adoption. There are currently one national agency and seven regional HTA agencies that collaborate with the Spanish network of HTAs and perform reviews individually. These HTA agencies consider similar criteria as those used for national reimbursement decisions. However, while the use of economic evaluation is not mandatory in Spain, these agencies as well as the hospital committees are increasingly incorporating information on cost-effectiveness when developing their pharmaco-therapeutic guidelines.

And these committees consider the cost of drugs in context. "Hospitals give a lot of importance to Budget Impact Analysis (BIA)," says Laura Sampietro-Colom, Deputy Director for Innovación at the "Hospital Clinic" in Barcelona.

Sarría-Santamera also emphasized the budget impact in evaluating new drugs. "There isn't the same kind of aversion to cost effectiveness in Spain that you see in Germany, but we're not so in love with cost effectiveness as they are in the U.K.… Spain is somewhere in the middle," he commented, explaining that it's important that companies get local information to guide their expectations about pricing.

Planning for Data Generation and Successful Negotiation

Spain's macroeconomic struggles mean that there are fewer resources available to spend on pharmaceuticals. Sarría-Santamera commented that "pharmaceuticals represent almost 20% of healthcare costs in Spain and reducing this cost is a top priority for the Spanish government. To meet these goals, the government can change pricing of drugs at any time; reductions of up to 20% have occurred." This pressure makes economic data for pharmaceuticals a critical consideration for MSSSI and HTA agencies, and for hospital drug committees.

"It is not very easy for a company to enter the market in Spain because of the recent financial crisis," says Sampietro-Colom. She added that this has caused a greater focus on the value of products.

She also emphasized the importance of working with regional authorities as early as possible in the process. Since they make recommendations to hospitals about which drugs to use, it's important that manufacturers work directly with them to understand their concerns and make sure they are providing the data that these authorities will consider valuable. Sarría-Santamera also brought up the importance of working with both federal and regional authorities, adding that the regional and even hospital-level decision-makers are sharing more information about drugs, to alleviate unnecessary duplication of efforts.

Challenges and Opportunities

In an effort to limit drug expenditures, the Spanish government has primarily focused reform efforts on increasing patient co-payments and removing specific classes of drugs from national reimbursement, as opposed to focusing on cutting product prices like other EU countries have done. In fact, between 2011 and 2012, the prices for about 73% of marketed drugs remained constant, including most patented products.[4] Nonetheless, the increase in co-payments has already reduced the volume of drugs sold, which may create long-term problems for manufacturers operating in this market.

Going forward, additional changes in the Spanish healthcare system are likely. In fact, according to José Fernández-Rañada, Partner at J&A Garrigues, S.L.P., the Spanish government is currently redeveloping the rules regarding pricing and reimbursement of medicines. This regulation seeks to introduce a new process including a national therapeutic positioning report (Informe de Posicionamiento Terapéutico) that intends to rationalize, standardize and expedite the assessment of new drugs. As in other countries, manufacturers will need to develop product value throughout the life cycle as regional HTA agencies and hospital drug committees will be more likely to evaluate the real benefit of drugs by conducting continuous evaluations of products based on real world prescription and patient data.

One challenge that manufacturers need to be aware of is the time it takes to get through the regional HTA. Currently, there is not a centralized process in Spain. "We hope to get there someday and there is a move to share data and adopt common practices, but we are not there yet" says Sarría-Santamera. "Pharmaceutical companies need to "relax and be flexible."

REIMBURSEMENT REQUIREMENTS IN THE EUROPEAN G5: UNITED KINGDOM

Reimbursement Process and Key Players

Healthcare in England is public (there is increasing interest in private insurance), provided through the National Health Service (NHS). Similar services exist in Wales, Scotland and Northern Ireland. Funding comes mostly through taxation (80%). Health coverage includes physician visits, emergency care, surgery, and some dental and eye care. Healthcare is one of the largest items on the British budget; in 2012/2013 it is expected to cost around £130 billion, about 5% of the U.K.'s GDP.

Although funded centrally, the NHS is administered primarily at the local level. Starting April 1, 2013, clinical commissioning groups (CCGs) are responsible for commissioning most services, making general practitioners (GPs) the direct overseers of NHS funds. Although drug formularies are developed by NHS Trusts, they are adapted locally by the commissioners.

