Declines in new drug launches: myth or reality? Retrospective observational study using 30 years of data from the United Kingdom.

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Declines in new drug launches: myth or reality? Retrospective observational study using 30 years of data from the United Kingdom.

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Keywords: Innovation; pharmaceutical; new drugs; drug launches; United Kingdom.

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ABSTRACT

Context: There is wide concern that pharmaceutical innovation is declining. Reported trends suggest that fewer new drugs have been launched over recent decades, despite increasing investment into research and development.

Objective: To describe trends in new drugs launched from 1982 to 2011 and test the hypothesis that the rate of new drug introductions has declined over the study period.

Design: Retrospective observational study.

Setting and data source: Database of new preparations added annually to the British National Formulary (BNF).

Main outcome measures: The number of new drugs entered each year, including new chemical entities (NCEs) and new biologic drugs, based on first appearance in the BNF.

Results: There was no significant linear trend in the number of new drugs introduced into the UK from 1982 to 2011. Following a dip in the mid-1980s (11-12 NCEs/new biologics introduced annually from 1985 to 1987), there was a variable increase in numbers of new drugs introduced annually to a peak of 34 in 1997. This peak was followed by a decline to approximately 20 new drugs per year between 2003 and 2006, with variable rates thereafter. Sensitivity analyses show that the increasing trend between the mid-80s and 1997 peak, and the subsequent declining trend to 2009, when examined individually, were both statistically significant. Extending the timeline further back with existing published data shows an overall slight increase in new drug introductions of 0.16 per year over the entire 1971 to 2011 period.

Conclusions: The purported 'innovation dip' is an artefact of the time periods previously studied. Reports of declining innovation need to be considered in the context of their timescale and perspective.

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ARTICLE SUMMARY

Article focus

- There is wide concern that pharmaceutical innovation is declining. Reported trends suggest that fewer new drugs have been launched over recent decades, despite increasing investment in R&D.

Key messages

- Whilst there are dips and peaks during specific time periods, the longer-term trend contradicts the widely held view that pharmaceutical innovation is declining, suggesting that annual numbers of newly launched drugs may have increased since the early 1970s.
- It is important to take into account the start and end dates included in analyses when interpreting time trends.

Strengths and limitations of this study

- This is the most up-to-date study of trends in the launch of new drugs in the UK, using 30 years of complete data. The results are consistent with data on US and worldwide drug launches.
- Although numbers of NCEs and new biologic agents launched are a useful indicator of trends in pharmaceutical innovation, they are not the sole metric. Our data do not differentiate between varying degrees of novelty or clinical importance, which may represent different levels of innovation.

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INTRODUCTION

Despite increasing pharmaceutical research and development (R&D) times, costs and spending,[1-5] there are concerns that these increasing efforts are not being reflected in the numbers of new drugs being brought to market. Indeed, it is widely reported that there has been a decline or dip in the rate of development of new drugs over recent decades.[1;6-10] Within the context of drug development, a new innovation is generally defined as the discovery, development and bringing to market of a new chemical entity (NCE)[11] defined as 'an active ingredient that has never been marketed... in any form'.[12] These new entities may be relatively minor modifications of existing drugs or represent radical new breakthroughs.

Much of the evidence for an 'innovation dip' comes from North America. Data from the United States Food & Drug Administration (FDA) show a downward trend in the number of NCEs introduced throughout the 1990s and at the start of the new millennium,[13,14] with the 18 new medicines approved in 2007 'the lowest figure in a quarter of a century'.[1] A decrease has also been noted in patented medicines granted market access in Canada between 1997 and 2008.[15] Worldwide data also indicate a decline in NCE introductions between 1982 and 2002/03;[16,17] however studies that include earlier decades suggest that this may be an artefact of a peak in 1996, with a return to historic levels thereafter.[5;18,19] More recent trends also show an increase in new biologic agents[5;13;16;18] and orphan products,[16] which suggests a shift in the focus of innovation. Papers focussing specifically on the United Kingdom (UK) report a decline in NCEs launched from 1960 to the late 1980s,[2;20,21] although the downward trend is considerably weakened by omitting the years 1960-63.[21] Numbers of NCEs authorised in the UK between 1972 and 1994 also show no consistent annual trend, although there was an increase in authorisations of new biological entities and products of biotechnology.[22] By contrast, numbers of all newly launched medicines, including new formulations of existing drugs and generic drugs, show no decline in new product introductions in the UK subsequent

