PRMA Insights Focus:
The Impact of AMNOG on Pricing and Reimbursement in Germany and Beyond

This PRMA Insights Focus report provides in-depth analysis of the evidentiary and methodological issues of benefit assessment and price negotiation in Germany, and highlights key success factors to improve the likelihood of a favorable assessment to support premium pricing, impacting market access in Germany and beyond.
Market access in Germany has become significantly more challenging since the AMNOG legislation was introduced. Even though the outcome of benefit assessment is a key driver of price negotiations, manufacturers have not always prepared dossiers adequately, compromising the outcome of the assessment and subsequent price that is agreed. In some cases, manufacturers have withdrawn from the German market in the face of substantial rebates. Lower prices in Germany will have a ripple effect across Europe and beyond, particularly in countries that use reference pricing, with implications for strategy and launch sequence.

This PRMA Insights Focus report provides in-depth analysis and understanding of the evidentiary requirements and benefit assessment process, and sets out practical recommendations and key success factors for manufacturers to ensure adequate preparation and likelihood of success.
Introduction

The benefit assessment process that was introduced as part of the AMNOG legislation in 2011 has presented manufacturers with many new market access challenges. The methodological and evidentiary requirements are stringent, and preparation of the dossier is a time-consuming and expensive task: our experts liken it to preparing the EMA submission dossier, at a likely cost of €300,000–600,000 for dossiers of 400–600 pages and up to €1 mn for a large dossier.

Analysis of the first 3 years of benefit assessment indicates that many manufacturers have not clearly understood—or met—the requirements in terms of the appropriate comparator, patient subgroups, acceptable endpoints, and methodology. Of 62 benefit assessments finalized to date, considering 112 subpopulations, a resolution of "additional benefit not proven" was returned on 70 (62.5%); however, this was for technical reasons in the majority of cases: the dossier was incomplete in 22 (31%), the evidence was considered inappropriate by the G-BA in 28 (40%), and the appropriate comparator was not considered in 14 (20%).

Clearly this has major implications for pricing, given that the G-BA’s decision on the extent of additional benefit relative to the appropriate comparator is a key factor in the pricing negotiation, and a poor benefit assessment result will severely compromise the final reimbursed price that can be achieved. Indeed, manufacturers have seen some substantial cuts in price. Lower prices in Germany will have a ripple effect across Europe and beyond, particularly in countries that use reference pricing.

This has significant implications for strategic decisions about launch sequencing—whereas Germany has long been considered a key market in which to launch early, this may no longer be the case.
Key facts

A decision of “no additional benefit proven” was returned for 62% of the 112 subpopulations considered in 62 benefit assessments to date. However, the decision of “no additional benefit proven” was for technical reasons in 91% of cases, not because the drug did not provide additional benefit.

**Benefit assessment results**
- Non-proven: 63%
- Significant: 9%
- Marginal: 20%
- Non-quantifiable: 7%
- Less than 1%

**Reasons for no additional benefit proven**
- Evidence inappropriate: 38%
- No benefit shown: 10%
- Appropriate comparator not considered: 20%
- Evidence incomplete: 32%

Based on 113 subpopulation in 62 benefit assessments completed to 31 October 2013

This PRMA Insights Focus report provides in-depth analysis and understanding of the evidentiary requirements and benefit assessment process, and sets out practical recommendations and key success factors for manufacturers to ensure adequate preparation and likelihood of success.

**PRMA Strategic Insights**
Developed by our in-house experts, PRMA Strategic Insights provide critical advice to manufacturers in planning their market access strategy.

**Key Success Factor**
Crucial factors and practical information that significantly increase the chances of a successful benefit assessment and therefore market access are highlighted.

**Case Study**
Case studies based on individual benefit assessments are used throughout the report to illustrate key points.

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Not all manufacturers have communicated with the G-BA to discuss the technical issues and challenges around preparation of the benefit dossier, or earlier to discuss the clinical trial.

**Key issues**

**Benefit assessment**
- How will an NCE entering the German market be assessed?
- What are the processes for orphan drugs? How do these differ from those for other NCEs?
- What information needs to be included in the benefit dossier?
- How are surrogate endpoints considered in the benefit assessment process?
- What can be done if the pivotal trial comparator is not the appropriate comparator defined by the G-BA?
- Will indirect treatment comparison be successful?
- How should manufacturers prepare for subgroup analysis by IQWiG and the G-BA?
- Which marketed drugs will be called for benefit assessment? What impact will this have on the reimbursed price?

