It´s difficult to meet HTA criteria according AMNOG – reason why ?

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AMNOG in Germany

A combined HTA and reimbursement process

- since January 1st 2011
- the reimbursed price of a new chemical entity (only R_x-products) has to be negotiated between the manufacturer and the national association of SHI
- based on the results of an assessment (conducted by IQWiG, AQUA Institute), decision maker G-BA
- a dossier (HTA) describing the new product in detail and ranking its therapy-relevant patients benefits against a standard appropriate comparator therapy

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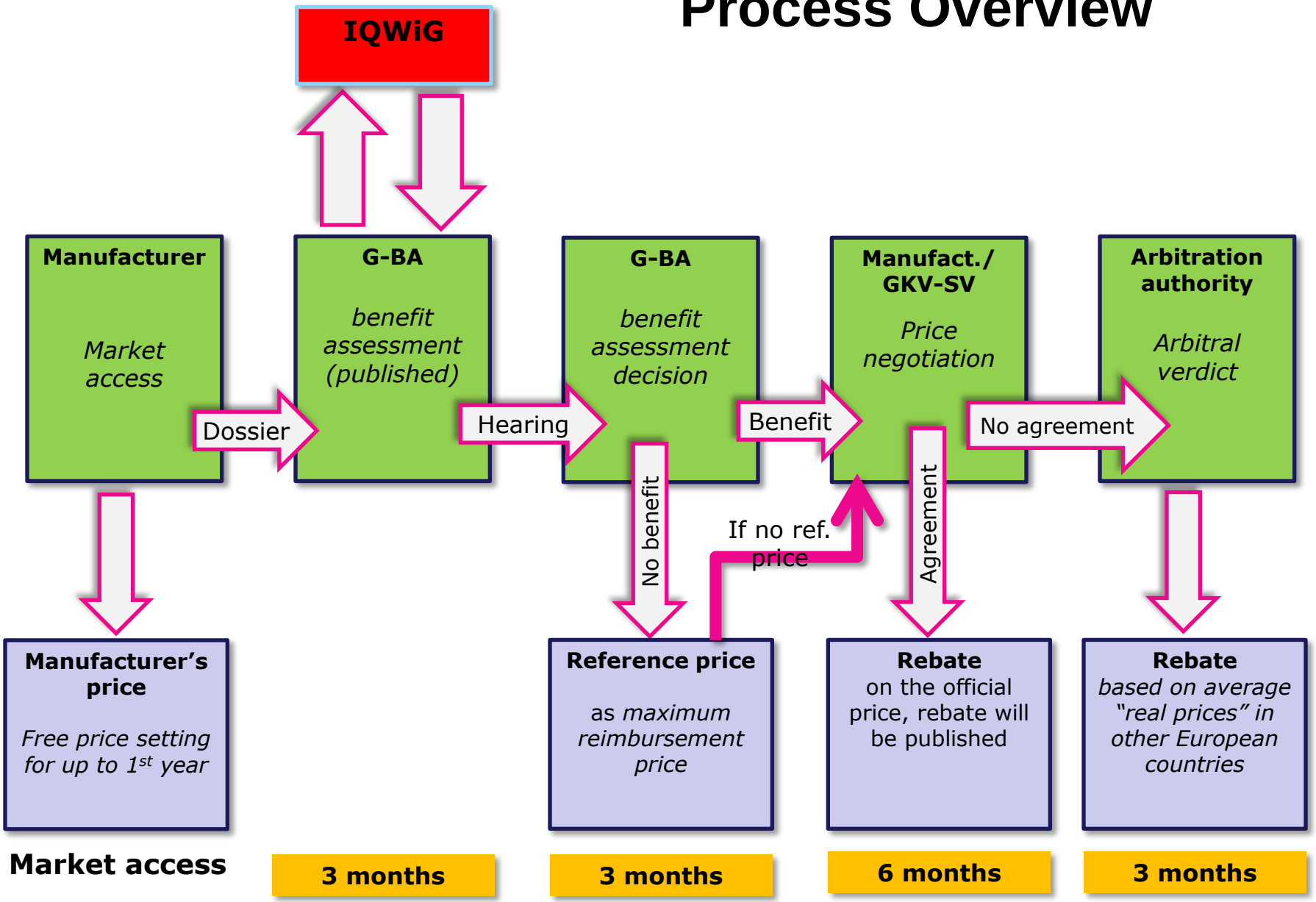
Process Overview



How to find an appropriate comparator?

- Appropriate comparator therapy (ACT) needs an approval in same indication (could also be a non-drug treatment)
- ACTs are favored when outcomes are well-proven via clinical trials and ACTs are established in daily practice
- ACT has to be line with existing guidelines and general economic considerations (ATC has to be paid by SHI)
- If several ACTs are existing, the most economically advantageous therapy has to be chosen
- **ACT is the also the price anchor later in the Process!**

Classification of benefit

1) Major (“erheblich”)

2) Significant (“beträchtlich”)

3) Minor (“gering”)

4) not quantifiable (“nicht-quantifizierbar”)

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5) No additional benefit documented

6) The benefit is lower than the use of the ACT

Certainty of results will be given as proof (“Beleg”), hint (“Hinweis”), indication (“Anhaltspunkt”) or “not proven”.

