

**»Criteria for the evaluation of
drug innovations«**

Position paper of the

DPHG

Deutsche Pharmazeutische Gesellschaft

in collaboration with

APV

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Enormous challenges face the health care system in Germany. Medical progress and demographic developments as well as appropriate quality and economic efficiency in health care are key issues in the current debates on health policy. Savings, particularly in the field of drug supply, are to be achieved in future by forgoing those drugs that supposedly offer little or no added therapeutic benefit compared with a drug in a compound class that has been launched as an innovation. However, how is it possible to tell at launch if a new drug really offers no further therapeutic benefit?

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With this position paper on criteria for evaluating drug innovations, the Deutsche Pharmazeutische Gesellschaft (German Pharmaceutical Society) takes a close look at whether or not it is only quantum leaps in drug research that bring success, or perhaps the allegedly minor improvements, so-called incremental innovations, that ultimately lead to major success and therapeutic breakthroughs.

This position paper does not aim to favour the pharmaceutical industry or criticize current health policy. Rather, it hopes to present some of the scientific aspects that ought to be considered if the standard is to be set at the right level.

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1. Preamble

Issues relating to the assessment of the benefit of drugs - especially how and when to assess the innovative value of a new drug - have assumed considerable significance since the introduction of new provisions under the German health service modernization law (GMG) in early 2004.

The law aims to institutionalize the evaluation of drug benefits via a newly founded »Institute for Quality and Economic Efficiency within the Health Care System« (IOWiG)¹. This is designed to motivate the pharmaceutical industry to concentrate its efforts more on genuine innovations offering added therapeutic value². However, the GMG fails to define either in the wording of the law or in its justification of the law what actually classes as a »genuine innovation with added therapeutic value«.

On behalf of the Federal Joint Committee (G-BA), the new »Institute for Quality and Economic Efficiency within the Health Care System« is to assess the benefit, particularly of »every drug containing patented substances that is to be approved for the first time«³.

According to the legislation, the IOWiG itself is to stipulate »standard methods« for preparing such assessments⁴. A procedure is to be devised which should »make the evaluation criteria transparent to everyone while guaranteeing involvement by allowing for the relevant rights to co-participation and consultation.«⁵

The German Pharmaceutical Society (DPhG) is to take part in the debate on scientific issues and policies concerning the evaluation of new drugs. This position paper issued by the DPhG »Criteria for the evaluation of drug innovations« is its first contribution. It outlines a catalogue of criteria for assessing pharmaceutical innovations. Special significance is attached here to new chemical entities, although this is not always the only key criterion. It would not be justified in pharmaceutical or medical terms to restrict evaluation of a drug's innovative value - as does Social Security Code V (health insurance) (SGB V) - to the drug substance alone. The position paper therefore considers that dosage forms can also boast innovative value.

The benefit assessment which, in line with the GMG, is to be submitted for all drugs with new substances is to differentiate between⁶

1. Drugs with an improved action whose active ingredients reflect a new mode of action (Level A),
2. Drugs with an improved action whose active ingredients reflect an existing mode of action (Level B),
3. Drugs with no improved action whose active ingredient reflects a new mode of action or a mode of action already known from existing drugs (Level C).

The yardstick for assessing the benefit of a new drug should be the »best possible therapy«⁷ currently available. Neither this expression nor the formulation »genuine innovation with added therapeutic value« are legally defined terms within the framework of the GMG.

Evaluation of the benefit through the Institute for Quality and Economic Efficiency within the Health Care System has two effects:

○ The evaluation should constitute the technical basis for the drug guidelines⁸ to be approved by the Federal Joint Committee (G-BA) which stipulate if - and if so under what conditions - certain drugs or drug classes may be prescribed at the expense of the health insurance funds;

○ The evaluation constitutes the technical basis for the decisions to be taken by the G-BA as to the groups of drugs for which reference prices may be stipulated⁹. Even drugs with patented substances are to be included in reference price groups according to the provisions of the GMG. The only drugs excluded are those with patented substances reflecting an »innovative mode of action« and which also reflect a »therapeutic improvement with fewer side effects«¹⁰. A drug substance only classes as innovative for as long as the drug substance which was first

CONTENT

1. Preamble	3.3.1 Absorption
	3.3.2 Bioavailability
2. Different types of innovation: definitions, characteristics, relevance, examples	3-3-3 Biotransformation
	3-3-4 Elimination characteristics
2.1 General definitions of an innovation	3-3-5 Elimination half-life
2.2 Radical innovations	3.4 Pharmaceutical-technical criteria
2.3 Incremental innovations	3.4.1 Problematic excipients
2.4 Sham innovations	3.4.2 Solutions
	3.4.3 Modified-release dosage forms and drug targeting
3. Criteria for potential innovations	3.4.4 Administration routes
3.1 Substance criteria	3.4.5 Stability
3.1.1 Enantiomer purity	3.4.6 Robustness
3.1.2 Solubility and stability	3.4.7 Can it be easily administered?
3.1.3 Prodrug principle	3.5 Interaction criteria
3.1.4 Structure, functional groups	3.5.1 Metabolism enzymes
3.2 Pharmacodynamic criteria	3.5.2 Transport systems
3.2.1 Selectivity for target structures	3.5.3 Protein binding
3.2.2 Range of action	
3.2.3 Indications	4. Results
3.3 Pharmacokinetic criteria	

1) §35b SGBV

2) Legal justification of § 35b SGB

3) § 35b para. 1 SGB V

4.) loc. cit.

5) Legal justification of §35b para. 1 SGB V

6) Legal justification of §35b para. 1 SGB V

7) Legal justification of §35b para. 1 SGB V

8) §92 SGB V

9) §35 para. 1

10) §35a para.3 clause 4 SGBV

to be marketed in the reference price group is still under patent¹¹. As soon as this first drug substance is out of patent, other substances in the same group - even if they are still patented - may be included in a reference price group along with the initial substance and derived generics. That also applies to completely new and still patented drugs with a similar mode of action.

The question is, will these German regulations - which reflect the aim of the GMG - really do anything to help »promote the development of innovative drugs«¹² or will they - if one believes the even more ambitious claims of the GMG - even improve conditions for innovations by »creating the incentive to encourage pharmaceutical companies to concentrate their efforts increasingly on genuine innovations with added therapeutic value«. Such incentives would only be effective if it is possible to foretell when the new development is started if this will be rated at launch as »genuinely innovative« or only as a sham innovation. Patent protection of the new development would only make economic sense if the drug were classed as a »genuine innovation« as only then would there be any guarantee that the new drug does not fall immediately into the reference price category. And only then would the »manufacturer have any chance of achieving higher prices if this drug is to be reimbursable«¹⁴.

