REALITY IN MARKET ACCESS IN GERMANY AND FRANCE

COMPARATIVE ANALYSIS OF ADDITIONAL BENEFIT APPRAISALS OF PHARMACEUTICAL THERAPIES

Leprêtre M[1], PhD
Dröschel D[2]
Chicoye A[1], MSc

1. ESSEC Business School, Paris-La Défense, France 2. Riedlingen University, SRH FernHochschule, Riedlingen, Germany

Background & Objectives

Adoption in Germany of the AMNOG law has introduced since January 2011 a systematic assessment of the additional benefit (AB) for new entities versus existing treatments, graded according to a scale. This approach appears to have been inspired by the Improvement of Medical Benefit (ASMR) grading prevailing in France, and both are serving pricing purposes. Manufacturers are now required in Germany to submit a dossier to the Federal Joint Committee (G-BA), which will perform the assessment in the first year after launch (under recommendation of the IQWiG). In France, manufacturers have to apply for reimbursement before launch and submit a dossier to the Transparency Commission (TC) at the Haute Autorité de Santé (HAS). In both cases, appraisals are made public.

The objectives of this study is to assess how far the scales are comparable, by determining to what extend the assessment of AB of new pharmaceuticals are convergent/divergent and characterizing the differences.

Material & Methods

This comparative analysis includes all pharmaceuticals either applied for initial admission to reimbursement (France) or first launched (Germany) for which full assessment both by the TC and the G-BA have been published between Jan 1st, 2011 and Dec 31st, 2013.

The databases of the HAS[1] and of the G-BA[2] and IQWiG[3] were searched systematically to identify the products and collect their benefit assessments reports. An analytic grid was set up, addressing different areas of interest : level of benefit (Table 2), appropriate comparators, clinical trials, indirect comparisons, endpoints, target population(s).

Table 2. *Additional Benefit (AB) quantification in France and in Germany*

TC		IQWiG/G-BA	
SMR	**ASMR**	**Level of proof**	**Extent of AB**
Reimbursement Y/N and rate	Price premium or discount versus comparator(s)	No proven AB ➔ Reimbursement tariff for group of comparable drugs Proven AB ➔ Reimbursement amount negotiation	
Important	I : Major	Proof	Major
	II : Important		Considerable
Moderate	III : Moderate	Indication	Minor
	IV : Minor		Non-quantifiable
Low	V : No	Hint	Less
Insufficient	/	Not proven	No

Results

Between January 1st, 2011 and December 31st, 2013, 110 new pharmaceutical entities have been assessed for additional medical benefit in France by the TC and 55 in Germany by the G-BA. Among those products, 38 were common to both countries. Those 38 medicines are found in eleven therapeutic areas (Table 1).

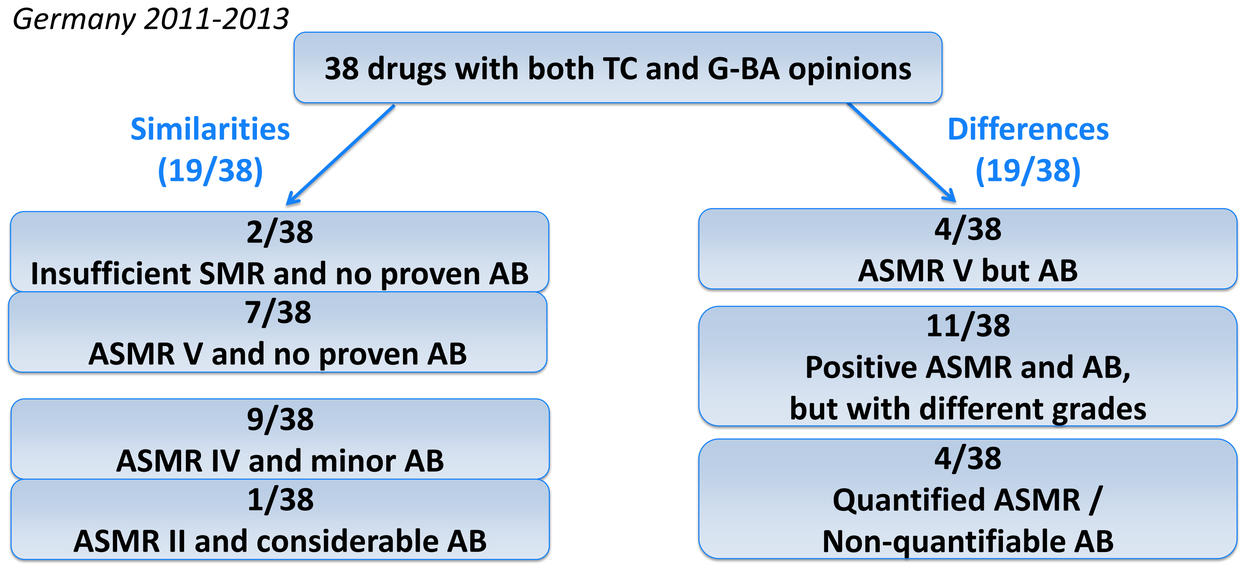
Table 1. *38 new pharmaceuticals with full benefit assessment by the G-BA and the TC*

Brand Name	INN
Cardiovascular system	
BRILIQUE®	Ticagrelor
ELIQUIS®	Apixaban
Dermatology	
PICATO®	Ingenol mebutate
Endocrinology	
KOMBOGLYZE®	Saxagliptin/ metformin
TRAJENTA®	Linagliptin
SIGNIFOR®*	Pasireotide
Immunology	
BENLYSTA®	Belimumab
Infectious diseases	
INCIVO®	Telaprevir
VICTRELIS®	Boceprevir
EDURANT®	Rilpivirine
EVIPLERA®	Rilpivirine, emtricitabine, tenofovir disoproxil
STRIBILD®	Emtricitabine, cobicistat, elvitegravir, tenofovir disoproxil
DIFICLIR®	Fidaxomicin
Neurology	
GILENYA®	Fingolimod
FAMPYRA®	Fampridine
FYCOMPA®	Perampanel
TROBALT®	Retigabine
VYNDAQEL®*	Tafamidis (meglumine)

