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How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001–2012

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ABSTRACT

Objectives: Innovative new drugs offer potential benefits to patients, healthcare systems, governments and the pharmaceutical industry. Recent data suggest annual numbers of new drugs launched in the UK have increased in recent years, and we sought to understand whether this represents increasing numbers of highly innovative drugs being made available or the introduction of increasing numbers of drugs with limited additional therapeutic value.

Design and setting: Retrospective observational study of new drug entries in the British National Formulary (BNF).

Primary and secondary outcome measures: Number of new drugs launched in the UK each year (based on first appearance in the BNF) from 2001 to 2012, including new chemical entities and new biological drugs, categorised by degree of innovativeness according to published criteria that incorporate both clinical usefulness and the nature of the innovation.

Results: Highly innovative, moderately innovative and slightly innovative drugs made up 26%, 18% and 56% of all newly launched drugs, respectively, for the study period (n=290). There was an upward trend in annual numbers of slightly innovative drugs from 2004 onwards (R^2=0.44), which aligned closely with the recovery in total numbers of new drugs launched each year since that time. There were no discernible time trends in the highly or moderately innovative categories. New drugs for malignancy and skin disease were most likely to be characterised as highly innovative (44% and 57%, respectively).

Conclusions: Highly innovative new drugs comprise only around a quarter of all new drug launches in the UK. In contrast, drugs categorised as only slightly innovative comprised well over half of all new drugs and annual numbers in this category are increasing. Current policy initiatives that seek to increase the supply of innovative new drugs have long-lead times to impact, and will need careful assessment to ensure they deliver their aims without unintended consequences.

Strengths and limitations of this study

- This is the most up to date and complete study that considers the innovativeness of new drug introductions into the UK.
- The study used published criteria that adopt a broad perspective of innovation, and incorporate clinical usefulness (offering a therapeutic advantage) and the process through which an innovation arises (ie, through a revolutionary or disruptive transformation and incorporating an assessment of pharmaceutical novelty).
- However, the criteria used to categorise innovativeness do not take into account the public health need, health service impact or commercial success of newly launched drugs.
- This study did not consider new indications for existing licensed and marketed drugs.

INTRODUCTION

Innovative new drugs offer potential benefits to patients, healthcare systems, governments and the pharmaceutical industry.[1] However, during the first decade of the new millennium, many commentators noted an apparent temporary lack of pharmaceutical innovation and a reduction in new drug launches, despite increasing research and development (R&D) spending,[2–5] though some attributed this to reduced numbers of rapidly developed 'me-too' or 'follow-on' versions of small molecule high volume drugs.[6] Within the context of drug development, innovation is generally defined as the discovery, development and bringing to the market of a new chemical entity[7] (NCE); "an active ingredient that has never been marketed…in any form,"[8] and the most straightforward way to measure innovation is to separate drugs into 'first in class' and 'follow-on' drugs, those which largely duplicate the action of

existing drugs and are chemically similar.[9] Ferner *et al*[10] have proposed a more sophisticated classification, which identifies a range of features related to a drug's molecular structure, synthesis, pharmacodynamics, pharmacokinetics, delivery, pharmacogenetics and application. However, this does not account for all possible aspects of innovativeness, in particular therapeutic advantage over existing drugs. In considering how the National Institute for Health and Care Excellence (NICE) should incorporate innovation into UK decision-making, Kennedy proposed that an innovative medicine should offer improvements over existing therapies and a "step-change in terms of outcomes for patients."[11] Building on these approaches, Aronson *et al*[1] defined innovation using a broad perspective, including health and non-health elements, that incorporates both clinical usefulness (offering a therapeutic advantage) and the process through which an innovation arises (ie, through a revolutionary or disruptive transformation and incorporating an assessment of pharmaceutical novelty). In this approach, a new drug for a condition that is inadequately treated using current approaches is considered the most clinically useful and the process through which it is developed may be considered 'highly innovative' if it utilises "a new target or novel mechanism," involves "improved identification of patients…likely to benefit or be harmed" and/or uses the "novel application of an existing compound."