At first glance, the new legal provisions could prove to be one suitable means of stopping manufacturers from developing a new drug that from the outset offers no therapeutic improvement - a new development designed solely to secure a market share with a similar substance (»me-too product«). The impact of such a procedure would be welcome - at least at first glance. However, the procedure could also discourage those manufacturers who are planning a new development with therapeutic improvements and who are willing to invest considerable - intellectual and financial - resources to do so. This is compounded by the fact that it is only possible in exceptional cases to plan and decide at such an early stage how a new development will be classed later on since,

1) at the start of development, it is

often impossible to tell what the yardstick will be following marketing authorization. This can be explained by the fact that, on the basis of the generally available results of basic research, new drug development projects are often started at more or less the same time or with little delay. It is virtually impossible to tell which project will be completed first and what the outcome will be;

2) it is impossible to plan in advance for a development project to be classed as a radical innovation (as opposed to an incremental innovation).

Incremental innovations are no longer of much interest in light of the GMG regulations. They run the risk of not being classed as therapeutic improvements; that would mean that, in accordance with the provisions of

DPhG

the GMG, they could automatically be included on entry to the market in a reference price group which already covers generics of older drugs that are considered comparable (be this justified or not). The resulting price level does not make for attractive new developments.

Against this background, the new regulations of SGB V cannot be expected to have no impact on companies' readiness or possibilities for contributing gradually to improving the profile of therapeutic and adverse effects of a group of compounds - as was often the case in the past.

Moreover, at the time of marketing authorization or launch - other than in exceptional cases which are usually only identified in retrospect - it is no longer possible to make a sufficiently reliable assessment of the new drug. It is therefore very often difficult, indeed impossible, to class and assess the benefit of these drugs at an early stage.

It is therefore feared that in future Germany will be forced much more often than in the past to resort to improved therapies from countries abroad such as the USA or Japan where the basic conditions for the search for drug innovations are considerably more favourable.

How and when a decision is to be taken about the innovative value of a new drug limits the conditions allowing for innovation¹⁶. If a decision about the innovative value of a new drug is taken at the wrong time and/or that decision is inappropriate, this will inevitably have considerable negative repercussions for the research and development of new drugs. The position paper makes this clear with recent examples from modern drug research.

According to the authors of this position paper, the basic conditions of the GMG must be implemented in such a way that progress remains possible or, even better, that the incentive to secure further progress is increased. Deciding on the innovative value and benefit of new drugs too early obstructs the empirical processes essential to medico-pharmaceutical progress. This would theoretically be welcome if new product launches with no added therapeutic value were made financially unattractive, giving a much clearer overview of the pharmaceutical market. However, we also see a problem in that - contrary to hopes - research activities will not be redirected along innovative development paths if the added therapeutic benefit cannot be assessed reliably at the time of launch. It is often the case: the therapeutic benefit is still unclear at the time of launch for many modes of action, especially those that prevent further disease-related complications.

n) §35 para. 1 clause 4 SGB V12) legal justification of §35 para.1aSGBV

13 Legal justification of 535b SGB V

14) Legal justification of §35b para. 1aSGB V

15) Reference prices are the maximum prices for reimbursement. They may occasionally be exceeded; because the difference compared with the reference price is payable by the insured person in addition to the legally required co-payment, reference prices generally appear to be the maximum prices possible: Apart from the few exceptions to date, manufacturers saw themselves forced to reduce their prices to the reference price level. It remains to be seen if this situation will continue now that even patented drugs can be included in a reference price group in accordance with the GMG. The case of the lipid-lowering drug atorvastatin (Sortis®) could be seen as a sign that the industry is beginning to rethink its response to date which was to lower its prices to match the reference price level.

16) This formulation is a play on Kant's »Criticism of common sense«. Kant sees the philosophies of »space« and »time« as the sine qua non allowing us to gather experience.

It must be ensured that potential therapeutic improvements are not overlooked at the time of launch. This position paper outlines criteria that merit attention when assessing the innovative value of a new drug.

Innovations do not necessarily have to reflect quantum leaps in development. Rather, numerous minor innovations within a compound class can together signify a quantum leap for drug therapy.

In the case of drugs, innovations can include improvements in pharmacodynamic, pharmacokinetic, technological or toxicological terms. All these aspects should be elucidated in respect of their relevance and innovative value¹⁷.

2. Types of innovation: definitions, characteristics, relevance, examples

2.1 General definition of an innovation

The term innovation has been used in French since the 13th century and in English since the 16th century, in both cases referring nonspecifically to "something new". At first there were no qualifying connotations. In German, the term has been used since the turn of the 18th to the 19th century, at first exclusively in legal and botanical contexts¹⁸.

According to modern usage of the term innovation, the merely descriptive character of the term (in the neutral sense of something new) has been supplemented by two levels of qualification. The first level rates the (genuine) novelty value of a new development. A second level includes the (additional) usefulness as a criterion. The distinction between »genuine« innovations and »sham innovations« may refer to either of the two levels alone or to a combination of the two.

Evaluation of an innovation according to the criterion novelty value may well be foreseeable at the time of discovery. This only applies to a certain degree in the case of the (more important) evaluation of an innovation according to the criterion added benefit. It is often only possible to assess an innovation in retrospect (and often a long time after the original discovery was made). An evaluation presupposes that the innovation will be subject to much broader experience. The intrinsic value must be compared with competitive (old or even other new) solutions before an adequate (albeit never final) evaluation can be made. This also applies to innovations in the field of medicinal products.

2.2 Radical innovations

Radical innovations include drugs that have been developed from scratch and bear no relation to previously known substances and, as the first representatives of a new compound class, signify major therapeutic progress. Prominent representatives of radical innovations include, for example, cimetidine (H₂-receptor-antagonist), propranolol (β-adrenoceptor-antagonist), lovastatin (HMG-CoA-reductase inhibitor), captopril (ACE-inhibitor), omeprazole (proton pump inhibitor) and sumatriptane (5-HT_{1B/1D}-receptor agonist).

However, it is only possible to identify radical innovations reliably later, that is on the basis of widespread therapeutic evidence and day-to-day experience. This is particularly true in the case of medicinal products to avoid disease-related complications (for instance, arterial hypertension, hyperlipidaemia, diabetes mellitus), where findings are initially limited to surrogate parameters until the desired effect on mortality, morbidity and quality of life has been confirmed. Various aspects of drug safety (rare, but serious side effects) again only become apparent when the product has been used by a much larger number of people.