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to the implementation of the Medicines Act (1968) in 1971, though there had been a fall in new drugs launched in the early 1960s following the thalidomide tragedy.[21] However, even though there is disagreement on the crude rate of drug launch, it does at least seem certain that the rate per R&D spend has declined. Scannell and colleagues calculated that the rate of new drugs per billion dollars spent on R&D has halved approximately every 9 years since the 1950s.[10]

We aimed to test the widely held belief that annual numbers of new drugs launched in the UK have declined or are declining. New drugs include both NCEs and new biologic agents, which are medicinal products created by biological processes rather than chemical synthesis. New biologics include vaccines, blood products, allergenic extracts, somatic cells, gene therapies, tissues, recombinant therapeutic proteins, or living cells used therapeutically.[23] We primarily considered the period from 1982 to 2011, but also incorporated existing published UK data[2;20,21] in order to consider the entire period from the implementation of the Medicines Act (1968) in 1971.

METHODS

Data collection and classification of entries

We obtained data on the numbers of new drugs (NCEs and new biologic 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, not all of which are available on the National Health Service (NHS). Information on the active ingredient for every item in the 'new preparations' section of each edition of the BNF from edition 3 in 1982 to 62 in 2011

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was obtained and entered onto a database. As the BNF also includes non-drug products, these were excluded (nutraceutical and medical foods, natural products, devices and diagnostic products – definitions are given in appendix 1) leaving only drugs (NCEs, existing chemical compounds, new salts or esters of existing chemical compounds, new biologic agents and existing biologic agents). Different dosages of the same product (e.g. 5mg and 10mg tablets) were counted once; different formulations of the same product, e.g. 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.

Definition of new drugs

Entries were classified as new (NCE or new biologic agent) by checking whether the drug substance appeared in previous editions of the BNF. New formulations, generic versions and new salts or esters of existing drugs were therefore not classified as new. Commercial pharmaceutical databases (PharmaProjects V5.2, Informa Healthcare. and Adis R&D Insight, Wolters Kluwer Pharma Solutions) were used to determine whether it was a new drug at the date of UK launch. Where preparations could not be found in commercial pharmaceutical databases, we undertook internet searches for scientific articles or patents relating to the substances.

Analysis

Time trends in the numbers of new drugs introduced in the UK were analysed using linear regression (SPSS v17.0, IBM). The primary analysis included all new drugs (NCEs and new biologics) added to the BNF from 1982 to 2011, with a sub-analysis of the 12-year periods pre-and post-1997. These time periods were selected to allow periods of equal length either side of the 1997 peak previously identified in the published literature on worldwide NCE

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launches.[16] The secondary analysis incorporated existing published UK data to include all new drug introductions from 1971 to 2011. Data on NCE launches was originally reported by Lis & Walker[2] using published sources including the BNF, the Monthly Index of Medical Specialties (MIMS; Haymarket Group) and Scrip (Informa), up to 1987; this was extended up to 1990 by the Centre for Medicines Research (CMR; now Centre for Medicines Research International, The Thomson Corporation, London).[20] Where there was overlap (1982 to 1990), we took the average of the two values.

RESULTS

Analysis 1: New drugs launched from 1982 to 2011

Figure 1 shows the number of new drugs launched annually in the UK from 1982 to 2011. The mean number of new drugs introduced each year was 23.9 (SE 1.16). The lowest was 11 in 1985, and the highest was 34 in 1997 and again in 2010. These data suggest only a minor upward linear trend in the annual numbers of new drugs launched, a result that was not statistically significant (new drugs launched: $y = -291 + 0.158 \times year$, $r = 0.218$, $p = 0.247$.

[Insert Figure 1 here]

Figure 1: New drugs launched in the UK from 1982 to 2011.

The analysis was repeated for the 12-year periods pre- and post-1997 (Figure 2). For 1985 to 1997 there was a statistically significant upward trend (new drugs launched: $y = -2.680 + 1.357 \times year$, $r = 0.738$, $p = 0.004$) while for 1997-2009 there was a statistically significant downward trend (new drugs launched: $y = 1567 - 0.769 \times year$, $r = 0.640$, $p = 0.018$).

