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.

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Market access success

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 In some cases, manufacturers have withdrawn from the German market in the face of substantial rebates.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.

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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.

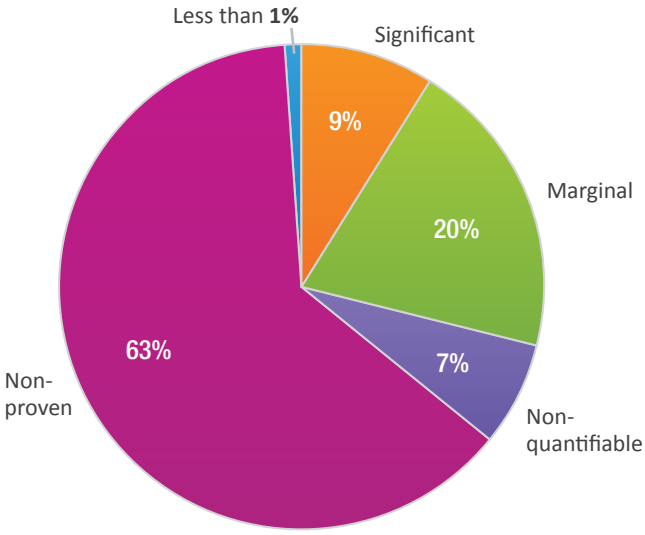
This has significant implications for strategic decisions about launch sequencing – whereas Germany has long been considered a key market in which to launch early, this may no longer be the case.

Key facts

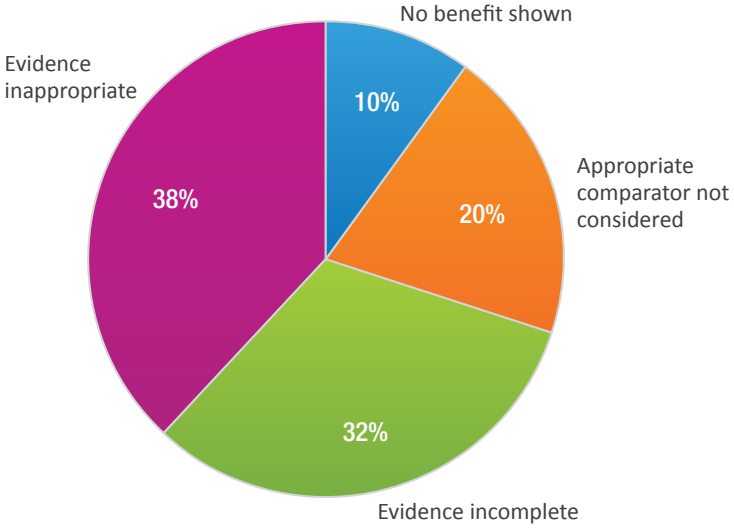
A decision of "no additional benefit proven" was returned for 62% of the 112 subpopulations considered in 62 benefit assessments to date.

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



Reasons for no additional benefit proven



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

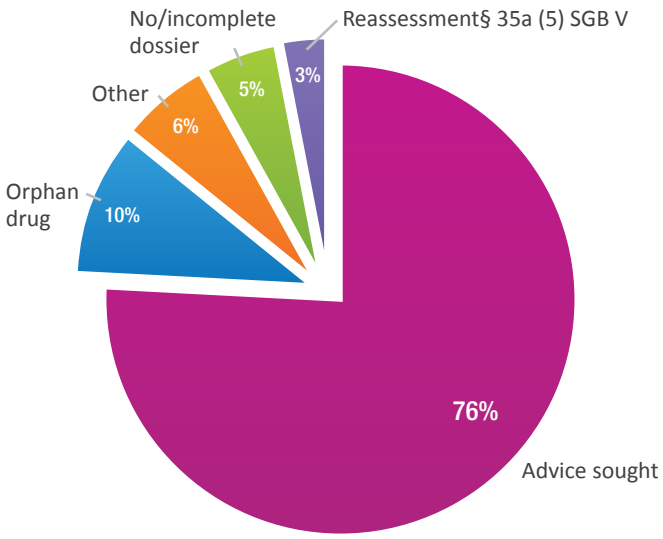
Crucial factors and practical information that significantly increase the chances of a successful benefit assessment and therefore market access are highlighted.