It is therefore rarely possible at approval to make a satisfactory scientific evaluation of a new drug or a new dosage form.

Radical innovations have the highest innovative value, but they often still show weaknesses in terms of the drug substance (for example, too little selectivity for the desired target structure, unfavourable pharmacokinetic properties, et cetera). Later drugs with the same mode of action may demonstrate improved properties of therapeutic significance

within the meaning of incremental innovations. In certain cases such incremental innovations have superseded radical innovations when, after widespread use, the latter has been found to have toxic effects, leading to the suspension or withdrawal of marketing authorization. Recent examples of radical innovations whose marketing authorization was withdrawn include tolcapone (catechol-O-methyltransferase inhibitor) and troglitazone (»insulin sensitizer«), both of which were withdrawn from the market owing to liver toxicity. Following repeat safety evaluation by the European regulatory authority EMEA, marketing authorization was re-issued for tolcapone on 7 March 2005. Had no successor products been developed in parallel through incremental innovations, for instance entacapone (catechol-O-methyltransferase inhibitor) or pioglitazone or rosiglitazone (»insulin sensitizer«), there would have been no more approved drugs in these compound classes.

17) Note: Owing to the changes to the royalties system under the GMG, pharmacies virtually no longer suffer in economic terms from delays in the launch of innovations or the fact no innovations are forthcoming at all. Unlike prior to these new regulations, revenues from generally higher-priced innovations are no higher, all things considered, than if older, lower-priced treatment regimens were used. On the contrary: Stockpiling very expensive drugs now involves a considerable risk for the pharmacy. Nonetheless, pharmacists still have a professional interest in ensuring that the incentive to develop drug innovations and achieve progress in drug therapy is maintained.

18) cf. Joachim Ritter, Karlfried Gründer (publ.), Historisches Wörterbuch der Philosophie, Volume 4; in a botanical context, innovation describes the rejuvenation of a plant organism through shoots generated at older parts of the plant. The analogy with what is described below as (incremental) innovation is obvious.

However, it remains to be seen if clinical studies with glitazone confirm the presumed improvement in the prognosis for type-2 diabetics.

Radical innovations are not the prerogative of pharmaceuticals, but also (in the case of already marketed drugs) of the dosage form. Over the last few decades, the development of innovative dosage forms has culminated in considerable advances in therapy. Examples include the first launch of metered dose inhalers, powder inhalers, transdermal therapeutic systems, oral sustained-release products or parenteral depot systems such as implants or biodegradable microparticles. As in the case of drugs, many a radical innovation in dosage form has been superseded by incremental innovations with an improved benefit-risk ratio. For instance, CFC-containing metered dose inhalers were replaced by CFC-free metered dose inhalers and powder inhalers and the early transdermal reservoir systems have now been superseded by modern, smaller, more robust matrix systems. The further development of and modifications to dosage forms and the underlying principles by means of incremental innovation can go a long way to improving both the therapeutic opportunities and drug safety.

2.3 Incremental innovations

Progress does not require huge steps to be made, but often simply continued development of previous achievements, in other words by innovations introduced step by step. Taken together, minor steps are often just as valuable as radical innovations.

Incremental innovations in terms of drug substances usually¹⁹ involve gradual optimization of known substances. Drug substances produced this way often fail to be classed as innovative or the innovative value is rated as low at the most since often only minor changes are made to the molecular structure of the original compound. However, a structural change that on paper appears to be of little significance can have a substantial impact on the pharmacological properties, thus significantly increasing the therapeutic benefit,

as is illustrated below with some examples. The improvements within a compound class in terms of therapeutic effect, side effects, treatment range or administration routes are usually achieved in the case of drugs offering the greatest therapeutic value by gradual, minor alterations. The many drugs described as the second or third generation of a compound class bear testimony to this fact. The systematic classification of

DPhG

medicinal products, based on the chemical structure, and the highlighting of certain pharmacological properties in common should on no account lead us to decry all drug substances succeeding the lead substance in a compound class as imitations or »me-too products«. The vast majority of the most prominent substances today are the result of incremental innovations.

The process by which drug substances are altered by gradual changes to their structure was modelled on nature. The following, for instance, only differ in one methyl group, yet their profile of action is considerably different:

- Noradrenaline and adrenaline
- Morphine and codeine
- Theophylline and caffeine

The following only differ in one hydroxyl group, yet their pharmacological properties are quite different:

- Dopamine and noradrenaline
- Digitoxin and digoxin

A few examples serve to demonstrate that key medicinal substances were created through gradual structural changes:

○ Adrenaline (nonselective adrenergic agonist) → isoprenaline (β -selective agonist) → terbutaline (β_2 -selective short-acting antiasthmatic) → salmeterol (antiasthmatic suitable for long-term treatment)

○ Carbutamide (oral antidiabetic agent with undesirable chemotherapeutic component) → tolbutamide (pure oral antidiabetic agent) → glibenclamide (considerably increased potency)

○ Penicillin G (can only be administered by parenteral means; narrow range of action) → Penicillin V

(can be administered orally; narrow range of action) → ampicillin (broad range of action; not readily absorbed) → amoxicillin (spectrum as for ampicillin, but more readily absorbed)

○ Cimetidine (low potency; but antiandrogenic effect in higher doses and inhibits the metabolism of other substances) → ranitidine or famotidine (greater potency, low risk of antiandrogenic effects and drug interactions)

Even β -blockers, diuretics, ACE-inhibitors, calcium channel blockers, gyrase inhibitors, cephalosporines, H_1 -antihistamines, aldosterone receptor-antagonists, et cetera are all examples of substances that have been optimized by gradual structural changes (compare Chapter 3).

Indeed, key drug substances have been created through gradual changes to natural substances: cortisone → prednisone, ergometrin → methylethergometrin, tetracycline → doxycycline, progesterone → norethisterone, estradiol → ethinylestradiol, et cetera. In fact, it was the latter incremental innovations that triggered the development of oral contraceptives.

Incremental innovations are also possible by introducing new dosage forms that improve the therapeutic possibilities. The first transdermal therapeutic systems were membrane patches in which the substance was contained in a reservoir with release controlled via a membrane.

Incremental innovations have also prolonged the duration of action, reduced the use of excipients that irritated the skin, made release more robust through the change to matrix systems, while considerably reducing the thickness and size of the patch.

