Something New Every Day
Defining Innovation and Innovativeness in Drug Therapy

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Abstract: The word “innovation” comes from the Latin noun innovatio, derived from the verb innovare, to introduce (something) new. It can refer either to the act of introducing something new or to the thing itself that is introduced. In terms of commerce, it is defined in the Oxford English Dictionary as “the action of introducing a new product into the market; a product newly brought on to the market,” a definition that illustrates both aspects of the word’s meaning. “Innovativeness” is the property of being an innovation. Here I identify several different types of innovativeness in drug therapy, including structural, pharmacological or pharmacodynamic, pharmaceutical, and pharmacokinetic innovativeness, and I stress the over-riding importance of clinical innovativeness, which should result in a better benefit to harm balance at an affordable cost.

Keywords: benefit to harm balance, drug therapy, innovation, innovativeness

I nnovation and innovativeness have not been well defined in official documents in which the need for innovation has been discussed at length. For example, innovation has been only briefly defined in one UK Government document as “the generic term for the successful exploitation of new ideas” (Department of Trade and Industry, 2002). In one US Government document, no definition is offered, beyond the suggestion that collaboration is a defining feature of innovation (National Governors Association, 2002), and in yet another there is no definition at all (Food and Drug Administration, 2004). An early version of a nonofficial document, The Erice Statement on Drug Innovation, defined innovation as follows: “An advancement in science, knowledge and/or technology potentially able to be translated in actions, tools and/or interventions that eventually should yield a benefit for users and innovator(s)” (Giampaolo Velo, personal written communication). However, this definition did not make clear the difference between an invention and an innovation and ignored the dual nature of the word innovation (the act and the thing). The definition was subsequently revised as follows: “Innovation is . . . the process of making improvement by introducing something new that should potentially yield a benefit for users, in terms of a tangible impact at the level of society” (Erice Group, 2007). This is an excellent formulation, although it could be improved, for example, by changing “society” to “individuals and society” and by recognizing that innovations can cause harms as well as benefits and must be affordable. These are points that I shall deal with below.

Attempts have been made to quantify innovativeness in drug therapy, using the seriousness of the target disease, the availability of previous treatments, and the extent of the therapeutic effect (Motola et al., 2005, 2006). Such analyses could be improved (Aronson, 2005), but they confirm that innovativeness is at an ebb; for example, only 20 to 30 new
drugs are approved by the Food and Drug Administration in the United States each year (Cohen, 2005). So it seems surprising that such an important concept has not been subjected to wider definitional exploration. Furthermore, such definitions as we have are economically biased and do not relate to clinical outcomes. What we need is a proper definition of innovativeness in therapeutic intervention. Here, I restrict myself to attempting to define innovativeness in drug therapy.

TOWARDS A DEFINITION OF MEDICINAL INNOVATIVENESS

Medicinal innovativeness has several aspects. For example, a compound may have a novel chemical structure (structural innovativeness). However, if it does not have a novel mechanism of action (pharmacological innovativeness), one would not regard it as innovative. For example, antihistamines (H1 receptor antagonists) have many disparate structures, but only the first was pharmacologically innovative.

A compound that is not pharmacologically innovative from the point of view of its therapeutic target may nevertheless be innovative by virtue of other pharmacological actions. For example, the first clinically useful H2 histamine receptor antagonist was cimetidine, a truly innovative compound with a novel mechanism of action. Burimamide and metiamide, which were both tested on humans, were too toxic for routine clinical use and could be regarded as its preinnovators. However, the next such drug to appear, ranitidine, was not mechanistically innovative. On the other hand, it was innovative in another respect—it lacked some of the adverse effects of cimetidine. No other H2 receptor antagonist that has since appeared can be regarded as innovative in any way. Similarly, enalapril was not innovative by virtue of its mechanism of action (angiotensin-converting enzyme inhibition); it did, however, display minor innovativeness in that it had fewer adverse effects, such as taste disturbance; furthermore, it was pharmacokinetically innovative—it could be used once a day.

This means that there may be a fine line between drugs that are truly innovative and so-called “me-too” drugs. Furthermore, small successive pharmacological differences between consecutive drugs may lead eventually to a major difference that can be regarded as being in some respect innovative. For example, of the many β-adrenoceptor antagonists that have been developed, only 15 have survived to be included in the British National Formulary. In the following list, the dots represent intermediate drugs that have not survived (Baber et al., 2004):

- propranolol, sotalol, ● oxprenolol, pindolol, acebutolol, atenolol, timolol, metoprolol,
- labetalol, nadolol, celirol, esmolol, bisoprolol,
- carvedilol, nebivolol