Negotiation of reimbursed price
(a scientific decision mixed up with budget impact)

- Negotiation between sick funds and pharmaceutical company are based on G-BA decision (benefit dossier)
- expected cost impact to the healthcare system is also of relevance (calculated yearly therapy costs per patient)
- each product will have a single reimbursed price, even if different subgroups have different proven benefits
- final reimbursed price will be published and will influence European reference price system
- no agreement in negotiation, -> arbitration board (average prices from 15 countries: Aus, Bel, Cze, DK, Esp, Fin, Fra, Gre, UK, Irl, Ita, NL, Por, Swe, Slo)

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More than 50% of all assessments reached no added benefit

May 2014:

79 active ingredients

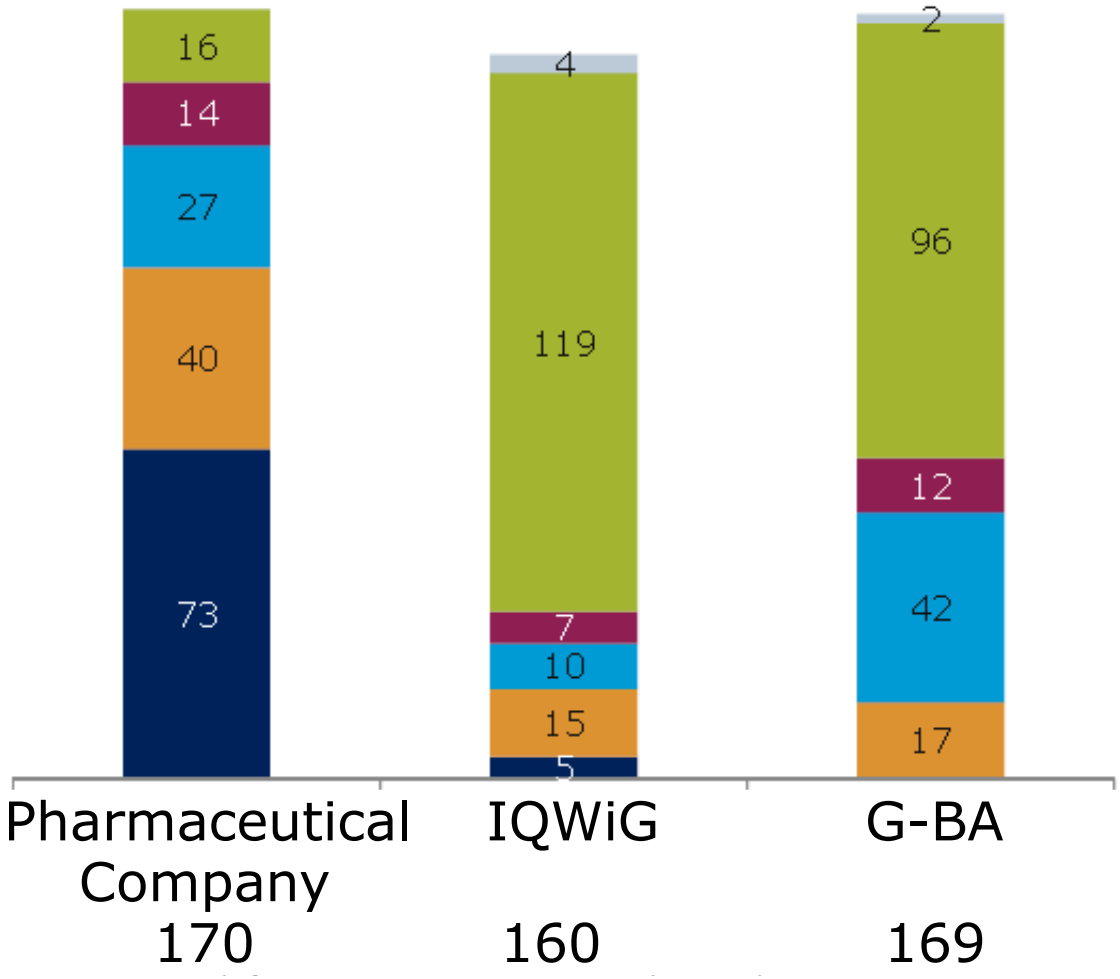
95 approved applications

169 sub populations

G-BA decisions (subgroups):

Added benefit	percent
Major	**0 %**
Significant	**10 %**
Minor	**25 %**
Not quantifiable	**7 %**
Lower as ACT	**1 %**
Not proven	**57 %**

In 73 subpopulations companies claim for major added benefit, never certified by G-BA



Reason why

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A combined HTA and reimbursement process, but not a combined HTA and approval process