Another example are the oral osmotic systems (OROS), which allow for release that is not affected by the hydrodynamic conditions of the body. The first product launched that contained indomethacin as active ingredient and potassium chloride as osmotic excipient did indeed allow for the desired release profile, but also caused deaths as a result of side

¹⁹ One exception, for instance, are substances such as zolpidem or zopiclone which differ from benzodiazepines in chemical structure, but which in principle bind to the same receptor (albeit at a different position) and reflect at the most an incremental innovation compared with benzodiazepines.

effects induced by the potassium chloride. Consequently, the product was withdrawn from the market while the OROS principle was called into question. It was some time before OROS were relaunched on the market, this time with sodium chloride as osmotic excipient. Another incremental innovation was the development of two-chamber systems (push-pull systems), in which polymers that swell readily were used instead of osmotic excipients. Two-chamber systems can also be used to administer substances that are not readily soluble.

2.4 Sham innovations

»Sham innovations« (»me-too« substances) are drug substances that address the same target structure as another marketed substance while offering no significant therapeutic novelty. Even where a substance is directed at a new target structure, it is still classed as a sham innovation in political debates if it can be assumed - in the absence of any compelling evidence to the contrary - that it offers no therapeutic improvement over known drugs. According to the working party, this view is too restrictive.

For the working party, substances based on a new mode of action are not sham innovations, but genuine innovations - in respect of the mode of action. Even if it transpires that the substance with the new mode of action offers no added benefit, it should still be classed as novel and hence as scientific progress. This would then be an innovation with no added benefit. It will, however, be difficult to decide at the time the drug is approved or launched if the new drug with the new mode of action will be more effective or not. This can only be assessed with sufficient clinical experience.

Summary of the term »innovation«

Drug substances demonstrating a new mode of action and a new chemical compound class as well as completely new dosage forms are generally accepted as (radical) innovations.

However, very often major endpoint studies have not been conducted by the time of launch so that the therapeutic value and the safety profile of radical innovations can only be evaluated reliably at a later date.

The innovative value of incremental innovations, both in terms of drug substance and dosage form, is often hard to estimate at the time of launch so that the added therapeutic value of some of these drugs only becomes apparent much later. This problem should be borne in mind when assessing the innovative value at launch.

For example, might it have been possible to suspect when AT₁-receptor-antagonists were launched that they offered no advantage over ACE-inhibitors, which were capable of inhibiting the renin-angiotensin system to the same degree, despite being based on a new mode of action? At any rate, we feel the term »sham innovation« would have certainly been inappropriate. AT₁-antagonists do in fact offer advantages in certain cases.

Against this background it seems inappropriate to class as »sham innovations« all drugs in »Level C« (»drugs with no improved effect and whose active ingredient is based on a new mode of action or is equivalent to the mode of action of a previously approved drug«)²⁰.

This classification may be debated however for every new drug whose mode of action is the same as that of a previously approved product.

A fair assessment of the innovative value demands that precisely these drugs are given a chance to prove their therapeutic value in day-to-day practice. This applies equally to both new drug substances and new dosage forms.

From a pharmaceutical point of view, particular criticism is due when only the drug substance and rarely the specific dosage form is considered when assessing an innovation in terms of its novelty value and additional usefulness.

This inadmissibly belittles the problem as it is not drug substances that are approved, prescribed and used, but finished medicinal products. The usefulness is not determined by the individual components of a substance alone, but by the medicinal product as a whole.

Until studies have confirmed in such cases that the drug has advantages (in terms of its pharmacodynamic, pharmacokinetic or technological properties), we can only speak of sham innovations (me-too).

At the same time, we find it problematic that new medicinal products that are after all still under patent should be included in a reference price group immediately after launch along with other older products with the same mode of action. Sanctions of this nature should be applied with caution. Potential pros and cons within a class of drugs with the same mode of action are often impossible to identify sufficiently reliably when the new drug is launched.

20) § 35b Legal justification of para. 1

3. Criteria for potential innovations

Various criteria can characterize an innovation. These can encompass an improvement in the properties of the substance such as the solubility or stability of the compound, or the pharmacological/toxicological profile, and last but not least a more favourable »formulation« of the drug, all of which may go towards optimizing therapy.

3.1 Substance criteria

3.1.1 Enantiomer purity

Many synthetic drugs are marketed as racemates, irrespective of the fact that enantiomers often differ greatly in their pharmacological activity or that an enantiomer has no clinically significant effect (distomer) and thus as a foreign substance puts an unnecessary strain on the body in terms of therapeutic effect.

Whether or not using an enantiomeric form makes more therapeutic sense than using a racemate depends on the specific substance; there is no one general answer to this question.

A lower dose is not an advantage in itself. The main criterion for assessing a medicinal product is the benefit-risk ratio. The amount of substance administered is unimportant provided the dose does not affect the benefit-risk ratio. Consequently, if omitting an enantiomer which, compared with the racemate, is ineffective does not improve the benefit-risk ratio, but merely halves the daily intake of foreign substance, this cannot be classed as improved action.

Dexibuprofen is the S(+)-enantiomer of the racemic ibuprofen and, like the latter, is used for the symptomatic treatment of pain and inflammation. The mode of action is based on non-selective inhibition of cyclooxygenase, whereby dexibuprofen is the enantiomer with the more potent pharmacological effect (eutomer). However, we know that the R-enantiomer of ibuprofen is converted enzymatically to the S-form, while the S-form is not subject to racemization. As a result, the use of the enantiomeric pure dexibuprofen has no therapeutic advantages compared with the racemic ibuprofen.

Esomeprazole, the S-enantiomer of the racemic omeprazole, by blocking the H^+/K^+ -ATPase, suppresses the secretion of hydrochloric acid in the stomach. Like all other proton pump inhibitors, omeprazole is a prodrug that is transformed to the active achiral form where the parietal cells of the stomach present a highly acid environment. R- and S-forms differ in their pharmacokinetics: esomeprazole has the higher bioavailability, due primarily to the fact that it is metabolized mainly by the slower isoenzyme CYP_{3A4}, while the R-enantiomer is metabolized almost exclusively by the much faster CYP_{2C19}. This would basically suggest giving preference to esomeprazole. In terms of clinical efficacy, the differences between the racemate and esomeprazole are not very convincing.