Brand Name	INN
Oncology	
CAPRELSA®	Vandetanib
ZELBORAF®	Vemurafenib
YERVOY®	Ipilimumab
XALKORI®	Crizotinib
INLYTA®	Axitinib
JAKAVI®*	Ruxolitinib
ZYTIGA®	Abiraterone acetate
JEVTANA®	Cabazitaxel
DACOGEN®*	Decitabine
PIXUVRI®*	Pixantrone dimaleate
ADCETRIS®*	Brentuximab vedotin
PERJETA®	Pertuzumab
HALAVEN®	Eribulin
ZALTRAP®	Aflibercept
Ophthalmology	
JETREA®	Ocriplasmin
Orthopedics	
XIAPEX®	Collagenase C. histolyticum
Pneumology	
ESBRIET®*	Pirfenidone
EKLIRA GENUAIR®	Aclidinium bromide
BRETARIS GENUAIR®	
KALYDECO®*	Invacaftor
Urology-Nephrology	
NULOJIX®	Belatacept

*** Orphan drugs**

Figure 1. *Comparison of the benefit assessment of new pharmaceuticals in France and in Germany 2011-2013*



The G-BA concluded that two third had an AB (29/38) : 10 considerable, 15 minor and 4 non-quantifiable AB. No major AB was found. For 9 products, no AB has been granted. The TC acknowledged an AB for 25 drugs with 1 ASMR II, 9 ASMR III and 15 ASMR IV; no ASMR I was found. One third (13/38) were rated as having either no AB (11 with an ASMR V) or an insufficient Medical Benefit (SMR) (2/38). Convergent appraisals were found for 50 % of the products (19/38), assuming grades are equivalent (Figure 1). But differences were found for the other 50%, with 4 products with no ASMR in France and a proven AB in Germany , and 11 products with a different appreciation of the magnitude of AB between the two countries.

Differences can be explained as follows:

- ✓ **Difference in grids of quantification of AB** (Table 1) **:** not quantifiable AB is specific to the German scale, and ASMR III to the French one ;
- ✓ **Comparators :** appropriate comparators are designated by the G-BA, and the absence of a robust comparison (mainly head to head trials) leads to a not proven AB. In France, companies can argument the choice of the comparator(s) (amongst the most prescribed, last enlisted, cheapest); TC's opinion may differ or refer to "usual treatments" ;
- ✓ **Patient segmentation :** appeared detailed in Germany (especially by the IQWiG with up to 19 drugs with patient segmentation and 6 subgroups defined for one drug), with negative appraisals in many subgroups (50% of all sub-groups with no AB by the G-BA). In France, differentiated SMR/ASMR depending upon subgroups of the market authorization population is less frequent and is more often combined with lines of treatment (7 drugs - 71% with an important versus insufficient SMR depending upon subgroups) ;
- ✓ **Endpoints :** mortality, morbidity and Quality of Life (QoL) are systematically reviewed in Germany. In France, relevant endpoints depend upon therapeutic area with no systematic review of QoL ;
- ✓ **Reassessments :** in Germany, companies could submit another dossier when the initial dossier failed for technical, or "formal" reasons (comparators, sub-populations) (found in 8/38) whereas only one reassessment following submission of new data was found in France in the course of the initial reimbursement procedure ;
- ✓ **Level of proof :** is a key parameter in qualifying an AB in Germany, whereas it is considered in France, according to doctrine[4], but not integrated explicitly in the French grid of AB level quantification. In both cases, the methodology of indirect comparisons is scrutinized and mostly not accepted for assessing an AB.

Discussion

- ✓ Consistency is observed for 19 products out of which 18 have no or minor AB, whether because of level of proof or quantity of effect.
- ✓ Differences in appraising the extent of AB have to be interpreted with caution, given the differences in scales.
- ✓ Discrepancies are more alerting for 4 products, with no ASMR in France but an AB in Germany (KOMBOGLYZE®, EDURANT®, EVIPLERA® and ZALTRAP®).
- ✓ Designation of appropriate comparators by the G-BA can be explained by the objective to determine whether a reference price is relevant. In France, the therapeutic strategy positioning is also fully integrated in comparator(s) choice.
- ✓ Impact on pricing is not investigated in this research. However, previous observations indicated that in Germany there is so far no strong correlation between AB and required discounts by the payer[5]. In France, although drugs with ASMR I to III are entitled to be granted the minimum price observed in 4 reference countries (Germany, Italy, Spain, UK), it was not yet fully achieved in 2012, and ASMR IV products prices are well below European reference ones[6].
- ✓ Further research is required, but is made difficult given the restricted access to German prices and the existence of confidential price/volume agreements in France.
- ✓ Introduction of cost-effectiveness analysis in France for products claiming ASMR I to III may challenge the impact of ASMR criteria in pricing decisions, whereas medico-economic evaluation is considered in Germany only exceptionally.

Conclusions

Introduction of the AMNOG in Germany considerably affects the Health Technology Assessment (and pricing) environment in EU and distinct German requirements have now to be considered in the clinical development plans. AB assessment over existing drugs based on international medical evidence standards is determinant in assessing value of new entities, but contextualization remains prevalent, even in those two close EU countries

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Contacts
marie.lepretre@essec.edu
daniel.droeschel@hs-riedlingen.de
chicoye@essec.fr

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