[Insert Figure 2 here]

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Figure 2: Comparison of trends in new drugs launched pre- and post-1997

Analysis 2: New drugs launched from 1971 to 2011

This analysis used new drug data collected for this study from the BNF and NCE data from the CMR to extend our timeline back to 1971 (Figure 3). The mean number of new drugs introduced each year was 22.7 (SD 6.0). The lowest was 9 in 1985, and the highest was 34 in 1997 and 2010. These data showed a modest upward linear trend in the annual numbers of new drugs launched between 1971 and 2011, a result that was statistically significant. In addition, the rate of annual increase was very similar to that seen in our data for the period 1982-2011 (new drugs launched: $y = -296 + 0.160$ x year, $r = 0.321$, $p = 0.040$).

[Insert Figure 3 here]

Figure 3: New drugs launched in the UK from 1971 to 2011.

DISCUSSION

This is the most complete study of the number of new drug introductions in the UK, with 30 years complete data on new products. The BNF includes all medicinal products available for dispensing in the UK and is updated every six months, providing an accurate and reliable account of new drugs launched in the UK each year. We found no statistically significant linear trend in new drug introductions between 1982 and 2011, however a statistically significant, though modest upward trend was observed after extending the data further to include the years 1971 to 1981[20,21], contradicting the widely held view that the number of new medicines being launched is declining. Although there was a dip in new drug

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introductions from 1997 to 2009, this was preceded by an increase from 1985 to 1997. Additionally, the peak number of new drugs added to the BNF in 1997 was matched in 2010.

The main limitation of the study is that it only describes trends in launch and cannot attribute causes to changes; nor do we here disaggregate the data to explore different trends for different treatments and different disease groups. We included all new drugs in the analysis, but did not separate these into 'first-in-class' and 'me-too' drugs, which arguably represent different levels of innovation and significance. It has been asserted that the true 'innovation crisis' is due to the majority of new drugs being chemically similar to existing ones and offering few therapeutic gains.[19] We also excluded new indications for existing drugs, which in some cases can be as important as new drug launches.[24]

The findings are consistent with published reports of decreasing drug introductions, but only during the mid-1990s to early 2000s.[1;2;7;13;16,17;20] In particular, there was consistency with the CMR data for UK NCE launches up to 1990;[20] minor variations were likely to be due to differences in the data sources used. However, the data do not show a longer term decline. Clearly the start and end dates included in analyses can influence the interpretation of time trends. Furthermore, the trend gradients for the present study data and the longer time trend are very similar, only reaching statistical significance with sufficient data points. Taken together they indicate a gradual increase in the annual number of new drug introductions (approximately 0.16 new drugs per year).

Whilst the data do not show a reduction in absolute numbers of new drugs, it has been argued that the pharmaceutical industry has become less productive, as the number of new drugs launched has not increased relative to R&D time and expenditure or the availability of more advanced technology.[5;7;10;20;25] The cost per new drug produced is estimated to have grown at an annual compound rate of 13.5% since the 1950s.[5] This may be a cause for concern, and

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certainly for disappointment in the pharmaceutical industry. Advances at the drug discovery stage (e.g. the introduction of high throughput screening in the late 1980s and early '90s) in theory means that more new compounds can be investigated more quickly and the introduction of target-based drug discovery in the mid-1990s was a further promising breakthrough. However, drug development times have been increasing; the time taken to bring a new drug to market rose from approximately 3 years in 1960[2] to 12 years at the start of the new millennium,[3] reflecting more rigorous processes and requirements, and higher rejection rates in establishing the safety and efficacy of new drugs.[7] It has also been suggested that we are approaching the scientific and economic limits of innovation,[26] so there may be a ceiling limiting drug discovery.

The nature and context of pharmaceutical innovation have changed considerably over the last half century. We now need a further exploration of the detail of the nature of the drugs launched and of the events surrounding the innovation timeline to elucidate the factors underpinning the apparent steady state.

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Contributors: All authors were involved in the study conception and design, contributed substantially to the interpretation of the data and to subsequent drafts of the paper, and approved the final version. OM collected and analysed the data, and produced the initial draft of the paper. 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. DW is guarantor.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) DW, OM, SS and AS have support from the National Institute for Health Research for the submitted work; (2) DW, OM, SS and AS have no relationships that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) DW, OM, SS and AS have no non-financial interests that may be relevant to the submitted work.

Ethical approval: Not required.