Levocetirizine is the active R-enantiomer of the racemic cetirizine. It is indicated in allergic diseases such as seasonal and perennial rhinitis and chronic urticaria. It takes effect by blocking the histamine H₁ receptors. As the R-enantiomer has double the affinity for binding to the human receptors compared with the racemate, it is almost solely responsible for the antihistaminergic effect. A single dose of levocetirizine is 5 mg, that of the racemate 10 mg.

3.1.2 Solubility and stability

By altering the chemical structure, we can change the physico-chemical properties of medicinal substances, such as solubility in water and lipophilic properties. This can ultimately mean that a substance hitherto only possible to administer by parenteral means can now be given orally, and vice versa. One example of a substance that was later available for peroral administration is the 5-fluorouracil-derivative capecitabine.

An example of improved solubility in water is the insulin analogue insulin glargine. Structural changes to the insulin molecule led to a change in the isoelectric point - with the result that it can be administered subcutaneously as a clear solution free from the problems of handling a suspension that precipitates.

Proteins tend to be unstable given the enzymatically catalyzed proteolytic metabolism.

Combining a protein with polyethylene glycol (PEG) molecules, so-called pegylation, allows for considerably longer half-lives. Examples include the peginterferons, pegfilgastrim or pegasparaginase.

3.1.3 Prodrug principle

Prodrugs are substances that in themselves are biologically more or less inactive and which are only converted to an active form in the body by enzymatic or non-enzymatic means. The prodrug principle can be applied in many ways in an effort to improve the pharmacokinetic, pharmacodynamic or toxicological properties of a drug substance.

One typical example of an improvement in absorption is the antiviral agent valganciclovir. A valin-ester of ganciclovir was developed, improving the bioavailability after oral administration from 6 percent to 60 percent, in turn allowing a reduction in the dose required to achieve a therapeutically effective level of ganciclovir in the plasma. This amino acid ester - unlike the parent substance - is apparently absorbed by a transport system for di- and tripeptides.

3.1.4 Structure, functional groups

New drug substances whose basic structure is similar to that of a known compound class yet whose structure differs through the introduction of new functional groups are often described generally as analogues or as me-too products and are thus increasingly the target of criticism. This is justified if the chemical modification does nothing to improve the therapeutic benefit.

Basically, however, systematic further development of known lead structures and modes of action can lead to an improvement in the pharmacokinetic, pharmacodynamic and toxicological properties. Point 2.3 (Incremental innovations) lists numerous examples. Another example of a specific change to a known compound class is the development of glucocorticoids.

By introducing a double bond in the steroid structure and by means of halogenation on the one hand and methylation or hydroxylation on the other, the antiinflammatory effect was potentiated while the mineralocorticoid effect was eliminated.

The selective aldosterone receptor antagonist eplerenone was created by making a minor change to the spironolactone molecule. Findings to date show that eplerenone has fewer side effects than spironolactone thanks to the improved selectivity profile.

Even the development of gyrase inhibitors is an example of how specific molecular changes to substances with a limited range of action, low potency and unfavourable pharmacokinetics, produced highly effective antibiotics with a broad range of action that are effective against atypical pathogens and problematic microorganisms while penetrating the tissue more effectively.

3.2 Pharmacodynamic criteria

3.2.1 Selectivity for target structures

Good medicinal substances are generally expected to show highly selective binding to the relevant target structures for the treatment in question (receptor, enzyme, transport protein, et cetera). As a rule, this guarantees that the substance will be highly effective and well tolerated.

The basis for selectivity²¹ is typically higher affinity for the desired target structure compared with affinity for other target structures via which adverse reactions may be triggered.

When the first representative of a new mode of action (in the sense of a radical innovation) is introduced, selectivity is usually less than optimal (for example, propranolol as a nonselective β -adrenoceptor-antagonist). Structural changes often allow for considerable optimization potential in terms of selectivity, this is the basis for incremental innovations in respect of the chemical structure of a compound class (for example, β_1 -selective β -blockers such as metoprolol, bisoprolol).

Apparently an appreciable reduction in dose can increase the affinity for a target structure. However, it is not the dose that is crucial when assessing the added

therapeutic value, but the extension of the therapeutic range or improvement in the benefit-risk ratio. Appropriately designed clinical studies are essential to show that an increase in selectivity which has been demonstrated in pharmacological test systems will also lead to a significant clinical improvement. The case of selective COX-2 inhibitors recently demonstrated the need to test the theoretical pros and cons of increased selectivity in appropriately designed clinical studies.

It must be borne in mind that increased selectivity for a target structure is not automatically tantamount to therapeutic progress. For instance, neuroleptic drugs (for example clozapine), which show affinity for several neurotransmitter receptors, are valuable tools in the treatment of schizophrenia. If we look at antidepressants, despite the launch of selective reuptake inhibitors, which undoubtedly reflect therapeutic progress, the old nonselective tricyclic antidepressants are still of considerable therapeutic value in certain indications (eg elevated risk of suicide).

A benefit-risk analysis is only possible in the specific indication and after an appropriate period of use. Given the obvious heterogeneity of the patients in question, new substances only mean considerable progress for some of the population; for other patients, on the other hand, new substances may barely represent any progress at all, in some cases they may even prove hazardous. As a result, it would seem appropriate to avoid rating innovations generally for the respective treatment itself, but for the particular patient groups for whom this treatment is designed.

3.2.2 Range of action

The benefit of extending the spectrum of action of antimicrobial therapeutic agents is illustrated by the example of the fluoroquinolones. While the second-generation fluoroquinolones, such as norfloxacin, develop their antibiotic potency chiefly in the presence of gram-negative bacteria, fluoroquinolones of the most recent generation, such as levofloxacin or moxifloxacin, are effective against both gram-negative and gram-positive, but also against atypical pathogens and anaerobes.

3.2.3 Indications

If two drug substances differ in chemical structure, the indication declared following the appropriate clinical studies can usually be attributed easily to the different pharmacological properties of the two substances.

There are numerous examples of changes to indications following changes to the molecule, eg the development of diuretics and oral antidiabetic agents based on sulfonamides, the development of the first antibiotics through broad spectrum antimicrobials and many more.

Approval of a drug can even be extended for a product that, although it contains the same substance as a comparative product, does offer evidence to support an extension to the indication as demonstrated by additional clinical studies. Such evidence should be considered progress since there is evidence to support broader therapeutic application of an »old« substance.

Acetylsalicylic acid, for instance, was originally only used as an analgesic/antiinflammatory. Only later was its significance as a platelet aggregation inhibitor recognized and confirmed in large-scale studies. This must undoubtedly be classed as a significant innovation although it »only« involves an additional finding, but one which is of enormous benefit to many patients.