Case Study

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

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.

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.

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?

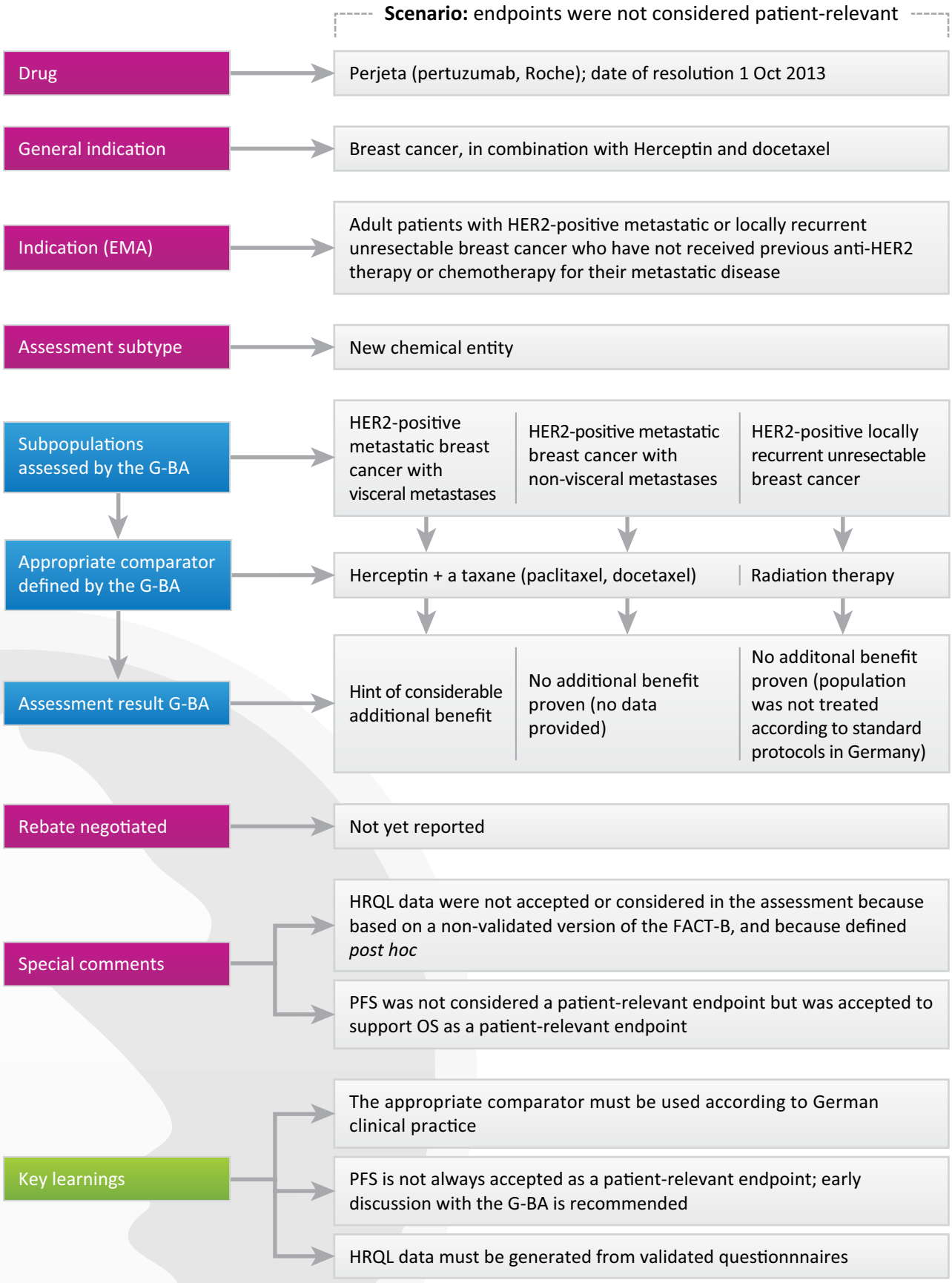
Pricing

- 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?