Data sharing: Please contact the corresponding author: o.i.martino@bham.ac.uk

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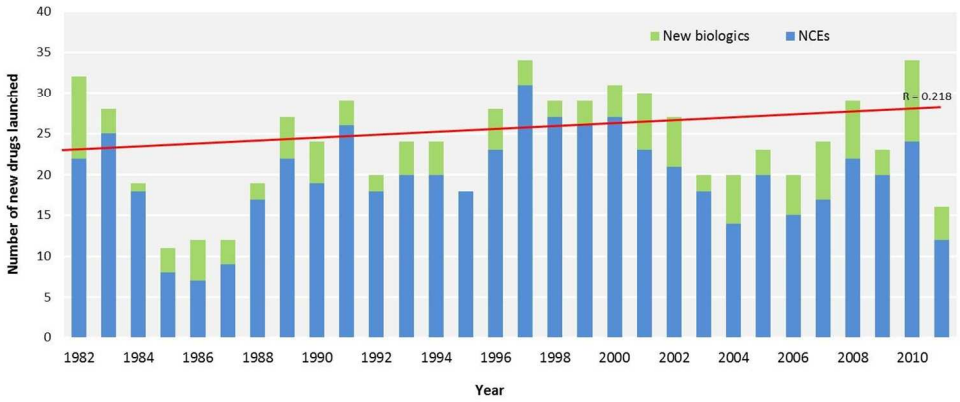

Figure 1: New drugs launched in the UK from 1982 to 2011.
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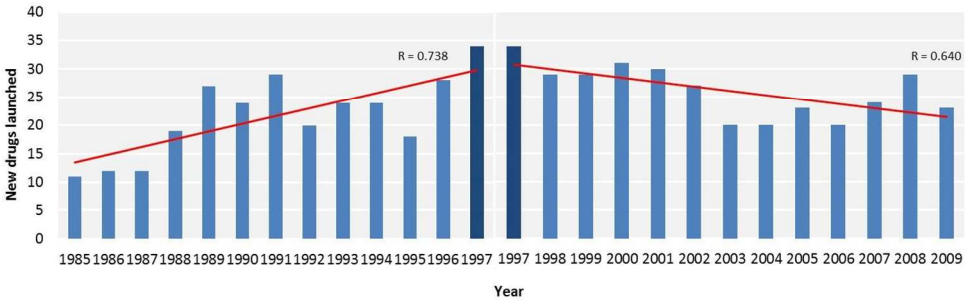

Figure 2: Comparison of trends in new drugs launched pre- and post-1997
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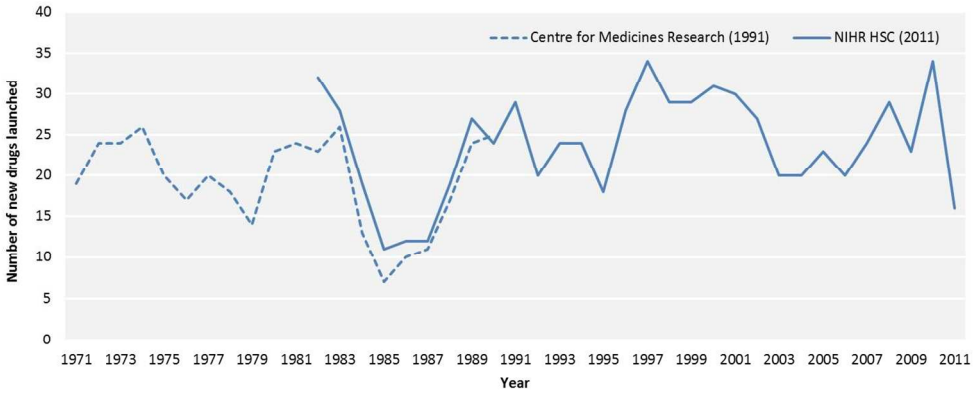

Figure 3: New drugs launched in the UK from 1971 to 2011.
249x107mm (150 x 150 DPI)

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Appendix 1: Definitions and frequencies of new products by category, 1982 to 2011.