3.3 Pharmacokinetic criteria

3.3.1 Absorption

If a substance that is not administered directly into the bloodstream is to take systemic effect, it is essential that it is absorbed by the body. Absorption is not desirable where the medicinal product is not intended to have a systemic effect, but is designed rather for topical use where it should take effect near the site of administration. These different goals must be taken into consideration when assessing the absorption properties.

21) Contrary to normal usage, the term selectivity is not used in pharmacology in the sense of exclusiveness, but in the sense of the preferred binding of a substance to a certain target structure as opposed to other possible target structures.

One important criterion for assessment where a systemic effect is desired after oral administration is whether absorption of the substance shows interindividual or intraindividual variations. In order to achieve easily controlled therapeutic effects, the absorption properties should be as good as and show as little variation as possible.

Specific examples:

O Less than 2 percent of acarboxis, which takes effect locally on the luminal side of the enterocytes, is absorbed. The development of a more readily absorbed analogue would be no advantage.

O Only around 20 percent of the systemic diuretic chlorothiazide is absorbed, while hydrochlorothiazide is absorbed 100 percent.

O The absorption rate of furosemide shows marked interindividual and intraindividual variations of between 20 and 70 percent; on the other hand, absorption of the structurally very similar torasemide is relatively stable at about 80 percent.

3.3.2 Bioavailability

The bioavailability of a substance is also important in determining its efficacy. High bioavailability is often, but not always, seen as positive. Restricting the bioavailability can be of therapeutic value, for instance where systemic effects are not desired. This in turn applies to »topical agents«, for example certain laxatives that are designed to take effect in the intestine only, or inhaled glucocorticoids which, administered locally, should only take effect in the bronchial tree.

On the other hand, in other cases where a systemic effect is desired, bioavailability should be as high as possible as this could allow the dose to be reduced compared with a substance with lower bioavailability. What is important is that bioavailability does not always correlate with the absorption properties. That is the case with substances with marked presystemic elimination (»first-pass effect«) which explains why these two parameters should be assessed separately. For instance, absorption of the β -blocker penbutolol is > 90 percent and the substance is almost completely bioavailable, while carvedilol shows

absorption of 90 percent but only 30 percent bioavailability due to a marked first-pass effect.

3.3.3 Biotransformation

Lipophilic substances can generally only leave the body once they have been biotransformed and thus rendered sufficiently hydrophilic. On the other hand, oxidative transformation steps in particular may involve a risk of allergenicity, mutagenicity and carcinogenicity. Consequently, changes in the metabolic pathways (possibly essential

DPhG

for elimination) can have both a positive and a negative impact.

The differences in the biotransformation of benzodiazepines, for example, are of therapeutic significance. Substances (such as diazepam) that first have to be prepared in phase I biotransformation (hydroxylation) for the coupling reaction that takes place prior to elimination (phase II biotransformation, for example glucuronidization) call for particular caution, especially in the elderly. While advancing age does not affect phase II biotransformation of benzodiazepines, phase I biotransformation decreases with age. Benzodiazepines, which only have to be coupled prior to elimination (phase II biotransformation), present a small risk of accumulation in elderly patients. Similar reservations apply in the case of beta-blockers. Atenolol, for example, does not require oxidative biotransformation for elimination, while metoprolol usually tends to be oxidatively metabolized.

3.3.4 Elimination characteristics

Liver and kidney diseases can have a crucial impact on the elimination of drugs. For instance, if the dose of a drug that is eliminated primarily via the kidney is not adjusted in the presence of renal insufficiency, this can have toxic effects, especially in the case of substances with a narrow safety margin. Countless cases of intoxication were observed, for example, when the cardiac glycoside digoxin was administered to patients with kidney disease.

On the other hand, there is no fear of side effects of this nature with digitoxin, which is eliminated both via the gall bladder and the kidneys.

Vice versa, substances eliminated hepatically would not be used, or if so under strict conditions, in the presence of liver disease. Adjustments can be made in one or the other direction by modifying the lipophilic / hydrophilic properties of the compounds.

3.3.5 Elimination half-life

Particularly in the case of long-term therapy, once-daily administration is desirable in the interests of compliance. In terms of the drug, however, this is only possible if it has the appropriate elimination half-life. On the other hand, a long duration of action can prove to be a disadvantage in view of the resulting risk of accumulation and the limited ability to control the plasma level. While a long half-life is desirable in the case of antihypertensives, substances with rapid elimination kinetics are essential in surgery and intensive medicine (eg the rapidly hydrolysable β -blocker esmolol).

3.4 Pharmaceutical-technological criteria

3.4.1 Problematic excipients

Omitting problematic excipients can improve the tolerability of medicinal products. One relevant example is the possibility of omitting preservatives by using innovative administration systems and packaging materials such as the COMOD system or by using unit dose vials. Important examples include nose drops, eye drops or solutions for nebulizers.

Another example is the use of mixed micelles instead of co-solvents (eg in the case of diazepam) or the use of nanoparticles in the case of injectable products in order to guarantee the solubility of the substances. Omitting problematic excipients is particularly important in the case of drugs for children.

For environmental reasons CFCs, which deplete the ozone layer, were replaced in metered dose inhalers by propellants with less toxic impact on the environment. In some cases, eg for beclomethasone dipropionate, it was possible to double the amount

deposited in the lungs compared with conventional metered dose inhalers as the substance is dissolved rather than being suspended.

3.4.2 Solutions

Using solutions instead of suspensions for drug substances that do not dissolve easily has a number of advantages. The solution is physically stable, the substance can be absorbed directly by the body, and there are no particles that can cause irritation, for example when administered to the eyes.

Many modern drugs are so difficult to dissolve in water that the efficacy of the drug is impaired. Certain applications have only become possible at all thanks to dosage forms that guarantee that the substance is dissolved rapidly and sufficiently well.

3.4.3 Modified release dosage forms and drug targeting

Modifying release is intended to have a positive effect on the pharmacokinetics of a medicinal substance. This can allow additional therapeutic goals to be achieved compared with dosage forms where release has not been modified.

For example, 5-aminosalicylic acid (mesalazine) can only be used in chronic inflammatory intestinal diseases if it is administered by means of a sustained-release dosage form. Mesalazine must act on the mucosa from the luminal side, yet it only reaches the deep recesses of the intestine if absorption in the upper parts of the intestine is prevented.