A recent systematic review by Kesselheim *et al*[12] sought to identify the range of approaches used to determine trends in pharmaceutical innovation. They developed a taxonomy of assessment strategies, and considered the conclusions drawn when using these differing definitions. They determined four main categories of study: "counts of new drugs approved, assessments of therapeutic value, economic outcomes and patents issued."[12] Studies based on counts of new drug approvals reported both positive and negative temporal trends in innovation, depending on the definitions used, geographical locations and time periods studied. However, studies published in the last decade that define innovativeness on the basis of therapeutic value all report a negative trend in the innovativeness of new drugs, despite using different approaches to measurement and reporting time periods varying from 1990–2003 to 2001–2010. The varied approaches to measuring therapeutic value included: the results from premarketing and postmarketing trials; pharmaceutical or technical innovation; comparison with available marketed alternatives or therapeutic novelty (giving greater weight to drugs for conditions with no existing effective treatment); and more general public health measures. Regardless of the approach used to measure therapeutic value, all these studies characterised only a minority of new drugs as highly innovative. Motola *et al*[13] considered all drugs approved by the European Medicines Agency (EMA) between 1995 and 2003 according to an algorithm that considered the severity of the target indication, availability of existing treatments and size of therapeutic benefit. The authors characterised 32% of new drugs as representing important therapeutic innovation; a figure which rose to 39% of drugs for serious conditions. A subsequent update to this work (including drugs approved to July 2004),[14] characterised an even lower proportion of new drugs as important therapeutic innovations (28%); for biotechnological products, this figure was just 25%. Joppi *et al*[15] also considered biotechnological products approved by the EMA between 1995 and 2003 and also characterised just 25% as representing therapeutic innovation on the basis of relative efficacy compared with existing treatments (including where no treatment previously existed or offering treatment to patients resistant to existing therapies). Similar data from Canada found that of all new branded medicines approved between 1990 and 2003, just 6% were designated as 'breakthrough' on the basis of providing the first effective treatment for a patient group or substantial improvement over existing products.[16]

The most recent evidence on numbers of new drug launches suggests that any decline seen since the mid-1990s is now being reversed.[17–20] We previously described a decline in new drug launches in the UK from 1997 to 2003, with a rise in new drug launches from 2004 onwards.[19] However, it is not clear whether increasing numbers of new drugs are indicative of radical new breakthroughs or more modest, relatively minor modifications of existing marketed drugs.[21] We aim to establish the most up to date description of the innovativeness of new drugs launched in the UK, and to understand whether the recent increase in drug launches represents increasing numbers of highly innovative new drugs being made available, or whether the apparent recovery in launch volumes is due to increasing numbers of drugs of limited additional therapeutic value. We adopted the criteria proposed by Aronson *et al*[1] to define the degree of innovation based on an assessment of clinical usefulness and the nature of the innovation (table 1).

METHODS

Data collection and definition of new drugs

We obtained data on the numbers and characteristics of new drugs (NCEs and new biological agents) launched in the UK each year from relevant editions of the British National Formulary (BNF). The BNF lists all preparations available for prescribing and/or dispensing in the UK, including prescription only and over-the-counter medicines. Information on the active ingredient and BNF chapter heading (organised into broad therapeutic areas) for every item in the 'new preparations' section of each BNF from edition 41 in 2001 to edition 64 in 2012 was obtained and entered onto a spreadsheet. The BNF also includes non-drug products (nutraceutical and medical foods, natural products, devices and diagnostic products), new salts and esters of existing chemical compounds, and generic or biosimilar preparations; these

Table 1 Criteria for determining clinical usefulness and nature of pharmaceutical innovation, adapted from Aronson *et al*[1] and Ferner *et al*[10]