- Added benefit dossier according AMNOG is an early health technology appraisal, dossier has to be submitted together with product launch
- EMA approval process and dossier preparation are in progress simultaneously
- Indication might change along the way, EMA and IQWiG requirements are not the same
- Last dossier update, three month before submission
- Approval process and reimbursement process do not match

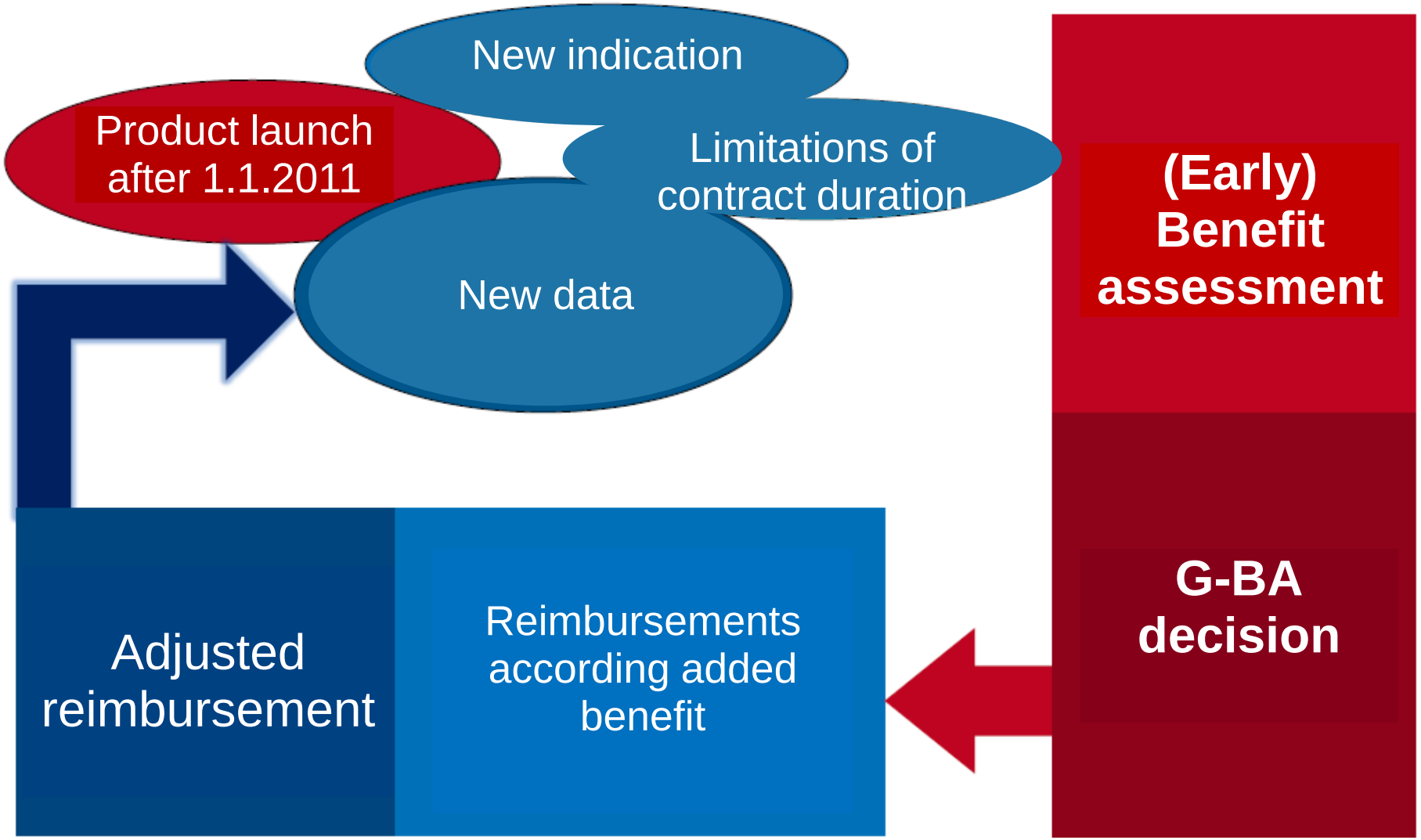
Cyclic “Deadline Problems”

AMNOG is nowadays an ongoing process, re-evaluations have to be expected

- G-BA decisions are limited in time (especially when an added benefit is certified)
- A new dossier has to submitted
- Duration of contract with sick fund is limited (in most cases only one year)

Regular added benefit update

Spitzenverband



Time limitations of decisions

Product	Company	Added benefit	Indication	Limitation
Fingolimod (Gilenya®)	Novartis	minor	Multiple sclerosis	3 years (29.03.2015)
Eribulin (Halaven®)	Eisai	minor	Breast cancer	2 years (19.04.2014)
Cannabis sativa (Sativex®)	Almirall	minor	Multiple sclerosis	3 years (21.06.2015)
Belatacept (Nulojix®)	BMS	minor	Kidney cancer	3 years (05.07.2015)
Ipilimumab (Yervoy®)	BMS	significant	Melanoma	5 years (02.08.2017)
Vemurafenib (Zelboraf®)	Roche	significant	Melanoma	1 year (06.09.2013)

