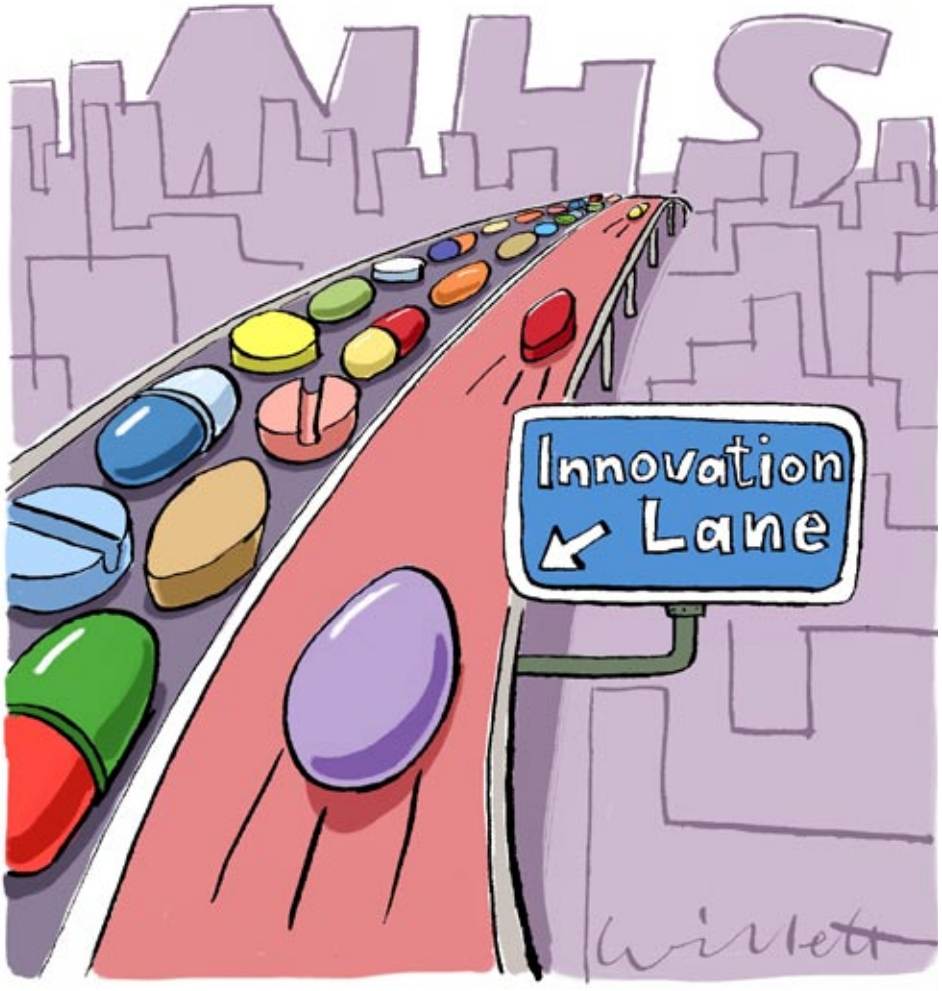
NICE and new: appraising innovation

Innovation is essential in drug development but is not cheap. **Robin Ferner, Dyfrig Hughes, and Jeffrey Aronson** examine the challenges of encouraging innovation while ensuring clinical benefit

Two recent reports propose that the NHS should treat innovative medicines favourably.[1 2] The Office for Life Sciences blueprint suggests that promising new drugs for which there are insufficient data for formal appraisal by the National Institute for Health and Clinical Excellence (NICE) should be granted an innovation pass, which will allow limited NHS use. The office has allotted £25m from the Department of Health to fund a pilot of the pass,[1] which it hopes will bring early benefit to patients and encourage the development of new medicines. Ian Kennedy, the former chair of the Healthcare Commission, has also recommended that NICE should consider offering incentives to drug companies for innovation.[2] Here we consider how innovativeness might be defined in health care, and how NICE and other organisations analysing health technologies might allow it to influence appraisal decisions.