Clinical usefulness*†	Process through which innovation arises: Nature of innovation‡	Process through which innovation arises: Successful examples§	Overall degree of innovation
Potential benefit in a condition with existing effective treatment	Highly innovative properties: A. New target or novel mechanism (pharmacodynamics) B. Improved identification of those who are likely to benefit or be harmed (pharmacogenetics)	A. Phosphodiesterase type V (sildenafil) B. HER2 (trastuzumab in breast cancer); HLA B*5701 testing (abacavir hypersensitivity reactions)	Highly innovative
Potential improvement in the treatment of a condition that does not have a consistently satisfactory treatment	Moderately innovative properties: A. New class of compound B. Fewer adverse reactions or drug–drug interactions C. Novel structure or method of synthesis (if it confers other therapeutic advantages)	A. Monoclonal antibodies B. Ranitidine vs cimetidine C. Low molecular weight heparins	Moderately innovative
Potentially safer treatment (eg, fewer adverse reactions or drug–drug interactions)	Slightly innovative (health-related) properties: A. Improved disposition (pharmacokinetics) B. Improved delivery (formulation)¶	A. Short-acting benzodiazepines B. Modified-release formulations¶	Slightly innovative
More convenient treatment	Slightly innovative (non-health-related) properties: A. Improved production B. Novel structures (eg, stereoisomers, whose marketing benefits the company but which carry little or no additional clinical benefit)	A. Recombinant techniques B. Escitalopram	

*Assumes a favourable benefit to harm balance in key patient-related outcomes (health-related quality of life and/or survival). Criteria taken from Aronson *et al*[1] and Ferner *et al*,[10] however Aronson also included a fifth category, 'more cost-effective treatment', but this was not assessed as part of this study.
†Ranked order, with higher categories potentially also including elements of lower ranked categories.
‡Aronson *et al*[1] and Ferner *et al*[10] also considered the novel application of an existing compound as highly innovative, but such examples were not included in this study (which was restricted to new drugs).
§Taken from Aronson *et al*[1] and Ferner *et al*.[10] Failed examples are also given in Ferner *et al*.[10]
¶Modified-release formulations might be moderately innovative if, for example, they reduced the risk of adverse reactions or drug–drug interactions.

products were excluded to leave only new drugs (full details given in online supplementary file 1).[19] In addition, active and passive immunisations were excluded from the data as these typically follow different development and National Health Service (NHS) market access pathways to other drugs. Commercial pharmaceutical databases (Pharmaprojects, Informa Healthcare; and Adis R&D Insight, Springer International Publishing) were also used to determine whether a substance was a new drug at the date of UK launch. Different dosages of the same product were counted only once; different formulations of the same product, for example, oral tablet and intramuscular injection, were counted once if they contained the same active ingredients, and multiple times if they contained different active ingredients. Different indications for the same product were counted once.

Determination of innovation level

The criteria proposed by Aronson *et al*[1] (table 1) were used to determine the degree of innovation at the time of launch for all new drugs identified as entering the UK market between 2001 and 2012 (inclusive). Clinical usefulness and the process through which the innovation arose (nature of the innovation) were determined by simple searches of online sources, including the NHS Evidence web portal (http://www.evidence.nhs.uk/), which incorporates results from all UK national and selected regional health technology assessment and medicines management bodies, the EMA website and two commercial pharmaceutical R&D databases (Pharmaprojects and Adis R&D Insight). Clinical usefulness was mapped to the nature of innovation, so that an effective drug for a condition with no current treatment was inevitably classified as highly innovative; improvement in the treatment of condition with no satisfactory existing treatment was classified as moderately or highly innovative depending on the nature of the innovation, but a more convenient treatment only could not be classified as highly innovative (table 1). Two analysts (AS and TG) independently applied these criteria to determine whether a drug was highly innovative, moderately innovative or slightly innovative. Inter-rater agreement between the two analysts was assessed using Cohen's κ statistic. Where the analysts disagreed, a third individual (DJW) acted as arbiter and made a determination based on discussion and further independent research (if necessary). All authors were able to review the final list of drugs and degree of innovativeness, and propose changes, which were then resolved by discussion between all authors.

Analysis

The proportion of new drugs categorised as highly innovative, moderately innovative or slightly innovative was calculated for the entire study period and for separate 4-year time intervals. Plots showing the numbers of new drugs categorised by degree of innovativeness (as absolute numbers and percentage of total new drugs launched that year) against year of launch were first visually inspected to identify potential time trends. Any potential trends in these data from 2004 onwards (taken as the end of the predefined dip in new drug launches) were analysed using linear regression (SPSS V.21, IBM), taking year as a continuous variable.