Comparison G-BA / IQWiG vs. NICE

basic methodology is similar, standard of evidence based medicine, preference of RCTs

NICE: in general more open, any kind of relevant evidence is requested (even non-RCTs), more flexibility regarding the comparator, surrogate endpoints are accepted more readily, modeling is expected wherever appropriate, uncertainty is quantified through sensitivity analyses

G-BA/IQWiG: assessment based on highest evidence, measurement of hard endpoints, surrogates have to be validated, no modeling of data, appropriate comparator assigned by GBA/IQWiG, fixed result categories

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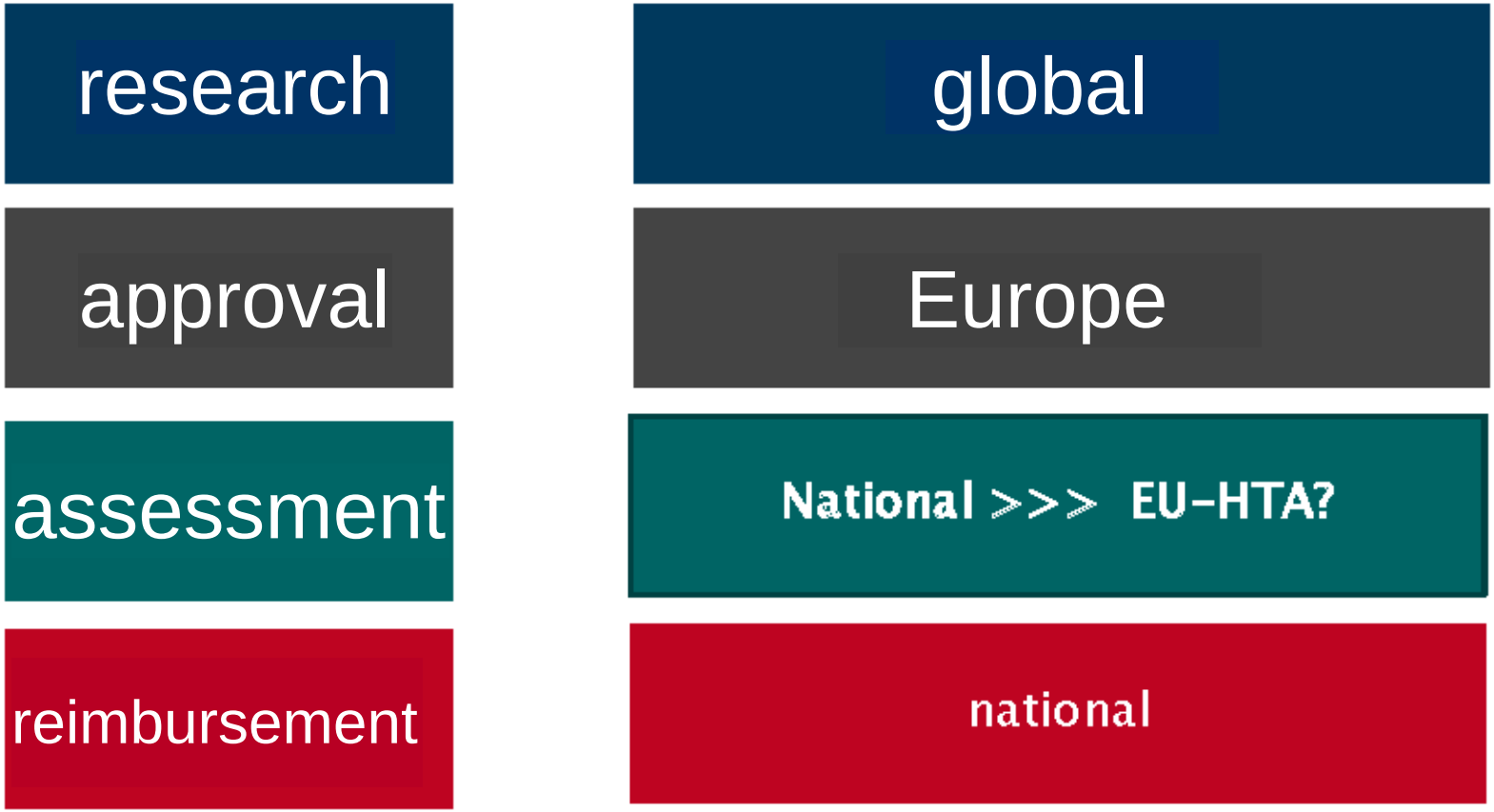
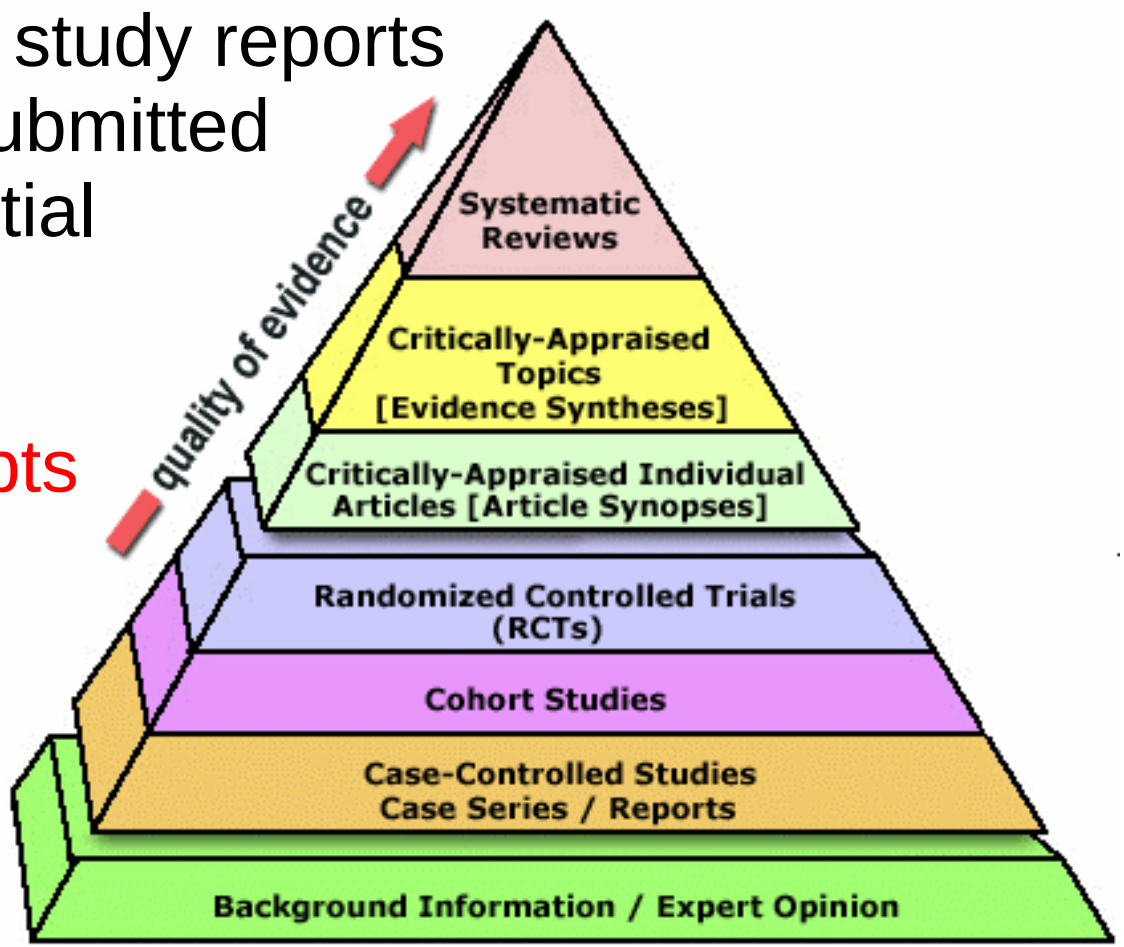
EMA requirements ≠ national reimbursements requirements