Innovativeness and usefulness

Kennedy suggests that an innovative medicine is one that is new, constitutes an improvement on existing products, and offers "a step-change in terms of outcomes for patients."[2] This last criterion requires a measure of clinical usefulness for NHS patients.

Step changes in clinical usefulness might arise in several ways. The most successful innovations are those that are effective in previously untreatable conditions. Such medicines are most likely to be directed towards a new pharmacological target or to act by a novel pharmacological mechanism. Sildenafil for erectile impotence is a successful example. However, success is not guaranteed, as the case of interferon beta in multiple sclerosis shows (table 1).

Cost effectiveness analyses compare new treatments with the treatments they replace, weighing up the increased cost against the increased benefit. The benefit is measured in quality adjusted life years (QALYs). Although, as Kennedy agrees, QALYs are "the best tool available," they are imperfect.[2] NICE therefore already takes into account the clinical usefulness of an innovative product, while accepting that the QALY will not capture every health benefit.[3] Responding to Kennedy, NICE proposes explicit tabulation of health benefits suggested by the groups consulted. "Where such benefits have not [been captured at all], or have not been reliably captured in the QALY calculation, the [Appraisal] Committee will be asked

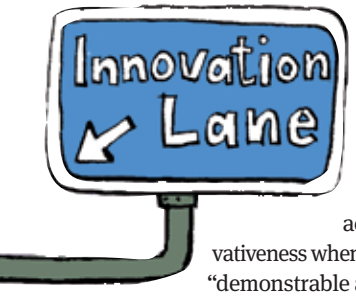
Table 1 | Classes of innovation in order of probability of clinical usefulness

		Examples	
Class of innovation	Likely form of innovation	Successful	Failed
To treat a condition with no existing effective treatment	New target or novel pharmacological mechanism	Sildenafil for erectile impotence	Interferon beta for multiple sclerosis*
To improve treatment of a condition that does not have a consistently satisfactory treatment	New target or novel pharmacological mechanism	Proton pump inhibitors for peptic ulcer disease	Mibefradil for angina pectoris†
To make treatment safer	New target or novel pharmacological mechanism	Rifampicin (in place of streptomycin)	Ximelagatran as an anticoagulant†
	More selective action	COX 2 inhibitors (gastrointestinal adverse effects)	COX 2 inhibitors (myocardial infarction)†
	Pharmacological or pharmaceutical changes that allow the drug to reach the site of therapeutic action but not the site of the adverse effect	Non-sedating histamine H_1 receptor antagonists	Indometacin†
To make treatment more convenient	Pharmaceutical reformulation	Depot intramuscular phenothiazines	Intranasal insulin*

*Failed because of inefficacy or cost ineffectiveness.
†Failed because of adverse effects or interactions.

Table 2 | Types of innovation ranked by degree of innovativeness

Degree of innovativeness	Type of innovation	Examples
High	New target or novel mechanism	Selective 5HT agonists (migraine)
	Novel application	Aspirin (prevention of stroke)
	Improved identification of those who are likely to benefit or be harmed (pharmacogenetics)	KRAS gene predicts efficacy (panitumumab, cetuximab)
		HLA B*5701 predicts adverse effect (abacavir)
Moderate	New type of compound	Monoclonal antibodies
	Fewer adverse effects or interactions	Ranitidine versus cimetidine
	Novel structure	Low molecular weight heparins
Slight (health related)	Improved disposition (pharmacokinetics)	Short acting benzodiazepines
	Improved delivery (formulation)	Modified-release formulations
Slight (non-health related)	Improved production	Recombinant insulin
	Novel structure	Meptazinol; esomeprazole versus racemic omeprazole
None	Remarketing	Standard release oxycodone



to describe how it has evaluated them and whether, and if so, how it has taken them into account in developing its guidance."[4] NICE already accommodates innovativeness when a technology brings "demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure" when the benefits implicitly accrue to patients.[5]

Innovativeness and usefulness need to be considered separately if we are to identify rewardable innovations—important advances that bring worthwhile clinical benefit (contrast tables 1 and 2).