These structural changes may be less significant than others in the EU, however. "The clinical commissioning groups are more of a change in title, really," says Mark Wilkinson, Chief Officer at NHS Barnsley Clinical Commissioning Group. "What organizations need to know is that there is an attempt to put GPs in charge of how decisions are made. Connected to that, there is an intent to have more local decision making. I think I would be right in saying that a lot of new drugs are specialty products, though, which are not purchased by the local groups. They're purchased by NHS England for the whole country, and that hasn't changed."

In 1999, the National Institute for Clinical Excellence (NICE) was established; and re-established as a Non Departmental Public Body called the National Institute for Health and Care Excellence in April 2013. NICE is responsible for formal evaluation and recommendations regarding the most appropriate technology to address health issues, based on clinical and cost-effectiveness.

In 2011, NICE launched an online tool for health care professionals which outlines all of NICE's clinical guidance on a topic in an electronic flowchart. 18 pathways were launched covering a range of diseases, intended to aid provider decision-making. Previously, it had been difficult to see everything NICE has said on a specific condition across all its separate published guidance.

NICE's role is set to change in 2014, as it becomes more involved in price determinations. By way of background, since the 1950's, pricing has been managed by the Pharmaceutical Price Regulation Scheme (PPRS). PPRS's intent is to ensure the availability of "quality branded pharmaceuticals at

reasonable prices." The PPRS agreement involves a non-contractual arrangement between the U.K. Department of Health (DH) and The Association of the British Pharmaceutical Industry (ABPI). PPRS has been renewed and revised every 5-6 years since its inception. Under this arrangement, manufacturers negotiate price directly with the NHS every 5 years. The current PPRS agreement came into effect January 2009, and is set to "retire" December 2013.

The Department of Health (DH) will replace the PPRS with a value-based pricing (VBP) approach. This approach defines the VBP process as a "QALY-plus" approach for pricing branded drugs marketed after January 1, 2014. The base for price determination would be calculated using the Quality Adjusted Life Year (QALY), assuming a "basic threshold" based on the opportunity cost of alternative uses of money by the NHS.[5]

Once the base price is calculated, the "plus" aspect would take into account the drug's ability to achieve one or more of the following:

- Effectively manage a disease that entails a substantial "burden of illness" in society
- Provides "greater therapeutic innovation" than comparators/ standard of care
- Demonstrates "wider societal benefits"

NICE will calculate the basic cost-per-QALY determination and "expert groups" will be engaged to calculate the "plus" element. In March 2013, responding to concerns about the lack of specificity around this plan raised by Parliament's Health Select Committee, the DH issued a formal response confirming that NICE will be responsible for the full value assessment under the VBP system. How that assessment proceeds has yet to be finalized; the DH's formal response specifies that it will build on NICE's existing technology appraisals, but that the scope of these assessments will expand to include considerations like burden of illness and societal benefits.

Planning for Data Generation and Successful Negotiation

Currently, NICE appraises health technologies at the request of the DH. These technologies include:

- Drugs
- Medical devices
- Diagnostic techniques
- Surgical procedures

The U.K. DH refers technologies to NICE for appraisal based on one or more of the following criteria[6]:

- Is the technology likely to have a significant health benefit, taken across the NHS as a whole, if given to all patients for whom it is indicated?
- Is the technology likely to have a significant impact on other health-related government policies (for example, reduction in health inequalities)?
- Is the technology likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated?
- Is there significant inappropriate variation in the use of the technology across the country?
- In the absence of such guidance is there likely to be significant controversy over the interpretation or significance of the available evidence on clinical and cost effectiveness?

For new medical technologies, the National Institute for Health Research (NIHR) Horizon Scanning Centre (NHSC) may assist NICE. The NHSC formally reviews emerging medical technologies to brief the NHS and NICE on the health and economic implications of the technology. This information may impact technology appraisals, and can help expedite reviews.