**Pricing**
- What can be achieved through arbitration? Is it still worth entering the German market with a low benefit assessment rating?
- Is it always a disadvantage to be included in a reference price group?

**Strategy**
- Can a profitable price still be achieved in Germany?
- How will the price achieved in Germany affect prices elsewhere?
- Is Germany still an optimal early market for launch?

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![Diagram of Consultation with G-BA prior to dossier submission]

Based on 62 submissions completed as at 31 October 2013

Each PRMA Insights Focus report is provided in a robust folder, with tabbed chapter dividers for easy navigation, and detailed tables and illustrations.
**Case study**

**Scenario:** endpoints were not considered patient-relevant

**Drug**
Perjeta (pertuzumab, Roche); date of resolution 1 Oct 2013

**General indication**
Breast cancer, in combination with Herceptin and docetaxel

**Indication (EMA)**
Adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease

**Assessment subtype**
New chemical entity

**Subpopulations assessed by the G-BA**
- HER2-positive metastatic breast cancer with visceral metastases
- HER2-positive metastatic breast cancer with non-visceral metastases
- HER2-positive locally recurrent unresectable breast cancer

**Appropriate comparator defined by the G-BA**
- Herceptin + a taxane (paclitaxel, docetaxel)
- Radiation therapy

**Assessment result G-BA**
- Hint of considerable additional benefit
- No additional benefit proven (no data provided)
- No additional benefit proven (population was not treated according to standard protocols in Germany)

**Rebate negotiated**
Not yet reported

**Special comments**
- HRQL data were not accepted or considered in the assessment because based on a non-validated version of the FACT-B, and because defined post hoc
- PFS was not considered a patient-relevant endpoint but was accepted to support OS as a patient-relevant endpoint

**Key learnings**
- The appropriate comparator must be used according to German clinical practice
- PFS is not always accepted as a patient-relevant endpoint; early discussion with the G-BA is recommended
- HRQL data must be generated from validated questionnaires
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Author profiles

The report has been written by AMNOG experts Monika Behrens and Rachel Bosshard, supported by PRMA Consulting's extensive cross-functional expertise in developing market access strategies.

Monika Behrens

Based in Germany, Monika has more than 15 years' experience in the pharmaceutical industry and statutory health insurance in Germany. Before joining PRMA Consulting, she was responsible for market access strategy at GlaxoSmithKline in Germany, the UK, and Europe for a broad range of disease areas, including oncology, hematology, neurology, urology, and vaccines. Monika has an in-depth knowledge of the German healthcare system, particularly the new AMNOG legislation, through regular attendance at workshops and training seminars, and through practical experience. She holds an MSc in Health Economics from the University of York and is a member of the DGGÖ, bdvb, and ISPOR.

Dr Helen Barham

Helen has led content development of multiple PRMA Insights titles, working closely with authors and contributors. She has broad knowledge of market access and P&R, combined with expertise in a wide range of therapy areas and more than 15 years’ experience in medical publishing. Helen has a PhD in Pharmacology from the University of Sheffield and conducted postdoctoral research in oncology at the former MRC Radiobiology Unit near Oxford.

David Sykes, Founding Partner

David has more than 15 years’ experience in P&R, market access, and health outcomes and has held senior leadership roles at Lilly and Johnson & Johnson. He has developed European and global P&R and market access programs to quantify, capture, and communicate product value. As PRMA Consulting’s founding partner, David provides leadership and strategic input around the complex issues that manufacturers face in bringing high-value innovative products to market across a broad range of therapy areas, particularly oncology and autoimmune disease.

Dr Mark Larkin, Partner

Mark has more than 10 years’ experience in strategy consulting and market access. At PRMA Consulting, he has led European and global projects across a broad range of therapeutic areas, including oncology, pain, and vaccines. These projects have included P&R analyses, payor advisory boards, GVDs, and systematic literature reviews, undertaken for emerging biotechs in support of in-house commercialization or out-licensing, as well as big pharma clients. Mark has contributed to many of the PRMA Insights series of global P&R and market access resources.

Dr Casey Quinn

Casey has 10 years’ experience in health economics and outcomes research, including economic evaluation, decision analysis, econometrics, and modeling methodologies, and in-depth understanding of the technical and evidentiary for HTA submissions in all the major markets. Casey leads a strong team of HEOR consultants and analysts providing evidence generation across economic modeling and evidence synthesis. Casey has a PhD in Health Economics from the University of York, and has taught economics, health economics, and statistics at universities in Australia, the UK, and the US.