How medicines are innovative

There are many ways in which a medicine can be innovative (table 1).[6] However, not all innovations are equal; judgment is required about how innovative any new treatment is. We suggest that characteristics of new products should be ranked in order of degree of innovation (table 2) and that a product should be at least moderately innovative before being afforded any special consideration. But innovation does not guarantee clinical usefulness, as the examples below show.

Chemical structure—The analgesic meptazinol, unlike other opioids, is based on a hydroazepine ring; it is chemically innovative but does not confer appreciable clinical benefit.

Synthesis—The chemical structure may be unchanged or changed only minimally, but be achieved by a different synthetic route (such as recombinant techniques for human insulin and biosimilars). Such synthetic innovation may bring economic advantages but generally makes no difference to the benefit to harm balance; low molecular weight heparin is an unusual exception.

New types of compound—The introduction of monoclonal antibodies was innovative. Even though other types of drug were available for many of the same indications, monoclonal antibodies improved care considerably in some cases (such as vascular endothelial growth factor antagonists for age related macular degeneration).

Pharmacodynamics—A drug may act in a new way—for example, at a newly defined target (such as a receptor subtype) or by a novel pharmacological mechanism (such as reversible inhibition of an enzyme). This is the most important type of innovativeness (table 2). Sildenafil, which inhibits phosphodiesterase-5 selectively, was innovative in this way and is useful. However, the innovative anti-anginal drug mibefradil, which acted on T-type calcium channels, had to be withdrawn from the market because of many pharmacokinetic interactions with other drugs.[7]

Pharmacokinetics—Innovation can arise from novel pharmacokinetic properties (absorption, distribution, metabolism, or elimination). The second generation antihistamines were innovative because of poor penetration into the brain, usefully reducing adverse effects on the central nervous system. The benzodiazepine triazolam was also pharmacokinetically innovative, with a shorter duration of action than other benzodiazepines; however, psychiatric reactions[8] reduced its usefulness, outweighing benefit.

Improved delivery through formulation—Pharmaceutical presentation can make a medicinal product innovative. Inhaled insulin (Exubera) represented an innovative approach to administering a drug that had been available for over 80 years; it did not, however, prove to be clinically worthwhile.[9]

Improved usefulness because of pharmacogenetics—Pharmacogenetic markers are generally delineated after a drug has been marketed, rather than as part of the strategy of drug development. However, the simultaneous development of a new drug and a diagnostic test designed to detect a specific pharmacogenetic marker that allowed doctors to predict which patients would benefit most would be highly innovative.

Discovery of novel applications—An established drug may later prove innovative if a novel indication is discovered. The value of aspirin in antiplatelet therapy was not recognised until 80 years after the drug was first introduced.[10]

Incremental innovation—Change is often incremental. Within a therapeutic class, innovation eventually gives way to tinkering to provide marginal, but marketable, health gains. New products generally become costly "me toos" that offer no real additional benefit. There are many examples: the *British National Formulary* lists 11 different angiotensin converting enzyme inhibitors, 12 benzodiazepines, and 15 β adrenoceptor antagonists. Kennedy suggests that such products should not warrant any special treatment.[2] However, incremental improvements can eventually result in innovation, and follow-on products can outperform their originators.[11] Bisoprolol and carvedilol, for example, have innovative features that are lacking in earlier β blockers and are clinically useful.

These examples show clearly that a measure of usefulness as well as innovation is required when assessing new treatments (table 1 and box).

Pragmatic approach

An innovative medicine is clinically useful only if it yields a worthwhile improvement in health, something that is clearly desirable if the cost is acceptable. UK policy commands government departments to harness "the power of innovation to produce better solutions at lower cost than would be possible without change."[12] However, new and innovative medicines are unlikely to reduce costs. We therefore propose a pragmatic approach to the appraisal of rewardable innovativeness in drug development.