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 additonal 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 questionnnaires

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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 Rachel Bosshard

Rachel has experience across a broad range of consultancy work, including systematic literature reviews, HTA reviews, PRO strategies, and development of the GHE strategy for an orphan drug. She also has in-depth knowledge and understanding of the P&R system in Germany and of benefit assessment and AMNOG in particular through practical experience and regular attendance at workshops and seminars. Rachel holds a PhD in Clinical Medicine Research from Imperial College London and an MSc in Natural Sciences from the Swiss Federal Institute of Technology, and has more than 5 years' research experience in oncology and microbiology, gained in academia and the pharmaceutical industry.

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 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 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.

The report has also been reviewed and validated by an academic with 15 years' experience in industry and consulting, specializing in healthcare and market access, and the directors and heads of market access of the German affiliates of two top-10 pharma companies, each with more than 15 years' industry experience.

2.5 Consultation with the G-BA

The G-BA offers the opportunity to discuss the content and structure of the benefit dossier. Whilst most manufacturers seek advice when preparation of the marketing authorization submission is underway, in fact there is currently no limit to the number of consultations. It is possible to approach the G-BA at much earlier stages, such as after completing Phase 2 to inform planning of the Phase 3 trials.

The consultation meeting is a good place to develop a mutual understanding about the content of the benefit dossier. For example, manufacturers faced with difficulty in demonstrating true clinical benefit without real-world data should initiate discussions at an early stage in order to explore Phase 3 trial design and choice of trial comparator. After Phase 3, an understanding about the required analyses to cover 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 through consultation.

The manufacturer can request consultation with the G-BA on the documents and studies to be submitted for benefit assessment (§ 35a (7) SGB V) relating to:

- the code of practice in general
- documents that are acceptable for submission
- studies relevant to assessing the benefit of the pharmaceutical
- compilation of benefit 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 2.5.1and 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. Practical information about the meeting is provided in Table 2.4.

This consultation should take place early during preparation of the benefit 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 benefit dossier development; however, EMA feedback may highlight issues that the G-BA (or IQWiG) would raise. The G-BA needs tangible information on which to base its recommendations, so it is important that the meeting is not too early.

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When deciding when to request consultation with the G-BA, manufacturers need to weigh up the benefits of waiting for EMA feedback that may highlight issues to discuss with the G-BA against the potential delay to development of the benefit dossier.

The consultation request must include details relating to the drug, the indication, the target population, the mechanism of action, and the expected use in Germany. The manufacturer sets out a list of specific questions to be discussed, including their point of view if they so wish. This means that, in reality, the overall market access strategy needs to have been developed.

The manufacturer 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.

In preparation for the meeting, the G-BA will check the completeness of the information submitted, search for potential comparators and endpoints, and will undertake a systematic literature search, including extraction of important information and will determine which of the manufacturer's questions will be discussed in the meeting (e.g., on potential comparators and endpoints). However, the G-BA does not evaluate the actual studies and data.

The advice meeting with the manufacturer will take place within 8 weeks of application. The face-to-face meeting is held in German and the agenda is determined and led by the G-BA. There is no formal presentation by the manufacturer other than a short statement of the benefit claimed. The focus of the hearing is to clarify controversial or unclear points. The G-BA will also communicate its choice of appropriate comparator to be used in the benefit assessment, if requested.

Preparation for the meeting with the manufacturer is considered to be part of the decision-making process, therefore the formal advice provided by the G-BA cannot be negotiated or modified during the meeting.

Key success factor

It is important to consider carefully the questions asked and how they are phrased, as the G-BA will only answer questions submitted ahead of the meeting. Manufacturers also need to consider how much trial data and strategic information to share with the G-BA at this stage. it should be borne in mind that the G-BA representatives at the advice meeting may not have been involved in the evidence review and so may not be fully informed.