Spitzenverband



High level of evidence

- Limited number of trials, publications
- Unpublished study reports have to be submitted in a confidential chapter
- IQWiG accepts only highest evidence



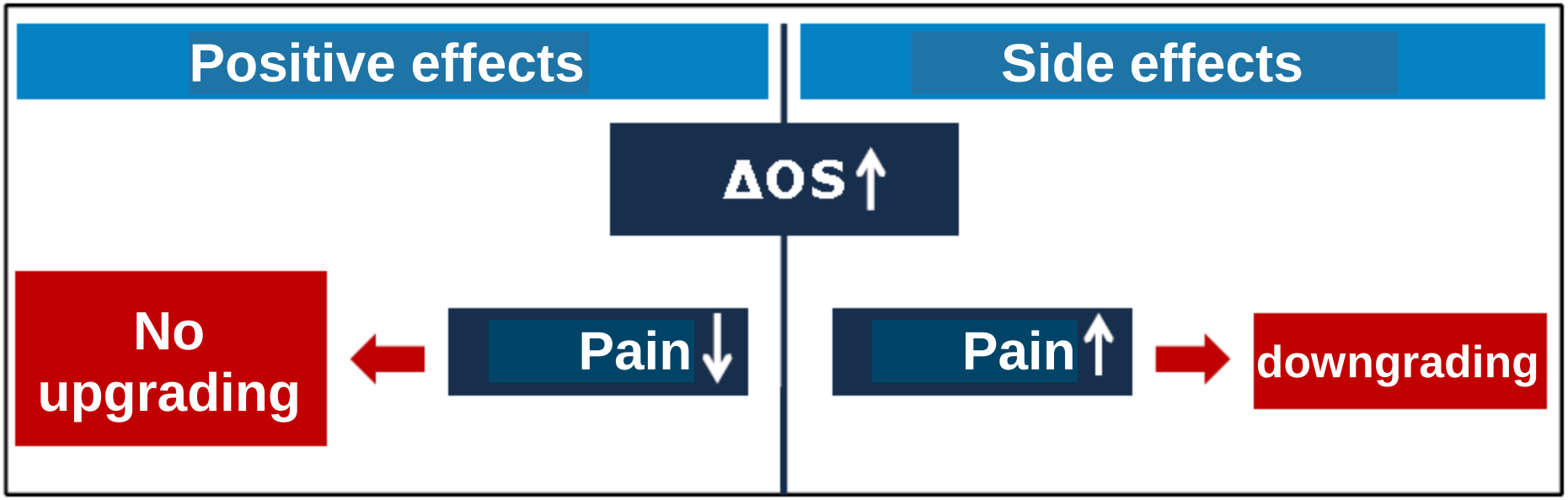
High levels of evidence
(IQWiG)