If a premium is to be paid for innovation, it would be sensible to reward innovative products that are most useful—that is, those that provide large mean gains in health. This is especially true if the reward is to be sufficient to encourage drug companies to concentrate on important gaps in health care. It would be reasonable, therefore, to specify that a medicine should achieve some minimum increment in health gain. The median of

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the QALY gains for 281 products submitted to the Scottish Medicines Consortium was 0.097—that is, a gain of about one month of full health compared with existing treatments. Only about one product in eight provided average gains of more than 1 QALY.[13] It might be possible to reward innovation in proportion to the QALY gain, but it would be more straightforward to choose a threshold value below which innovation would not be rewarded. A plausible, provisional gain of at least 1 QALY would be a reasonable threshold for judging the usefulness of a supposedly innovative technology at the time of licensing. NICE could relax this threshold when it judged that the QALY failed to capture all the health benefits, accepting that this represented a deficiency in the methods of obtaining QALYs, independent of innovation. We suggest the following strategy for potentially innovative medicines for which sufficient information is available to allow formal appraisal:

Step 1—As soon as sufficient information is available to allow NICE to appraise a new product, its potential effectiveness should be assessed. If the average predicted health gain is less than 1.0 QALY the product should, as a general rule, be considered by the standard NICE appraisal criteria. Depending on the cost per QALY, it would be approved or rejected in the usual way.

Step 2—If a gain of more than 1 QALY is predicted for the product, the degree of innovation should be assessed. If the product is judged moderately innovative or better (table 2), NICE should afford it special status and consider more than direct health benefits. It could adjust its calculations to bring the cost per QALY of the medicine down and increase the chances that it will lie below NICE's acceptable threshold for cost effectiveness. It could do this by appraising the product's cost effectiveness on the basis of broader economic perspectives that include costs other than those incurred by health and personal social services—for example, total public spending.[14] This is consistent with NICE's methods for developing public health guidance. A cost-benefit analysis, although theoretically appealing, would be too difficult. NICE could potentially accept an economic evaluation that considered a future health technology whose development depended on approval of the innovative medicine[15]; however, it would be almost impossible to make such an evaluation prospectively.

Step 3—Since all initial assessments will be provisional, and often very uncertain, the special status for innovative products should be time limited, and reviewed after (say) three years. If the predicted gains are not realised, the product should have its special status and privileges removed.

This strategy is independent of the proposed innovation pass.

Measures of usefulness of medicinal products (see also table 1)

Health related outcomes
- Improved clinical efficacy and effectiveness
- Improved safety
- Improved cost effectiveness
- Improved equity (eg, ability to treat a previously untreatable condition)
- Improved convenience

Non-health related outcomes
- Company profitability
- Improved employment
- Increased national wealth
- Improved environment

Funding innovative medicines

As the NICE cost effectiveness threshold represents the marginal value that society places on health,[16] it makes no sense to change it for innovative medicines. Some societal benefits (such as reduced spending on unemployment benefit) can in principle be offset against healthcare costs, effectively reducing the cost per QALY. But if innovation is to be rewarded because it brings benefits unrelated to health (box) that accrue to wider sections of society and drug companies, it is unreasonable to burden the NHS healthcare budget. Successful innovation will profit drug companies, and they could reasonably be asked to contribute, particularly since wider financial benefits can accrue globally to multinational companies. Furthermore, their contribution would represent an insurance against the failure of an innovation to achieve success during the trial period. Government contributions should come from outside the Department of Health, perhaps from the Department for Business, Innovation, and Skills.

Conclusions

What really matters to the NHS is that innovations bring benefit to patients. However, there may be wider benefits from rewarding innovation for its own sake. This can be done only if it proves possible to separate innovativeness from usefulness and if a sustainable method to finance the extra spending can be found. If it proves impossible in practice to reward innovativeness and provide incentives to develop useful medicines, we would argue strongly that NICE should keep its current methods of technology appraisal.

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