The drugs are presented in chronological order of their first appearance in the published literature (data from PubMed). Each of the dots represents another β-blocker that has not made the grade. Although these 15 drugs represent only 27% of the grand total of 55 β-blockers that I have surveyed, they represent 86% of the total published literature on β-blockers. (Many more β-blockers have been developed and have disappeared without trace, not even appearing in PubMed.) Even omitting propranolol, which has the lion’s share of publications, the other 14 represent 73% of the literature on the total of 54 β-blockers. It could be argued that even among the 15 named drugs, several did not offer substantial advantages over their predecessors, and that the main reason that so many β-blockers have been developed is simply that even a small share in a blockbuster market can be very profitable for a drug company. However, no two β-blockers are exactly alike, and gradual changes can eventually result in innovativeness. If we accept that the later β-blockers are innovative in comparison with the earlier ones, when did the innovativeness appear, if it emerged as the final outcome of a cumulative process? This is analogous to the sorites paradox (“Sorites paradox”, 2007)—how many grains of sand do you need to accumulate before you have a heap?
Conversely, if you take away one grain at a time from a definite heap, when does the heap disappear?

Although a novel mechanism of action (pharmacological innovativeness) is an important aspect of innovation, it is clearly not always necessary, as we shall see below. However, there is a converse to this: a novel mechanism may be insufficient to confer clinical innovativeness if it does not represent a therapeutic advance. For example, the thromboxane synthase inhibitor dazoxiben was regarded as innovative when it first appeared, but it did not prove its therapeutic worth. It was certainly pharmacologically innovative, but not clinically so.

A medicinal product may lack pharmacological innovativeness but be pharmaceutically innovative. For example, a formulation of insulin that could be used nasally would be highly innovative, provided that it was as clinically effective as insulin given subcutaneously. In a case of this sort, it is the medicinal product rather than the compound itself that is innovative.

Similarly, pharmacokinetic novelty may be innovative. Benorylate was innovative—it delivered paracetamol (acetaminophen) and aspirin by a novel pharmacokinetic mechanism, but did not offer pharmacological innovativeness.

In my view, the most important form of innovativeness is clinical innovativeness, since it is the end result that really matters. This can be judged from the answers to the important questions that one should ask about any new drug:
- Does the drug produce significantly greater benefit than its predecessors?
- Does it cause less harm?
- Is the cost affordable?

The extent to which a new drug is considered to do the first two of these would generally be based on the results of clinical trials, but in some cases may be subject to value judgments. Cost-effectiveness can be judged on objective criteria, but is subject to the vagaries of the pharmacoeconomic model used and the threshold at which cost-effectiveness is set (Appleby et al., 2007).

DIFFERENT TYPES OF INNOVATIVENESS

It is clear that there are different forms of innovativeness, the benchmark in each case being previous interventions. They can be defined as follows:
- **Structural innovativeness** may provide a route to other forms of innovativeness, but not necessarily.
- **Pharmacological or pharmacodynamic innovativeness** is possessed by a compound with a novel therapeutic target or one that has fewer adverse targets (including drug-drug interactions) than a predecessor with the same therapeutic target.
- **Pharmaceutical innovativeness** is conferred on a compound by virtue of a medicinal product that produces novel pharmaceutical properties; the compound itself need not be novel.
- **Pharmacokinetic innovativeness** is either primarily possessed by a compound or conferred on it by a medicinal product by virtue of novel disposition.
- **Clinical innovativeness** is possessed by a medicinal product that produces significantly more benefit than its predecessors and/or significantly fewer adverse effects (including drug-drug interactions), resulting in a better benefit to harm balance at an affordable cost.

It should be noted that innovativeness may be an attribute of the compound itself or may be conferred on it by the formulation that contains it. That is why I use the term “medicinal product,” which covers both. Finally, no amount of innovativeness can offset the failure of a product to be cost-effective, and therefore affordable. In the end, cost-effectiveness trumps everything.

In this issue of the *Journal of Ambulatory Care Management*, Apolone (2007) points out that the perceived value of a medicinal product varies from country to country, depending on differences in the diseases that demand attention and the priorities given to them, the system that delivers the health care, economics, cultural attitudes, and even genetics, although the last of these must be a rare determinant. He correctly concludes that the
value of a product depends mainly on its utility. He does so from a Marxian viewpoint, although my analysis shows that this conclusion can be reached otherwise. He also suggests that an exchange mechanism is necessary before a product is accepted as a commodity, and that its value depends on the exchange value, rather than its intrinsic value (e.g., the cost of the raw materials), and the market economy. He points out that the various forms of innovativeness, although important, are secondary to the final impact of an intervention on individuals and society. The implication of this is that only clinical innovativeness, as defined above, is of true value; the other forms of innovativeness only confer potential value.

Those who are at the forefront of innovation must keep this in mind. It is not enough to be innovative structurally, pharmacodynamically, pharmacokinetically, or pharmaceutically. Clinical effectiveness, measured by the balance of benefit and harm, at an affordable price, is everything.

REFERENCES