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2.5 Consultation with the G-BA

The G-BA offers the opportunity to discuss the content and structure of the dossier before final submission for assessment. The main reason for consultation is to discuss the evidence required for regulatory approval, i.e. to possibly approach the G-BA at an early stage, such as after completing Phase 2 to inform planning of the Phase 3 trials.

The consultation meeting is developed to mutually understand the content of the dossier. For example, manufacturers are faced with difficulty in demonstrating that the clinical benefit of non-world leaders should still be discussed on an early stage in order to explore Phase 3 trial design and choice of trial comparator. After Phase 2, is understanding about the required analyses to uncover missing data may be worthwhile. Methodology for indirect treatment comparison (ITC) and meaningful patient-relevant endpoints are currently the most controversial issues debated between G-BA/IQWiG and manufacturers – some of which could be addressed early in the consultation process.

The manufacturer can request consultation with the G-BA on the documents and studies to be submitted for benefit assessment (Annex 5.1(6) § 5v) relating to:
- the code of practice in general
- documents that are acceptable for submission
- studies relevant to assessing the benefit of the pharmaceutical
- completion of dossier documents
- the appropriate comparator
- endpoints
- the study population and relevant subpopulations.

Consultation can be sought at various stages, and more than once (see Sections 2.5.1 and 2.5.2).

2.5.1 Strategic advice from the G-BA

The request for a consultation meeting must be submitted via a form (in German), stating general information and specific questions and issues that the manufacturer wants to discuss with the G-BA. Further information about the meeting is provided in Table 3.4.

The consultation should take place early during the development of the dossier. However, manufacturers need to decide whether to wait for 120, 150, or 180 days from the EMA license application for answers to their questions. Waiting longer would potentially delay development of the dossier, and therefore deprive the company of valuable time to develop the dossier. It is the G-BA who highlights issues that the G-BA believes to be important and points out, in the consultation document (CDD), potential ways the company can consider to address these issues.

Consultation with the G-BA can be requested at various stages, either before the application for market authorization or in other cases. The consultation process is considered to be a more proactive step than the meeting. As explained above, whilst most manufacturers now seek advice from the G-BA through the consultation process, many are not aware that early consultation during the clinical trial program is also possible.

The advice provided by the G-BA can be used to develop the clinical trial program. G-BA’s line of thought.

Seeking consultation is critical to the outcome of the submission. Some manufacturers have failed to understand the importance of the meeting, and either did not see or were not given the advice. From our understanding, there is no reason not to consult the G-BA, and it is the only opportunity before submission to understand and modify the G-BA’s line of thought.

Key success factors
- Advice can be sought at any stage. A consultation can be valuable as early as during design of Phase 3 trials in order to assess risk.
- When approaching the G-BA for a consultation (around the time of licensing submission to the EMA), it is important to have developed an understanding of the German market access strategy as well as the benefit dossier submission strategy.
- The request for consultation should include specific questions, detailed information, and references. Through a timely consultation the manufacturer can ensure their maximum benefit.
- There is no official limit on the number of questions that can be posed, although 5-10 references. Thorough and timely planning is required to ensure that maximum benefit is obtained.
- The G-BA can request consultation at any stage of the consultation process.
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Manufacturers must also submit all scientific documents relating to the drug, including:
- all information available on completed, ongoing, discontinued, and planned trials sponsored by the manufacturer
- any other documents that should be discussed.

2.5.2 Early consultation

Consultation can be requested at various stages, either before the application for market authorization or in other cases. The consultation process is considered to be a more proactive step than the meeting. As explained above, whilst most manufacturers now seek advice from the G-BA through the consultation process, many are not aware that early consultation during the clinical trial program is also possible.

Early consultation is recommended to obtain advice on the design of the pivotal trial in terms of patient populations and subpopulations, the trial comparator, endpoints, diagnostic techniques, etc. The consultation meeting and evaluation of the information submitted are set out in detail in Chapter 11 of the PRMA’s Handbook. The trial design can be presented and the G-BA assess whether the data generated would be relevant, however, if this is not done, the G-BA will not take any considerations about what is expected to see in the benefit dossier. The G-BA’s reply is sometimes vague phrased “this might be critically assessed” however, this is still useful to estimate risk.

Key success factors
- Advice can be sought at any stage. A consultation can be valuable as early as during design of Phase 3 trials in order to assess risk.
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