RESULTS

There were 290 new drugs listed in relevant editions of the BNF for the 12 years from 2001 to 2012 (inclusive), a mean of 24.2/year (full list in online supplementary file 2). In the initial coding for degree of innovativeness, two analysts independently agreed on 210 drugs (72.4%, inter-rater agreement κ=0.56 (SE=0.039, p<0.001)), after which agreement was reached on all remaining drugs through discussion involving a third arbiter.

For the entire study period, 75 (25.9%) drugs were coded as highly innovative, 53 (18.3%) as moderately innovative and 162 (55.9%) as slightly innovative (table 2). Total annual numbers of new drug introductions fell from 27 in 2001 to 18 in 2006, before increasing to a highpoint of 29 in 2010 (figure 1). Visual inspection of the line graph showing numbers of new drugs assigned to different degrees of innovativeness by year (figure 1) suggested that there were no discernible time trends in the highly innovative and moderately innovative categories, but the annual numbers of drugs categorised as only slightly innovative had risen since 2004, broadly mirroring the overall increase in numbers of new drugs. An upward linear trend from the predefined 2004 point was observed for slightly innovative new drugs (r=0.67, R^2=0.44, y=1.03×year−2062.0 (p=0.051)) and total new drugs (r=0.81, R^2=0.65, y=1.20×year−2385.5 (p=0.009)). In contrast, no linear trends were apparent in moderately innovative or highly innovative new drugs for the same time period (r=0.19 and 0.04, respectively).

Considering BNF chapter headings, 6 of the 15 broad therapeutic areas represented over three-quarters of all new drugs, namely malignant disease and immunosuppression; infections; cardiovascular system; endocrine system; central nervous system; and nutrition and blood (table 2). Each of these provided at least 9% of all new drugs during the study time period, with malignant disease and immunosuppression making up 19.7% of the total. A statistically significantly greater proportion of drugs were coded as highly innovative in two broad therapeutic areas (malignant disease and immunosuppression (p=0.0003, one-tailed χ^2 test); and skin (p=0.028)) when compared with the total proportion coded as highly innovative (table 2). In addition, almost 40% of drugs in the nutrition and blood chapter were coded as highly innovative, though the difference from the overall proportion was not statistically significant (p=0.062). In contrast, a statistically significantly greater proportion of drugs were coded as slightly innovative in the chapters for eye disease (p=0.013) and immunological products

Table 2 Numbers of new drug launches in the UK and degree of innovativeness by BNF chapter heading, 2001–2012

	Degree of innovativeness							
	Slightly (n, % category)		Moderately (n, % category)		Highly (n, % category)		Total (n, % total)	
Year of new drug launch								
2001–2004	54	58.7	18	19.6	20	21.7	92	31.7
2005–2008	50	54.9	15	16.5	26	28.6	91	31.4
2009–2012	58	54.2	20	18.7	29	27.1	107	36.9
BNF chapter heading								
Anaesthesia	1	33.3	1	33.3	1	33.3	3	1.0
Cardiovascular system	20	58.8	6	17.6	8	23.5	34	11.7
Central nervous system	18	56.3	9	28.1	5	15.6	32	11.0
Ear, nose and oropharynx	2	100.0	0	0.0	0	0.0	2	0.7
Endocrine system	22	66.7	7	21.2	4	12.1	33	11.4
Eye	9	90.0*	0	0.0	1	10.0	10	3.4
Gastrointestinal system	1	33.3	1	33.3	1	33.3	3	1.0
Immunological products and vaccines	6	100.0*	0	0.0	0	0.0	6	2.1
Infections	23	60.5	7	18.4	8	21.1	38	13.1
Malignant disease and immunosuppression	19	33.3	13	22.8	25	43.9†	57	19.7
Musculoskeletal and joint diseases	9	56.3	3	18.8	4	25.0	16	5.5
Nutrition and blood	14	53.8	2	7.7	10	38.5	26	9.0
Obstetrics, gynaecology and urinary-tract disorders	8	80.0	1	10.0	1	10.0	10	3.4
Respiratory system	8	61.5	2	15.4	3	23.1	13	4.5
Skin	2	28.6	1	14.3	4	57.1†	7	2.4
Total	162	55.9	53	18.3	75	25.9	290	100