- Only head to head trials-RCTs were reflected so far
- Network meta analysis were never accepted
- Other indirect treatment comparisons were never accepted
- Only patient relevant hard endpoints were reflected so far
- Surrogates were never accepted

High levels of evidence
(IQWiG)

- Quality of life data were only accepted when measured with validated disease specific questionnaires
- Patient preferences were never reflected
- Treatment satisfaction questionnaires were never reflected
- Real life data were never reflected
- Non interventional trials were never reflected
- Register data were never reflected

Balancing



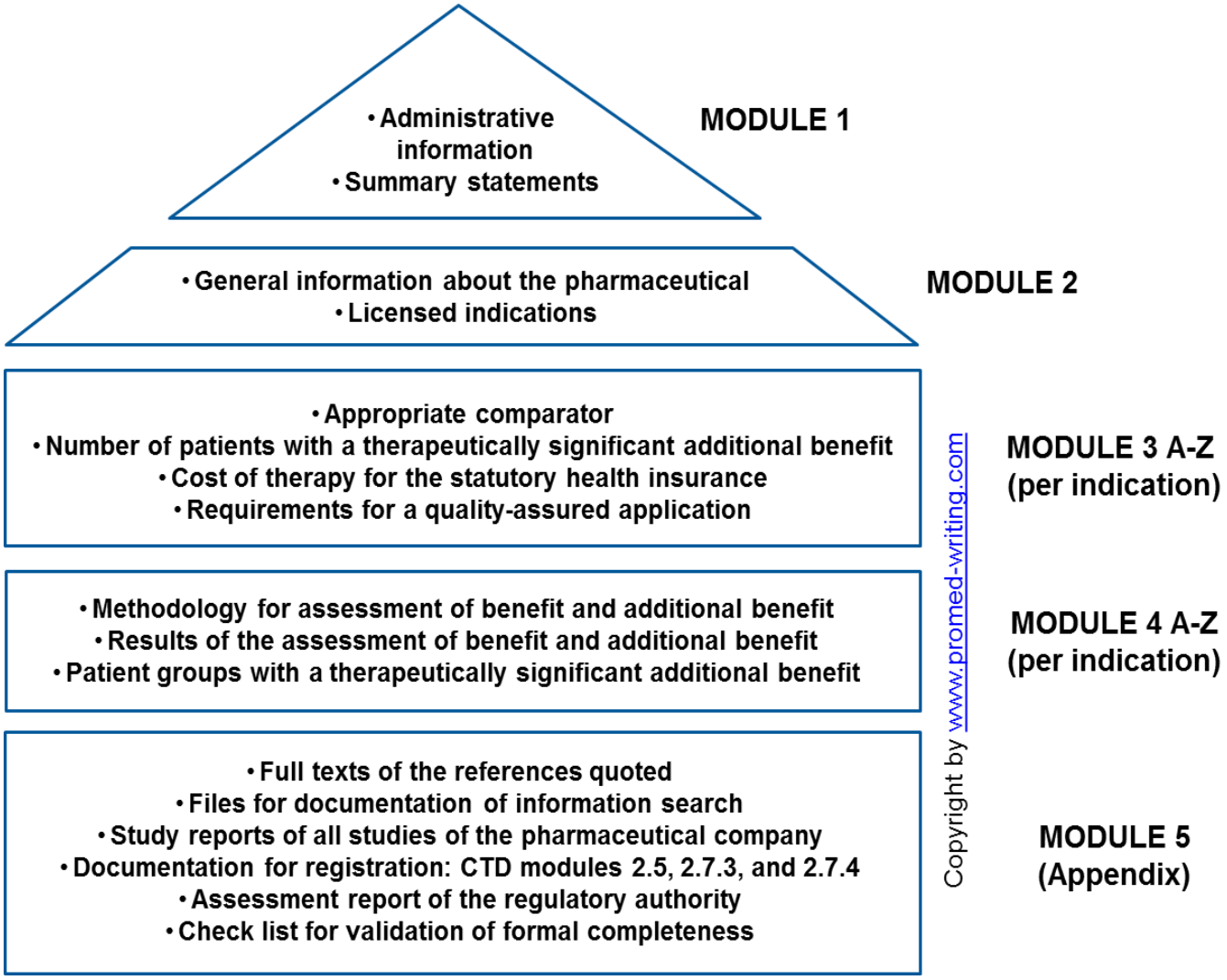
- Extreme value problem, skale limit, graduated results
- Missing appropriate comparator therapy has no side effects
- Double examination, e.g. side effects and QoL