The appraisal of a health technology is divided into 3 distinct phases:

1. **Scoping.** NICE defines the issues of interest, such as the disease and patient population(s), potential comparators, and principal outcome measures. Clinical and cost effectiveness questions are determined, perhaps in consultation with the manufacturers or sponsors of the technology, national groups representing patients, or organizations representing healthcare professionals.
2. **Assessment.** An assessment reviews and analyzes clinical and cost effectiveness compared with the appropriate comparator(s) defined in the scope. The assessment includes analysis of the quality, findings and implications of the available evidence. Strengths, weaknesses and gaps in the evidence are identified and evaluated.
3. **Appraisal.** An Appraisal Committee considers the evidence produced in the assessment phase, including clinical evidence (how well the medicine works), quality of life evidence (QOL), side effects, and likely impact on mortality. NICE also considers economic evidence that demonstrates how well the drug or treatment works relative to how much it costs -- essentially whether it represents value for money. Though other factors are taken into account, the key measurement is the Quality Adjusted Life Year (QALY).

Evaluation of effectiveness requires quantification of the effect of a new product against relevant comparator drugs, procedures and technologies. Relative effect of a product considers impact on survival, disease progression and quality of life; this impact is then used to estimate the QALYs. For most drugs, NICE has a cap

of £30,000 per QALY (although the cap was recently increased for terminal cancer drugs to £50,000).

In recent years, NICE has drawn criticism from both the industry and patient advocacy groups for rejecting treatments which were perceived as improving and saving lives. Many of the highest profile negative opinions from NICE have been for new generation cancer treatments -- expensive drugs that were popularly regarded as breakthroughs.

Following the review, a final appraisal is published and used by local-level NHS authorities in their funding decisions. A positive NICE appraisal means the NHS must reimburse for the technology. An unfavorable review means local NHS bodies (PCTs) may still reimburse a technology, but reimbursement is not required (and far less likely).

Again, starting in 2014, NICE's role is expected to expand beyond these at-request appraisals under the VBP system, and appraisals are expected to extend into other areas such as societal impact and burden of illness.

Challenges and Opportunities

NICE has historically evaluated products at the request of the NHS; most products haven't had to go through this process. However, as the role of NICE has expanded and it will now engage in broader value assessments under VBP in 2014, and as Clinical Commissioning Groups strive to deliver value for money from increasing pressed budgets, it will become even more critical for manufacturers to demonstrate the economic and clinical value of their products.

As a result, collaboration between pharmaceutical companies and payers could become more common, as Wilkinson explains: "While the thought of collaboration between manufacturers and payers has been and continues to be embryonic in nature, this shift in pricing model will be an encouragement for payers and pharmaceutical companies to work more closely together to clearly define the true value of a product." Wilkinson also added that "size of population potentially impacted by the use of a new drug remains very important and that there will be ever increasing emphasis on the economics of new drugs." When asked about the role of quality of life, Wilkinson commented that this has not been as strong an emphasis for evaluation as the economics of utilization, but this might change as physicians become increasingly involved in decision making.

A news release from the Department of Health dated June 20, 2013 indicates their support of increasing focus on quality of life, as well. According to the statement, value-based pricing will include factors like wider societal benefit. Health Minister Lord Howe explained "We cannot simply spend more and more on drugs -- this would mean spending less and less elsewhere. That's why we have asked NICE to look at the impact that drugs can have on people's ability to work or contribute to the economy and society."

NICE and other decision makers also face considerable pressure from the public to cover drugs and other interventions seen as truly innovative. "When you have something that is on the cusp, and you have people lobbying hard for its approval, it's hard to say no," says Chris Henshall, Ph.D., Chair of the Health Technology Assessment international (HTAi) Policy Forum and Honorary Fellow in the Centre for Health Economics at the University of York. Dr. Henshall also notes that although the perception has been that NICE was set up to control costs, the real driver has been a desire to increase the consistency and quality of NHS care.

When asked about the future value to payers that pharmaceutical manufacturers should be playing, Mark Wilkinson was articulate in describing needing go beyond the "sale of the pill." Manufacturers need to think more broadly about helping treat the disease and the patient. Successful collaborations between the NHS and pharma have included assisting patients with managing expenses of their care. Wilkinson described the future role of successful pharma companies as moving well beyond acute intervention and including approaches to assist in managing a disease more broadly.

Wilkinson also sees "risk-based" pricing as an increasingly important approach. He described the risk that pharma takes in developing a drug and the risk that payers take in paying for a new drug that may or may not play out as planned. "We are definitely looking for manufacturers to take on more of this post launch risk," Wilkinson said.

