Early benefit assessment of new drugs in Germany: Framework for submission of dossiers by pharmaceutical companies

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Abstract

For the early benefit assessment of new drugs in Germany, medical writers are involved in the preparation of dossiers submitted by pharmaceutical companies to the main decision-making body of the German statutory healthcare system, the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA). These dossiers are generally assessed by the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG). The present article summarises the documents that are publicly available to guide dossier preparation and to ensure transparency. These documents detail the requirements for the structure and content of the dossier, procedures for dossier submission, assessment by IQWiG, and decision-making by the G-BA. Medical writers should adhere closely to the available guidance to help ensure that the submitted dossiers fulfil the formal and content requirements.

Keywords: Medical writing, New drugs, Early benefit assessment, Dossier assessment, (German) Act on the Reform of the Market for Medicinal Products

Most industrialised countries make comparative assessments of the efficacy and/or effectiveness of drugs to inform national reimbursement decisions.[1] Until recently the price of a new drug in Germany (i.e. a drug with a new active ingredient) was not regulated or negotiated by a healthcare or governmental body but was set solely by the pharmaceutical company. This led to high prices of patented drugs and increasing costs in the pharmaceutical sector of the healthcare system.[2] In an attempt to counter this development, the Act on the Reform of the Market for Medicinal Products (*Gesetz zur Neuordnung des Arzneimittelmarktes*, AMNOG) was introduced on 1 January 2011.[3]

Social Code Book V (*Sozialgesetzbuch*) provides a legal framework for health services regulated by statutory health insurance (SHI). In accordance with Paragraph 35a of Social Code Book V, when a new drug (or an established drug with a newly approved therapeutic indication) enters the market, the pharmaceutical company must submit a dossier containing evidence of the drug's added benefit for patients compared with an appropriate comparator therapy (ACT).[4,5] The ACT is specified by the Federal Joint Committee (*Gemeinsamer Bundesausschuss*, G-BA), the main decision-making body of the SHI system.[6] The G-BA is responsible for the procedure of early benefit assessment.

Procedure of early benefit assessment

Medical writers (employed by pharmaceutical companies or contracting agencies, or commissioned as freelancers) are heavily involved in dossier preparation, which follows a standardised procedure. German-language writers are mainly involved, as the actual dossier text is in German. However, English-language writers may also prepare texts that are subsequently translated.

To assist pharmaceutical companies with dossier preparation and to ensure transparency, various documents (including those in English) relating to the early benefit assessment are published on the websites of the G-BA and the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*, IQWiG[7]) (Table 1).

In addition, the G-BA offers consultation on the documents and studies to be submitted and on the ACT. This consultation, which must be paid for by the companies, can take place at an early stage, i.e. before the start of Phase III studies submitted in the drug approval process.[9]

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Table 1: Publicly available information sources to assist dossier preparation and to ensure transparency for the early benefit assessment of new drugs in Germany[a]

Type of information	G-BA website	German	English	IQWIG website	German	English
Overall procedure						
General information	Summary information	X	X	Summary information	X	X
	Questions and answers	X	X			
Methods and other requirements	Rules of Procedure	X	–	General methods, Version 4.0	X	X
	Dossier template	X	–	Methods for classifying extent of added benefit[b]	X	X
For each new drug						
Dossier	Modules 1–4	X	–			
Assessment results of IQWiG	Full dossier assessment	X	–	Full dossier assessment	X	(X)[c]
				Executive summary	X	X[d]
				Health information	X	X
Commenting procedure	Submitted comments	X	–			
	Responses by G-BA	X	–			
	Minutes of hearing	X	–			
Resolution by the G-BA	Text of resolution	X	X			
	Reasons for decision	X	–			

G-BA, *Gemeinsamer Bundesausschuss*; IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*.
[a]Adapted translation.[8]
[b]Appendix to dossier assessment A11-02.
[c]An English extract of the dossier assessment is available (generally sections 2.1–2.6: executive summary, methods, results and conclusions).
[d]Included in the English extract.