Parenteral depot forms such as implants (eg goserelin) or microparticles (eg leuprorelin) can allow for steady release of a substance over weeks, months or even years. Tiresome dosage regimens are avoided through the prolonged intervals between doses. One of many examples is contraception through hormones, particularly in regions of the Third World where compliance is an enormous problem. Another means of modifying release is pulsatile release. In some treatments the therapeutic effect can only be achieved by fluctuations in the plasma level. While continuous infusion of gonadotrophin

leads to unwanted sterility, physiological pulsatile secretion of gonadotrophin is essential from a therapeutic point of view. Parenteral pump systems make this possible. The same substance can produce opposing effects, depending on how gradually the substance is released.

Drug targeting means approaches to transporting drug substances specifically to and accumulating these at the site of action. This can reduce the rate of adverse drug reactions considerably, especially in the case of highly potent substances such as cytostatics. This can prolong the therapeutic cycle, increase the success of treatment and improve the tolerability of drugs. For instance, the use of modified liposomes is one means of improving treatment with amphotericin or doxorubicin.

3.4.4 Administration routes

Use of drugs that cannot be administered orally (eg as they cannot be absorbed, high presystemic elimination or deglutition disorders) by injection or infusion is generally associated with pain at the site of administration. Some of these substances can only be administered in hospital. Alternative administration routes allow for pain-free administration and/or use at home. Pain-free administration is especially important in the case of children and the chronically sick. Options include sublingual or buccal, nasal and transdermal administration of drugs.

Another alternative to parenteral administration is inhalation which could be very useful, especially for systemic administration of insulin for which the registration application is running at present: the insulin is inhaled as a powder rather than being injected subcutaneously.

Drugs for local treatment often achieve the same effect as systemic therapy with markedly lower doses. If glucocorticoids are inhaled using an aerosol, the dose can be reduced to less than 10 percent of the oral dose. Local treatment considerably reduces the systemic side effects. This is highly significant in the case of long-term treatment, eg asthma.

3.4.5 Stability

Drugs with improved stability allow for easier handling and increased drug safety. Drug safety is increased where products do not require storage under special conditions or a cooling chain (eg desmopressin). The costs of out-of-date drugs can also be lowered by increasing the stability. If the stability of a liquid dosage form is improved, this can often ease otherwise very complicated handling of a drug. For example, this helps prevent mistakes in dosage or possible contamination during the production of solutions or suspensions from freeze-dried powders, thus increasing the safety of the drug.

3.4.6 Robustness

Modifying a dosage form can also produce greater resistance to physiological influences, which in turn can lead to more constant release of the drug.

For instance, replacing an erosion matrix with an oral osmotic system (OROS) while retaining more or less the same in-vitro release profiles leads to steadier release of the drug in vivo. While the erosion of the matrix system depends on the hydrodynamics in the gastrointestinal tract, this is not the case with OROS.

Another example might be coated dosage forms. If a crack develops in a coated controlled-release tablet, the release principle fails, causing sudden, uncontrolled release of the substance. A more robust formulation is a multiparticular dosage form, with which the dose of substance is distributed over several hundred pellets each with its own functional polymer coating. Even if individual pellets develop cracks, most of the dose is released as desired.

The resistance of release of peroral dosage forms to the effect of food is also of key significance. The type and amount of food can cause dramatic differences in release, particularly with controlled-release dosage forms.

Robust dosage forms can have innovative value compared with conventional forms.

3.4.7 Ease of administration

Numerous measures of varying importance have been grouped under the umbrella of easier drug administration. Some of these have revolutionized therapy and have become an integral part of our arsenal of drugs. Administration can be made simpler with appropriate dosage forms and devices, in turn making treatment more reliable. Compliance is improved and the number of errors made in therapy reduced. None of these products actually allows for a therapeutic effect that would not be possible with other simpler formulations and yet they all contribute to the success of treatment in day-to-day practice, some to a considerable, others to a lesser extent.

For example, insulin pens which have largely superseded the conventional insulin syringe. Turning to powder inhalers, there are now multi-dose devices that are simple to use, such as the Discus, Turbohaler, Novolizer or the Maghaleer in addition to capsule systems. As regards the parenteral dosage forms, two-chamber syringes are now on the market instead of vials and syringes (eg for leuprorelin). This makes preparation of the ready-to-use dosage form much easier, again increasing the safety of the drug.

Ease of administration is very important when administering solid forms to children. In the case of small children, one positive option are drugs that do not have to be swallowed but that can be given by nasogastric tube. A drug is easier to swallow if many tiny particles can be administered instead of a large tablet or capsule. Drugs are also easier to swallow if they can be given in the form of orodispersible tablets.

Dosage forms that, in terms of the respective site of administration, allow for longer intervals between doses can improve compliance. These include oral sustained-release forms including once-daily products, so-called uno-

products, parenteral depot forms, transdermal patches, vaginal rings, coils or eye inserts.

An important criterion for acceptance of a drug, especially in children, is the organoleptic quality in terms of taste, smell and texture. Measures taken to mask the taste increase compliance and improve the quality of life for patients, especially in the case of long-term therapy.

Many drugs have to be dosed individually and flexibly. That is of particular importance where drugs are to be used for children of different ages. Multiparticular solid forms with the appropriate metering aids or, to a certain degree, scored tablets make administration easier.

3.5 Interaction criteria

3.5.1 Metabolism enzymes

The hallmark of most interactions is that two substances interact via the same cytochrome systems - either inhibiting or stimulating each other. It is therefore an advantage if new substances are not metabolized via cytochrome P450.

Of the cytochrome P450 enzymes that are involved in drug metabolism, isoenzymes CYP_{1A2/2C9/2C19/2D6} and CYP_{3A4} are particularly important. CYP_{3A4} is also expressed in enterocytes and is partly responsible for the marked first-pass effect of many drugs (cyclosporin, midazolam, saquinavir, simvastatin). Serious drug interactions occur when the metabolism of medicinal substances with a narrow range of action that is catalyzed by cytochrome P450 enzymes is affected by induction (St. John's wort, rifampicin) or inhibition (grapefruit juice, ketoconazole).

For example, orally administered azole-antimycotics (ketoconazole, itraconazole) potentiate the arrhythmogenic side effects of terfenadine (this has been withdrawn from the market as a result) because they inhibit metabolism of the antiallergic agent that is catalyzed by CYP_{3A4}. St. John's wort induces

CYP_{3A4} and lowers the plasma level of CYP_{3A4} substrates, such as cyclosporin or midazolam.