SUMMARY OF G5 PAYER TRENDS

Table 1 below summarizes what decision criteria payers in the G5 countries are using and their implications as discussed in this paper.

Table 1. Decision-Makers, Criteria, and Considerations for Manufacturers

Country	Review Body	Key Decision Criteria	Specific Legislation & Trends	Implications for Manufacturers
France	HAS	Therapeutic benefit, choice of comparator, budget impact	Index Thérapeutique Relatif (ITR)	New assessment tool designed to confirm relevance of comparator, appropriate endpoints, and proper study design
Germany	IQWiG	Therapeutic benefit, choice of comparator, cost effectiveness, availability of alternative therapies	AMNOG	Choice of comparator is critical and patient-relevant outcomes in different clinical trial populations must be addressed
Italy	AIFA	Therapeutic value, cost effectiveness, availability of alternative therapies	Macroecomics-based reform	Manufacturers must demonstrate the economic and clinical value of their products
Spain	MSC/Regional HTA agencies	Therapeutic value, cost effectiveness, availability of alternative therapies, budget impact	Macroecomics-based reform	Greater need to demonstrate benefit of drugs in real-world settings as HTA agencies will increasing conduct evaluations of products based on prescription and patient data
United Kingdom	NICE	Therapeutic benefit, choice of comparator, cost effectiveness, budget impact (QALYs)	Value-based pricing (VBP)	Revised QALY system requiring that new products are innovative and have greater benefits to society

BUILDING THE ECONOMIC AND CLINICAL VALUE STORY

Commercial success is no longer a matter of just gaining regulatory approval. Real world data, patient relevant outcomes, health economic analyses, comparative effectiveness and engaged conversations with payers are fast becoming the standard for market access. Regulatory approval and commercial market access strategy development must occur in parallel, not serial, processes.

Examples of decisions made on proven additional benefit are accumulating rapidly. Recently, Astellas' new antibiotic, fidaxomicin (Dificlir) was determined under the new AMNOG process to have "no proof of an added benefit." The drug had been approved for sale in Germany since December 2011 for the treatment of adults with diarrhea caused by Clostridium difficile. Why was the drug given no additional benefit status? According to IQWiG, three treatment situations along with three existing comparators were defined for analysis of benefit. For diarrhea that was not severe but required treatment, fidaxomicin was compared to the generic metronidazole; in severe cases the drug was compared with the reference drug vancomycin.

Unfortunately Astellas failed to provide data comparing fidaxomicin with the generic metronidazole and in the vancomycin group, patients with severe and mild diarrhea were mixed together. IQWiG also recorded that Astella's dossier contained information on severe adverse events only for the total population and the data was not analyzed in appropriate subpopulation format.

Failing to provide an appropriate comparator has been a relatively common reason for IQWiG's rejection of pharmaceutical claims. Recent examples include, GlaxoSmithKline's Benlysta for systemic lupus erythematosus (SLE), Biogen Idec's Fampyra (prolonged-release fampridine) for multiple sclerosis (MS) and Boehringer Ingelheim's Trajenta for type 2 diabetes. In the case of Fampyra, IQWiG cited the drug as providing no additional benefit over physiotherapy in MS patients with walking disability, and that Biogen submitted data that only indirectly compared the two treatments.

It is the second major blow for GSK's Benlysta in recent weeks after the U.K.'s National Institute for Health and Clinical Excellence (NICE) said the drug should not be available for routine NHS use in England due to lack of evidence that it was a cost-effective use of resources.

Examples from the U.K. and NICE follow a similar pattern and provide clear "watch-outs" for manufacturers that expect optimal market access without compelling cost effectiveness data. The oncology drug bevacizumab (Avastin) was recently determined to be "not recommended as an NHS treatment for a type of recurrent, advanced ovarian cancer", according to the latest draft (April

2013) guidance published by the National Institute for Health and Care Excellence (NICE).

This draft guidance, which was delivered following public comment on earlier initial recommendations, concluded that bevacizumab (when used with the chemotherapy drugs, gemcitabine and carboplatin) "does not represent good value for money for the NHS."