*Proportion of slightly innovative drugs greater than total proportion of slightly innovative drugs, p<0.05 (one-tailed χ^2 test).
†Proportion of highly innovative drugs greater than total proportion of highly innovative drugs, p<0.05 (one-tailed χ^2 test).
BNF, British National Formulary.

and vaccines (p=0.014). In addition, 80% of new drugs in the obstetrics, gynaecology and urinary-tract disorders chapter, and all new drugs in the ear, nose and oropharynx chapters, were coded as slightly innovative, though these results were not statistically significantly different from the overall proportion (p=0.59 and 0.10,

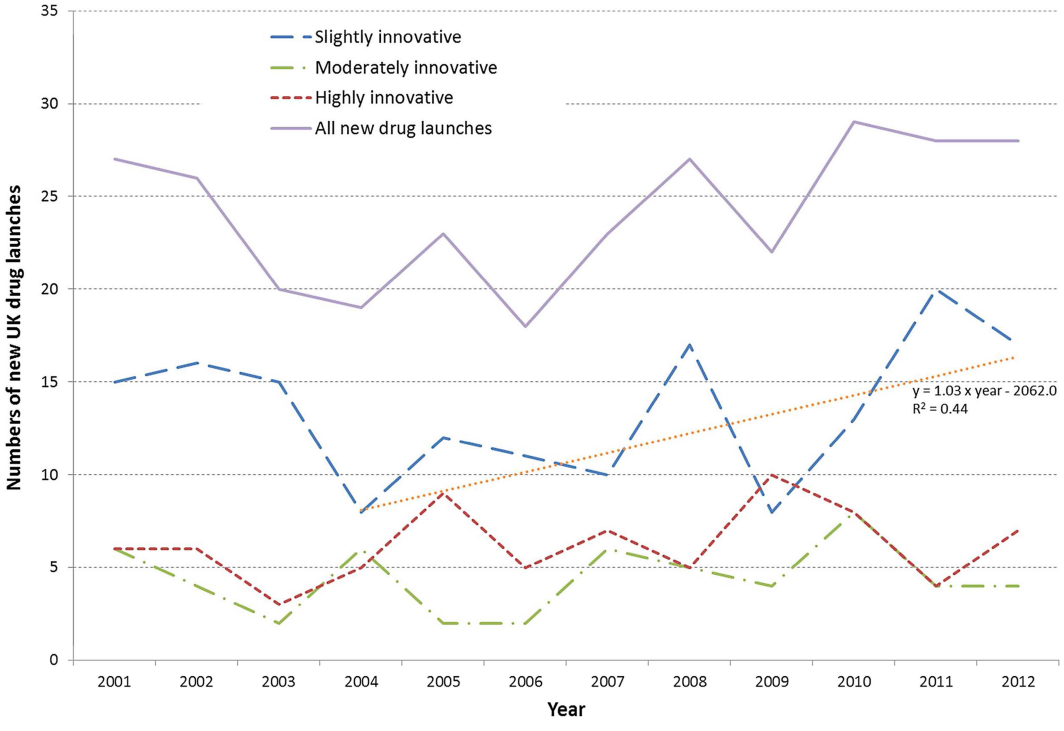

Figure 1 Numbers of new drug launches in the UK and degree of innovativeness by year, 2001–2012.

respectively), and the latter group included only two drugs.

DISCUSSION

This is the most up to date study that considers the innovativeness of new drug introductions into the UK. The BNF includes all medicinal products available for dispensing in the UK, and the printed editions were updated every 6 months, providing an accurate and reliable account of new drugs launched in the UK each year. We identified an upward linear trend in the annual numbers of slightly innovative new drugs launched in the UK since 2004, which aligns closely with the recovery in total numbers of new drug launches seen since that time.[19] No apparent similar increase in moderately innovative or highly innovative new drugs was observed. Just six broad therapeutic areas accounted for over three-quarters of new drug introductions, and of these, drugs for malignant disease and immunosuppression, and nutrition and blood disorders were also more likely to be categorised as highly innovative.