3.5.2 Transport systems

An efflux transporter that has an extremely marked effect on the bioavailability of drugs is the P-glycoprotein (P-gp), a transmembrane 170-kDa protein that belongs to the family of ABC-(ATP binding cassette) transporters. P-gp is expressed in the apical membranes of the epithelium of the small intestine, the proximal renal tubules and the blood-brain barrier and is responsible for both limited bioavailability of oral drugs and for rapid biliary and renal elimination of these substances.

In this way, the low oral bioavailability of paclitaxel is explained chiefly by the expression of P-gp in the endothelial cells of the duodenum. P-gp-substrates include digoxin and indinavir, the beta-blocker talinolol and the cytostatic agents paclitaxel and vinblastine. The bioavailability of the P-gp-substrate digoxin is increased dramatically by concomitant administration of the potent P-gp-inhibitor quinidine, with the result that inhibiting P-gp can induce drug interactions. Interestingly, the expression of both CYP_{3A4} and P-gp is controlled by the pregnane X receptor (PXR). This explains why the bioavailability of P-gp-substrates is lowered by St. John's wort extracts and other PXR-agonists. In this light, development of substances without a P-gp substrate would be classed as innovative.

3.5.3 Protein binding

Another pharmacokinetic parameter that is responsible for inducing interactions - because it can be controlled - is plasma protein binding. In their plasma transport form, drugs are generally bound to albumin. There can be various levels of binding. Although it is only the free substance that has a pharmacodynamic effect at the site of action, protein binding is only of clinical significance for distribution and effect if the drugs show pronounced protein binding (eg phenprocoumon).

4. Results

This position paper shows:

O The question of whether or not a new drug can be classified as more or less innovative cannot be answered solely on the basis of the innovative value of the structure of the drug, the resulting pharmacodynamic and pharmacokinetic properties or the innovative value of the dosage form. The key issue is whether or not the new drug brings about an improvement in the pharmacotherapeutic possibilities and the extent to which this is beneficial. However, it is both difficult and problematic to try to establish at an early stage if a new drug should be considered innovative or merely analogous (»sham innovation«) in view of patients' long-term welfare, especially if this triggers sanctions or rewards - as in the case of benefit assessment under the German health service modernization law (GMG). Classifications that were scientifically justified at the time the decision was taken may prove inappropriate at a later date. This is true, for instance, when a representative of a new mode of action has to be withdrawn from the market because of previously undetected risks with the result that a former analogue becomes the representative of that mode of action. Imposing sanctions can cause potential incremental innovations to remain undetected because the manufacturer does not want to run the risk of developing further representatives of the mode of action in view of the risk of merely being classified as an analogue. The time and nature of the decision as to the innovative value of drugs thus have a lasting impact on the conditions conducive to innovations. Making a decision too early, irrespective of what that decision is, can be dangerous. Both a false positive and a false negative classification can impede or complicate continued progress in drug therapy. In the event of a false negative classification (in the sense of a »sham innovation«) there is a risk that the manufacturer no longer has sufficient resources to continue research of a drug that is potentially of superior therapeutic value. Many a »pseudoinnovation« would not have reached the market under the conditions of the German health service modernization law while

likewise, several undoubtedly beneficial drugs would not be available, important therapeutic groups would have never become established, and we would have known nothing about the many therapeutically significant sub-groups of other products.

O A glance at the history of science - especially drug history - shows that incremental innovations should not be underestimated. Scientific progress does not always imply scientific revolutions, in other words a radical

DPhG

change in paradigms, but in phases of »normal science«, that is the gradual and continued development of knowledge²². This can also be applied to drug research. Biased rewards for radical innovations (eg exemption from reimbursement restrictions) hinders progress. Many key projects in drug research would have never been started if the prospects for reimbursement had depended on the project producing a radical innovation.

O Finally, there is no alternative: the conditions for a critical and rational debate about new drug developments must be improved continually and permanently. It is essential that at the latest when a drug is launched on the market all relevant research results are made public in an effort to allow the experts to make a justified judgment about the benefits and risks, the pros and cons at that time. This judgment should not be considered final simply because marketing authorization has been granted. It may be years after launch before the therapeutic value of an innovation can be assessed reliably.

O Novelty value must not be understood automatically as superiority. Experts and patients should know and their attention drawn to the fact that at a statistical level alone the risk of discovering serious side effects is greater with new product launches than with »old established« drugs.

The new »Institute for Quality and Economic Efficiency within the Health Care System« initiated by the GMG can make a key contribution to the debate on the therapeutic benefit of drugs, especially if information on discussions and decision-making processes within the institute are shared openly while the institute remains open to arguments from beyond its own walls.

When assessing the innovative value of a new drug the reasons behind the research and development of the drug are irrelevant. The reasons may be altruistic or highly egoistical. The main reason may be the will to do good - or the intention of rerouting an existing patent in order to secure profits for the company and its shareholders. All of this - scientific theory calls it the »generation context« of findings - is only a motivating factor, a contributory factor. Ultimately, it is only the result that counts:

How does an innovation help patients and the community to avoid unnecessary spending? Within the framework of pure science, the mere innovation itself may be of great value. Within the framework of drug research and development, however, as is usually the case in applied science:

22) The difference between phases of »normal science« and (greater or lesser) »scientific revolutions«, in which a change of paradigms takes place, can be traced back to the American scientific theorist and historian Thomas S. Kuhn (1922 - 1996) and his book »The Structure of Scientific Revolutions« (1962). The discussions around Kuhn generated a new understanding of the dynamics of scientific and technical progress.

23) see also: U. Holzgrabe, M. Schubert-Zsilavec, F. Stanislaus, E. Mutschler, T. Dingermann: Statement by the DPhG on disclosure of all clinical studies. PZ 149, 3194 (2004); DAZ 144,4992(2004)

The added benefit is of greater significance than the mere innovative value. Assessment depends rather on how plausibly, how stringently this can be supported, and how resistant to criticism the theory remains (in other words, the »justification context«). Looking back at the history of science, immediate consensus on the assessment of an innovation tends to be the exception rather than the rule.

Typically, the »scientific community« examines every argument at length for its ability to withstand criticism in a justification context. It takes time and well-designed clinical studies to be able to assess the therapeutic value of new drugs. New drugs must be able to prove their worth in day-to-day practice.

Restrictive intervention such as exclusion from reimbursement status or immediate inclusion of new drugs in the reference price system should be applied with great caution in order to avoid worsening the conditions even further for the development of (new) innovations. /