Sir Andrew Dillon, NICE Chief Executive, explained: "Although the independent Appraisal Committee acknowledged that bevacizumab may help to delay a person's cancer from spreading for a few months, it noted that clinical trial data was unavailable for around one in three trial participants, possibly due to discontinuation of treatment, side-effects or because they had been lost to follow-up, making it difficult to know what effect this had on progression-free survival rates. The committee also couldn't be sure the drug would help people live longer.

"The current evidence of benefit for patients does not support the cost of the treatment, which the manufacturer estimates to be just over £25,000 for one course for an average patient."

There is currently an opportunity to appeal against the draft recommendations. If no appeals are lodged, publication of the final guidance is expected in May 2013. Until then, NHS bodies should make decisions locally on the funding of specific treatments. Once NICE issues its final guidance on a technology, it replaces local recommendations across the country.

What about Risk Sharing?

There has been an increase in 'risk sharing' arrangements for drugs between healthcare institutions and pharmaceutical companies in Europe in an effort to control costs and provide continued comprehensive and equitable healthcare.

A good example is the recent NICE guidance recommending Lucentis (ranibizumab) for the treatment of patients with wet age-related macular degeneration (wet AMD). A key part of NICE's guidance was the implementation of the "Ranibizumab Reimbursement Scheme" (RRS), a unique collaboration between Novartis, the Department of Health (DH) and NICE. The RSS provides patients in England and Wales with universal access to ranibizumab, where the first 14 injections in the eye will be paid for by the NHS, and the drug cost of any subsequent ranibizumab injections will be reimbursed by Novartis.

Other examples include Celgene's Revlimid (lenalidomibe) for patients with multiple myeloma who have received prior therapy. Under this scheme, the manufacturer pays the cost of the drug if more than 26 cycles are needed for any patient (approximately 2000 patients in the U.K.) -- equating to any patient needing more than 2 years of therapy.

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ABOUT NUMEROF & ASSOCIATES, INC.

Numerof & Associates, Inc. is a management consulting firm focused on organizations in dynamic, rapidly changing industries like healthcare. For over 25 years, we've helped major pharmaceutical and medical device companies and hospital systems address the strategic and operational challenges to profitable growth and market leadership. Our work across the entire healthcare spectrum provides us with unique capabilities to develop systemic, customized client solutions. We help clients with three broad types of issues:

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ABOUT THE AUTHORS

DR. JILL E. SACKMAN, D.V.M., PH.D.

An internationally recognized surgeon, Dr. Sackman is a medical researcher and author with more than 25 years of experience in surgery, and the pharmaceutical and medical device industries. Her contributions included building clinically based strategy to accelerate global commercial growth as well as defining ways to incorporate clinical insight into pharmaceutical and device design to more effectively meet customer needs. She has designed and established data driven strategies for regulated pharmaceutical and medical device design and development in a variety of therapeutic areas as well as identified and evaluated licensing and acquisition opportunities. She has led complex projects, large, diverse research organizations and cross functional teams. She has also been instrumental in leading organizational efficiency assessments, designing and implementing organizational competency models, and managing organizational change to meet competitive business needs. Dr. Sackman has directed initiatives to define clinical and economic value implications for commercial strategy on a global basis for pharmaceutical and medical devices and diagnostics. Dr. Sackman has extensive experience working cross functionally within the medical device and pharmaceutical industries to define product portfolio strategy and positioning and served on global marketing teams accountable for developing new market development strategies.

DR. MICHAEL J. KUCHENREUTHER, PH.D.

Dr. Kuchenreuther, a Research Analyst for Numerof & Associates, Inc., has a distinct focus in the healthcare industry, having worked with major global pharmaceutical manufacturers as well as with healthcare delivery systems. He has provided solutions focused on the design and execution of bundled payments, episodes of care, development of care pathways and tools to manage variation and utilization of care. Dr. Kuchenreuther has also conducted product and portfolio risk assessments to help clients define and demonstrate the strength and effectiveness of their product's value message for payer audiences within a variety of therapeutic areas.

NAI
Numerof & Associates, Inc.

Four CityPlace Drive, Suite 430
St. Louis, Missouri 63141
314.997.1587
314.997.0948
www.nai-consulting.com