The flowchart of the early benefit assessment is shown in Fig. 1: the G-BA generally commissions IQWiG to assess the dossier and evaluate the probability and extent of added benefit of the drug. These 'dossier assessments' are published on the websites of the G-BA and IQWiG within 3 months after market entry, and the pharmaceutical companies responsible, as well as other specified scientific and commercial parties, are given the opportunity to submit comments in a written hearing, followed

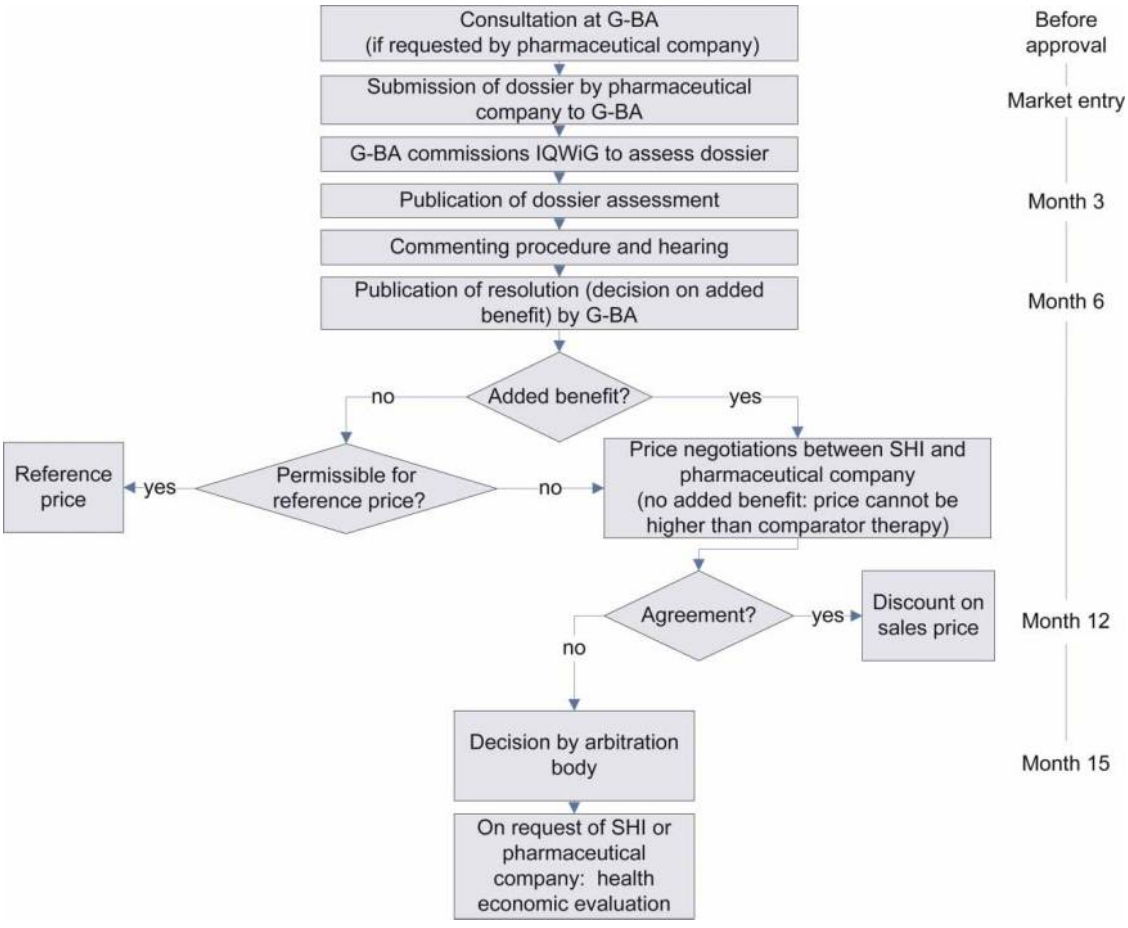

Figure 1: Flow chart of early benefit assessment (adapted translation from IQWiG presentation materials).

by an oral hearing. Three months after publication of the dossier assessment the G-BA passes a resolution based on the assessment and the results of the hearing; the main issues specified are the extent of added benefit of the new drug, eligible patient groups, requirements for quality-assured administration, and cost of treatment with the drug.[9] This resolution forms the basis for price negotiations between the SHI umbrella organisation and the pharmaceutical companies.