The criteria we used to determine innovativeness go beyond simple notions of chemical innovation to consider therapeutic advantage based on a very broad definition of clinical benefit. As such, we characterised a number of first in class drugs as moderately rather than highly innovative. However, we recognise that the criteria are qualitative rather than quantitative, requiring some value judgement to implement, and that some benefits or harms may not be apparent early in a product lifecycle, both of which could lead to misclassification (or differences in classification depending on viewpoint) that vary with time. Other commentators have further developed ideas of what constitutes therapeutic advantage and innovation to propose three axes of pharmaceutical innovation[22]: context of use (including existing treatment options), product novelty (chemical, pharmacological and pharmaceutical) and impact (efficacy, safety and ease of use with respect to existing therapies). However, none of these criteria take direct account of the public health and health service impact of a new drug (disease severity, patient group size and likely uptake); drugs in the highly innovative group include those for rare metabolic disorders and last line therapies as well as for diabetes mellitus and common malignancies. Patient group size is one factor related to commercial success,[23] but the link with pharmaceutical novelty is less clear. A study of new drugs approved in the USA found a small commercial benefit for first in class as compared with follow-on drugs of the same class.[24] However, this could be overcome by demonstrating a clear therapeutic advantage, launch in a therapeutic area characterised by 'cycling' of different drugs as initial therapy fails, and effective marketing. Other commentators have noted the high degree of drug utilisation relating to subsequent indications rather than the initial approved indication, and suggest that much innovation and commercial productivity is not captured when considering new drug launches only,[25] and this should be the focus of further study.

The low levels of innovation observed in this study are of clear concern to policymakers, who have responded with a range of initiatives to better reward innovation (including extending periods of market exclusivity in some circumstances[26 27]), speed access to market, increase the collaboration between commercial developers and health services (including joint scientific advice with regulators), fund basic and translational research programmes, and increase the productivity of pharmaceutical development through reducing the cost and complexity of drug development.[28] In the UK, technology appraisals undertaken by NICE permit 'the innovative nature of a technology' to be considered as part of its deliberations, allowing a higher opportunity cost than would usually be accepted.[29] In addition, the UK Medicines and Healthcare Products Regulatory Agency has introduced an 'Early Access to Medicines Scheme' that will allow patients with serious conditions access to designated 'Promising Innovative Medicines' that have not yet been approved where there is a demonstration of unmet medical need[30]; this sits alongside the EMA's adaptive licensing pilot, allowing staged approvals incorporating real-world data.[31] Other initiatives at the European level include a revision to the 2001 European Clinical Trials Directive, addressing concerns about its negative impact on translational research,[32 33] and long-standing financial incentives to develop drugs for paediatric use[27] and orphan indications, which are now a significant and increasing proportion of all new drug approvals.[34 35]

Many of these policy initiatives are in the initial stages of implementation, and though industry bodies have generally welcomed their introduction, other commentators have identified areas of improvement for industry itself, including reducing the numbers of late-stage failures through improved collaboration both with academia and between commercial developers,[36] as well as improved trial design and better use of real-world registry data.[23] In all cases, current actions and initiatives will have long lead times to impact, and will need thorough and careful assessment to ensure they deliver increasing numbers of innovative drugs without unintended consequences on public health and health service delivery and affordability. Alongside this, commercial developers require a full and comprehensive understanding of what policymakers (including publicly funded health services, such as the NHS) and patients value in pharmaceutical innovation in order to direct their innovation efforts towards commercially viable end points. Understanding the interplay between the various stakeholders competing needs will be an important area for future research.

Contributors AJS conceived the original study idea, and DJW and OIM contributed to the development of the study design and methods. OIM, AS and TG collected the data and carried out the initial analysis, while DJW advised on the classification of new drugs where required and directed further

analysis. All authors were involved in the interpretation of the results. OIM and DJW produced the initial draft of the paper, which was then circulated repeatedly to all authors for critical revision. DJW, AS, TG, OIM and AJS read and approved the final version. All authors had full access to all of the study data (including statistical reports and tables), and can take responsibility for the integrity of the data and the accuracy of the analysis. DJW is the guarantor.

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