Dossier for an early benefit assessment

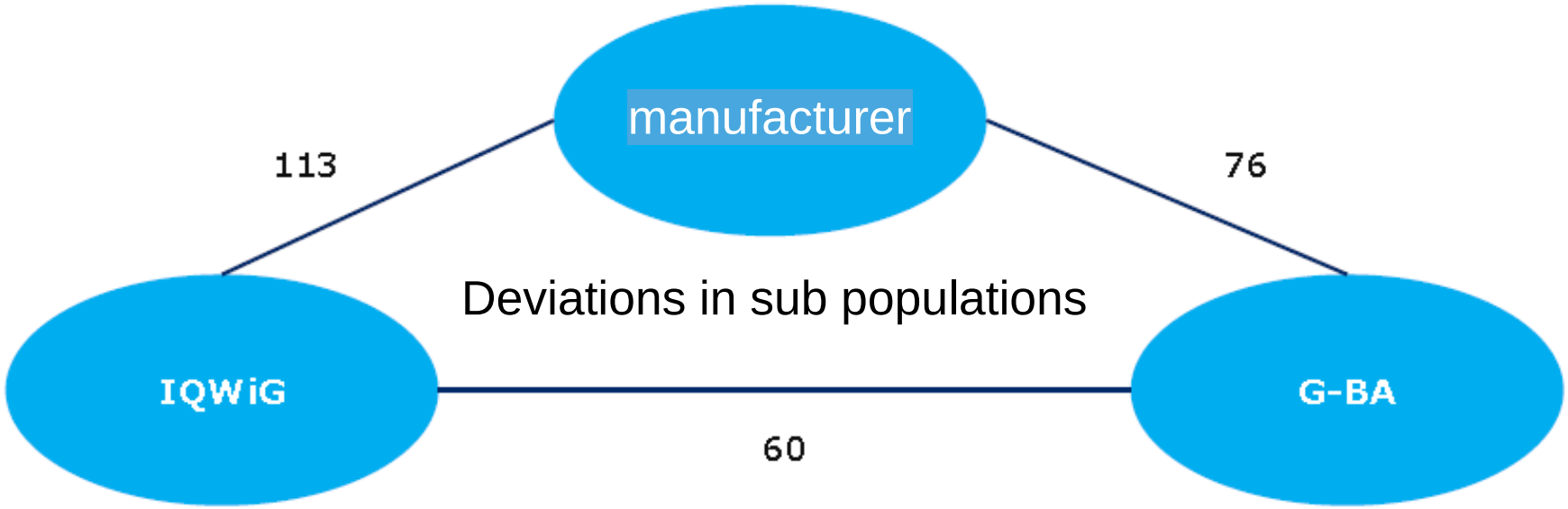
The added benefit dossier itself has to provide the following evidence:

- Authorized therapeutic indications
- Patient benefit, medical benefit
- Additional benefit in relation to appropriate comparative therapy
- Costs of therapy to statutory health insurance
- Quantification in the number of patients
- Description of the requirements for quality assured application

Structure of added benefit dossier



Sub populations



Sub populations often build up afterwards
(identify groups of patients that benefit most)