Exemptions to the above procedure apply for orphan drugs, where the main responsibility for the dossier assessment lies with the G-BA, and specific regulations apply.[10]

Legal requirements and methods

The G-BA's Rules of Procedure

Paragraph 35a of the Social Code Book V provides the overall legal framework for the early benefit assessment. Chapter 5 of the G-BA's Rules of Procedure[11] specifies detailed aspects of the assessment procedure, for example:

- Scope
- Specification of processes, e.g.:
  - consultation at the G-BA
  - submission, assessment, and publication of the dossier (and the dossier assessment)
  - conduct of the commenting procedure
  - publication of the resolution by the G-BA
- Specification of definitions, e.g.:
  - drugs with new active ingredients
  - ACT
  - benefit and added benefit
  - extent of added benefit (see categories below)
- Requirements for pharmaceutical companies for deriving proof of added benefit, e.g.:
  - *design of submitted studies*: preferably randomised controlled trials directly comparing the new drug with the ACT
  - *type of outcomes investigated*: preferably patient-relevant outcomes such as mortality, morbidity, and quality of life
  - assessment and consideration of study quality
- Requirements for dossier content (see below)
- Requirements for special situations (e.g. assessment of orphan drugs)

IQWiG's methods

The general methods applied in the early benefit assessment are published in IQWiG's methods paper.[12] The specific methods applied to determine the extent of added benefit are published in the appendix to the first dossier assessment for a newly marketed drug, ticagrelor.[13] In brief, on the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of a new drug compared with the ACT for each patient-relevant outcome (i.e. an outcome describing 'how a patient feels, functions, or survives'[14]). Depending on the number of studies analysed, the risk of bias, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into four categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) no conclusions can be drawn from the available data or no data are available at all.[12] Should an added benefit be shown, the extent of added benefit or harm is graded into three categories: (1) major, (2) considerable, and (3) minor. (In addition, three further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit.)[13] In a final step, the results for the various outcomes investigated are aggregated qualitatively into a single conclusion.

Structure and content of the dossier

The dossier has a modular structure and contains five modules (Fig. 2). Modules 1–4, among other things, contain a systematic review of the evidence, including the classification, by the pharmaceutical company, of the extent of added benefit. In this context, 'evidence' generally comprises results of all available (i.e. both published and unpublished) relevant clinical trials of the new drug directly compared with the ACT. In the absence of such direct comparisons, the evidence may also comprise trials that can be used for indirect comparisons. Regardless of the method chosen, it is required that study medications were administered in accordance with the approval status of the new drug and of the ACT. Furthermore, information on the cost of treatment is provided (drug cost only). Module 5, among other things, contains the full evidence base, including full clinical study reports of all manufacturer-sponsored trials of the drug under assessment.

The dossier must be submitted in specific templates, available on the G-BA website.[16] These templates not only provide the format of the dossier but also specify requirements for content (including methods). All template requirements should be followed because non-adherence increases the probability of submitting an inadequate dossier, leading to the conclusion that no added benefit of the new drug is proven. In addition, a completed checklist must be submitted for assessment of the formal completeness of the dossier.[17]