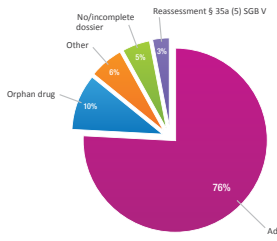
Table 2.4: Summary of consultation meetings with the G-BA

Term	
Attendees	There is no formal restriction on the number of manufacturer representatives (in contrast to other hearings during the benefit assessment process)
	An interpreter is allowed, at the manufacturer's expense
	Members of the BfArM and PEI can attend the consultation
Time line	Takes place within 8 weeks of application
	Written protocol and formal advice report provided within 14 days, including decision criteria
Fees	Three categories: €2,000, €7,000, €10,000
	The highest fee is required if advice on the appropriate comparator is sought
	May be modified according to complexity of application and number of subpopulations; for complicated cases, the fee can be doubled

BfArM (Federal Institute for Drugs and Medical Devices); PEI, Paul Ehrlich Institute – Federal Institute for Vaccines and Biomedicines

As shown in Figure 2.2, manufacturers have sought advice from the G-BA for about three-quarters of dossiers.

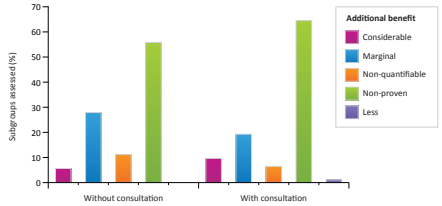
Figure 2.2: Summary of dossier submissions for which advice was sought (at any stage)



Based on 62 submissions completed as at 31 October 2013

The limited available data do not indicate that seeking advice from the G-BA before the submission of the benefit dossier increases the possibility of a higher benefit assessment rating, although a slightly higher proportion of benefit dossiers submitted after consultation achieved a rating of "significant" compared with benefit dossiers for which consultation had not been sought. Naturally, other factors also influence the outcome of the benefit assessment and the fact that consultation was requested by the manufacturer may indicate more thorough preparation of the benefit dossier.

Figure 2.3 Outcome of benefit assessment in relation to consultation with the G-BA



Based on 113 subpopulations assessed up to 31 October 2013; consultation was sought for 95 subpopulations or 47 drugs (76%)

2.5.2 Early consultation

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. This consultation should be used to evaluate risk in the trial design and to adapt it if possible. The trial design can be presented and the G-BA asked whether the data generated would be relevant; however, there is no discussion, and and the G-BA will not make commitments about what it expects to see in the benefit dossier. The G-BA's reply is sometimes vaguely phrased "this might be critically assessed"; however, this is still useful to estimate risk.

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Manufacturers should seek scientific advice at an early stage (before Phase 3) in order to explore options such as Phase 3 trial design and choice of active comparator; advice should be sought again before submission of the benefit dossier to develop a mutual understanding of the acceptability of the evidence available.

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 ask for the meeting or have ignored the advice. From our understanding, there is no reason not to consult the G-BA, as it is the only opportunity before the submission to understand (and maybe alter) 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 EMA the latest), it is imperative to have developed an understanding of the German market access strategy and, more importantly, the benefit dossier submission strategy.

The request for consultation should include specific questions, detailed information, and references. Thorough and timely planning is required to ensure that maximum benefit is derived from the meeting.

There is no official limit on the number of questions that can be posed, although 5–10 questions are normally covered in each consultation. To obtain detailed and insightful information, we recommend that manufacturers are realistic and present fewer questions that are well prepared and considered.

The consultation will be solely on the questions and evidence submitted by the manufacturer. It is therefore imperative to consider carefully how to approach the consultation, as the G-BA will not discuss or negotiate its point of view.

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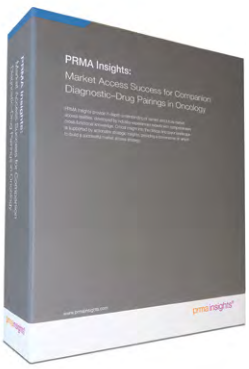

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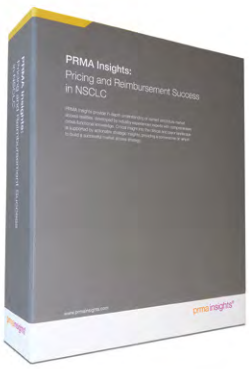

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