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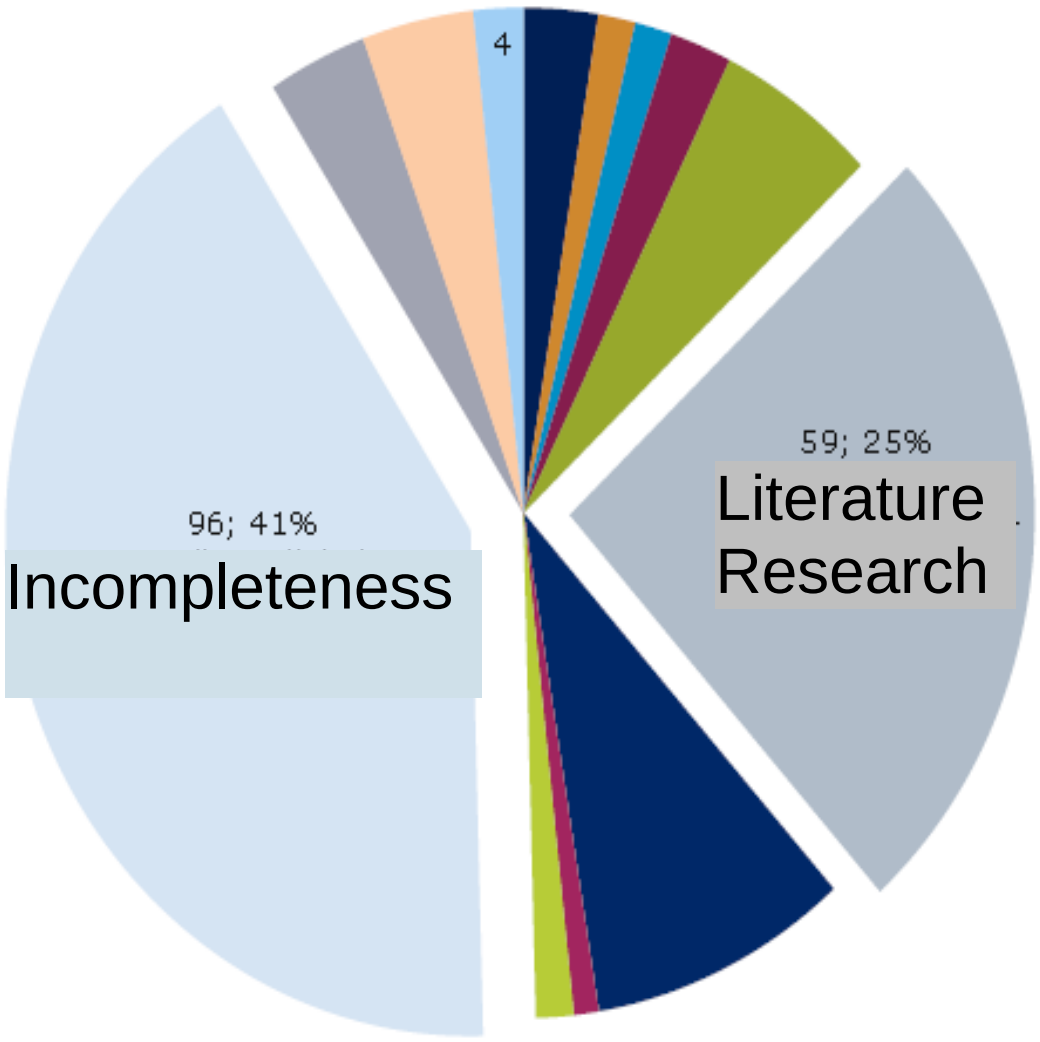
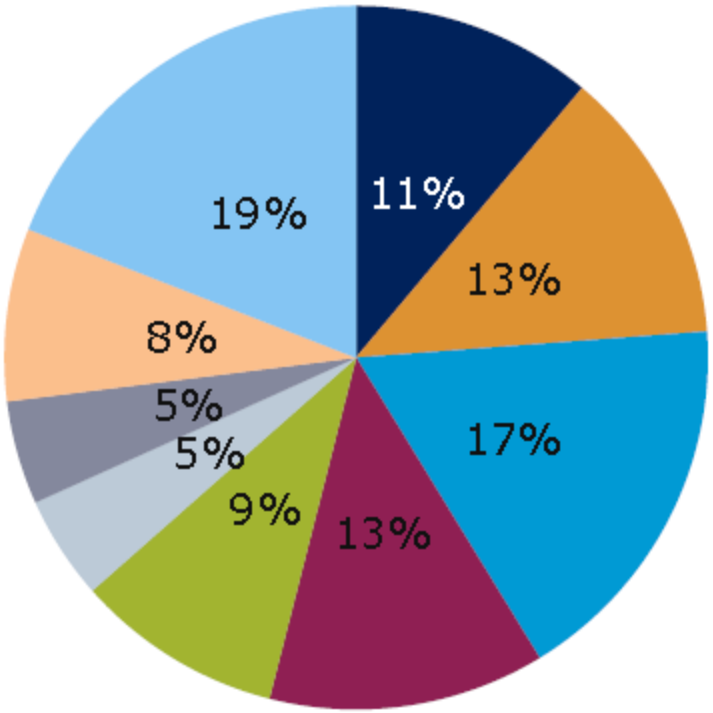
Formal mistakes in added benefit dossier

Quelle: https://www.g-ba.de/informationen/nutzenbewertung/



- Inconsistenty inclusion criteria
- Inconsistenty endpoints
- Inconsistenty wording
- Sources, inconsistent
- Sources, citation missing
- Mistakes in literature research
- literature research inconsistent
- translation
- Not submitted
- Attachments missing
- Description incomplete
- incompleteness, data sources
- incompleteness, SMPC
- incompleteness, comparator therapy

Biostatisticians should write description of methods on their own



- Mistakes in description of study population and building of subgroups
- Mistakes in description of endpoints
- unclear description of methods
- no explanation for missing data
- Bad description of target population
- Missing safety description
- No explanation for transferring results from one trial to another
- bad description of investigated therapy

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Coming next

New institute for quality assurance and transparency will be built up by G-BA

The institute will exclusively work for G-BA

The institute should develop new method how to investigate patient relevant issues

Thank you very much for your attention!

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