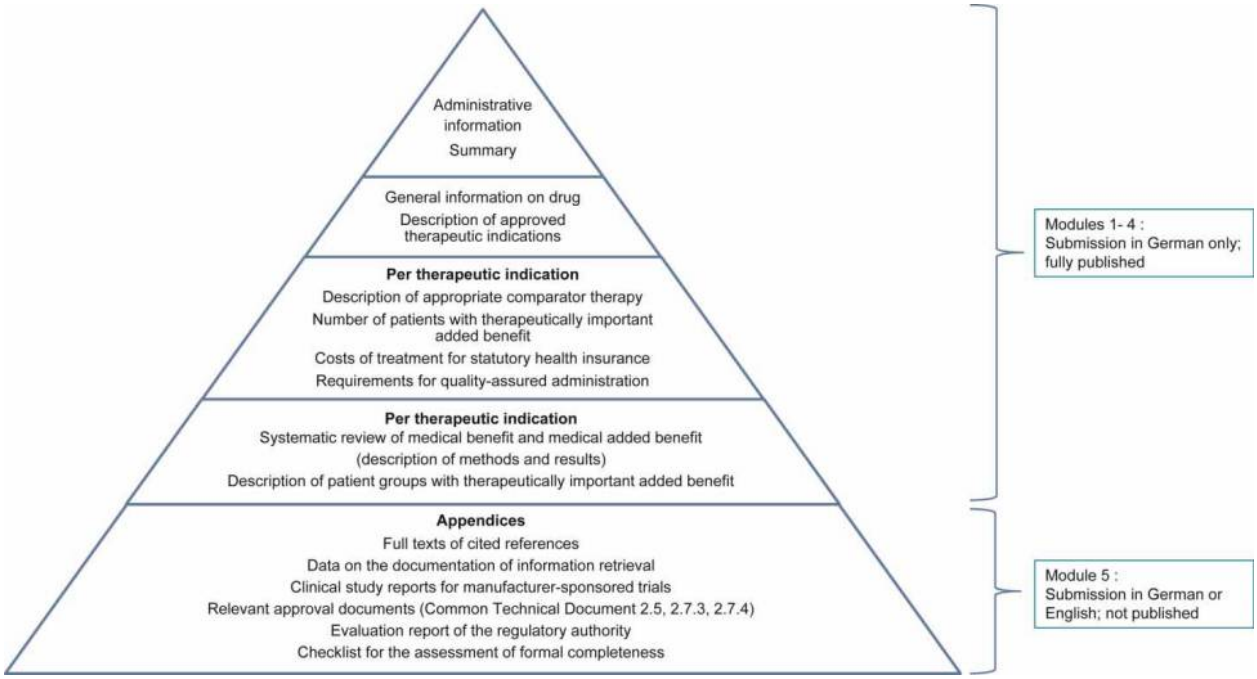

Figure 2: Structure of dossier: Modules 1–5 (adapted translation[15]).

Mandatory publication

To ensure transparency, there is a legal obligation for the G-BA to publish Modules 1–4 of the submitted dossiers, as well as the corresponding full dossier assessments and resolutions.[5] Various additional documents are also published, for example, health information for patients and consumers relating to the results of the dossier assessment (Table 1).

Results so far

Some 30 dossier assessments have so far been completed. A recently published analysis of the first 21 dossier assessments (excluding orphan drugs) showed that 13 of them provided adequate data for evaluation.[18] Some of the eight inadequate dossiers revealed gaps in the evidence or did not adhere to the ACT specified by the G-BA. However, all in all the findings indicate that the early benefit assessment of new drugs is feasible.

Assessment of older drugs

Assessment of the existing market, that is, of drugs already approved before the implementation of AMNOG, has been introduced as a further component of drug assessment in Germany. The first group of drugs assessed are gliptins for the treatment of type 2 diabetes,[19,20] meaning that for the first time an assessment covers a whole group of drugs (i.e. both older and newly approved), a further milestone in comparative effectiveness research. Further groups of drugs have been called up for assessment.[21]

Conclusions

Numerous documents to assist the preparation of dossiers for the early benefit assessment of new drugs in Germany are publicly available. Medical writers should closely adhere to the guidance on dossier preparation to help ensure that the submitted dossiers fulfil both the formal and content requirements.

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Conflicts of interest

Both authors are employed by IQWiG.

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A Great Books guide to when a medical writer should be involved in a project

'In the beginning was the Word'. So begins the most influential text in western history. It is from this Word that the Bible claims the Judeo-Christian God created the universe, including the ancestors of today's research scientists. Unfortunately, the Bible doesn't specify which word. It is nice to see the Word given such importance; certainly more flattering than 'the beginning of what we can theorise with probability was the Big Bang. Before that, well…'; however, this universe-from-a-Word business doesn't really make sense in any logical way. Let's move on.

Homer's *Iliad* and Virgil's *Aeneid*, pillars of the western classical tradition, would be more accurate for medical writers. Not because we are great warriors (although I'm sure some of us are, in our own gentler ways) or because we write in dactylic hexameter but rather because they start *in medias res*, that is to say, the writer gets involved somewhere in the middle of the project.

More realistic is Emily Bronte's *Wuthering Heights*. Not because it is a work with a high degree of human degradation but because it is a framed narrative. The narrator, who did not participate in the action or participated on the fringes, relates the story that he heard from someone who had. The action is over, the writer just describes what was done, why, and why it matters. The story's action is finished and we're getting it second hand. Legally, it's hearsay. It can make for great fiction but it's not the ideal pattern for medical writers and authors to follow.

The best model is Chaucer's *Canterbury Tales*, the first important piece of creative literature in English since the Norman Yoke. Chaucer died before he finished it, true, but it has some great lessons for the medical community. Really (you ask), a long and occasionally bawdy fourteenth century poem with an unreliable narrator? Yes (I answer), and here's why: the narrator/writer is involved from the beginning of the project. There is a strong project leader who keeps the project on course and doesn't tolerate any non-sensical digressions, all participants gave their consent, and whoever tells the best story wins a prize. (Do medical writers win prizes? No. Should we? Yes.) Lastly, the project design was hatched in an inn (or tavern), i.e. they had a kick-off meeting. And a tavern is a wonderful place for thinking and a good place to meet a writer before setting out on a (metaphorical) journey together.

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