Category		No. (%)	Definition
New drugs & biologics	NCEs	589 (21.1)	a) Appears in BNF for the first time and b) confirmed as being launched in the UK for the first time that year or late in the previous year, or may be defined as NCE on PharmaProjects.
	New biologics	127 (4.6)	Appears in BNF for the first time. Includes biologic drugs; blood products; vaccines e.g. first appearance for a particular disease; different strain of existing vaccine; new preparation technique for existing vaccine; and insulins e.g. new source of insulin; new type; new preparation technique.
Existing drugs & biologics	New salts/esters	31 (1.1)	Appears in BNF for the first time in that form, where previous forms of the compound have already been entered.
	Existing compounds	1,622 (58.2)	A drug substance that a) already appears in an earlier edition of the BNF, or b) is defined as *not* being a new chemical entity on Pharmaprojects at date of first launch.
	Existing biologics	217 (7.8)	Appears in earlier edition of BNF. Includes combinations of existing vaccines; and combinations of existing types of insulin.
Other substances	Nutraceuticals & medical foods	135 (4.8)	Includes vitamins, dietary supplements, foods for special diets, nutritionally complete or incomplete formulas for intravenous nutrition, and oral rehydration products.
	Natural products	22 (0.8)	A substance that occurs naturally and has not been chemically manipulated – although mechanical manipulation may have taken place.
	Devices	34 (1.2)	E.g. spacer devices, bandages. These have not been separated into new and existing technologies, as genuine innovation is more difficult to define with devices.
	Diagnostic products	4 (0.1)	E.g. tests for helicobacter pylori. These are products used for the detection and/or diagnosis of diseases rather than therapeutically.
	Uncoded	7 (0.3)	An entry where no specific substances (active or otherwise) have been named, e.g. 'cleansing solution'.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **PP.1-2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **P.2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **PP.4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **P.5**
Methods		
Study design	4	Present key elements of study design early in the paper **P.5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants **N/A**	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **PP.5-6**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **PP.5-6**
Bias	9	Describe any efforts to address potential sources of bias **N/A**
Study size	10	Explain how the study size was arrived at **PP.5-6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **P.6**
Statistical methods **P.6**	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants **N/A**	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data **P.7**	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data **P.7**	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results **P.7**	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses **PP.7-8**	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **P.8-9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **PP.9-10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **PP.9-10**
Generalisability	21	Discuss the generalisability (external validity) of the study results **P.9-10**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **P.11**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Decline in new drug launches: myth or reality? Retrospective observational study using 30 years of data from the United Kingdom.

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Keywords: Innovation; pharmaceutical; new drugs; drug launches; United Kingdom.

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ABSTRACT

Background: There is wide concern that pharmaceutical innovation is declining. Reported trends suggest that fewer new drugs have been launched over recent decades, despite increasing investment into research and development.

Objective: To describe trends in new drugs launched in the UK from 1982 to 2011 and test the hypothesis that the rate of new drug introductions has declined over the study period.

Design: Retrospective observational study.

Setting and data source: Database of new preparations added annually to the British National Formulary (BNF).

Main outcome measures: The number of new drugs entered each year, including new chemical entities (NCEs) and new biologic drugs, based on first appearance in the BNF.

Results: There was no significant linear trend in the number of new drugs introduced into the UK from 1982 to 2011. Following a dip in the mid-1980s (11-12 NCEs/new biologics introduced annually from 1985 to 1987), there was a variable increase in numbers of new drugs introduced annually to a peak of 34 in 1997. This peak was followed by a decline to approximately 20 new drugs per year between 2003 and 2006, and another peak in 2010. Extending the timeline further back with existing published data shows an overall slight increase in new drug introductions of 0.16 per year over the entire 1971 to 2011 period.

Conclusions: The purported 'innovation dip' is an artefact of the time periods previously studied. Reports of declining innovation need to be considered in the context of their timescale and perspective.

ARTICLE SUMMARY

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Article focus

- There is wide concern that pharmaceutical innovation is declining. Reported trends suggest that fewer new drugs have been launched over recent decades, despite increasing investment in R&D.

Key messages

- Whilst there are dips and peaks during specific time periods, the longer-term trend contradicts the widely held view that pharmaceutical innovation is declining, suggesting that annual numbers of newly launched drugs may have increased since the early 1970s.
- It is important to take into account the start and end dates included in analyses when interpreting time trends.

Strengths and limitations of this study

- This is the most up-to-date study of trends in the launch of new drugs in the UK, using 30 years of complete data. The results are consistent with data on US and worldwide drug launches.
- Although numbers of NCEs and new biologic agents launched are a useful indicator of trends in pharmaceutical innovation, they are not the sole metric. Our data do not differentiate between varying degrees of novelty or clinical importance, which may represent different levels of innovation.

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INTRODUCTION

Despite increasing pharmaceutical research and development (R&D) times, costs and spending,[1-5] there are concerns that these increasing efforts are not being reflected in the numbers of new drugs being brought to market. Indeed, it is widely reported that there has been a decline or dip in the rate of development of new drugs over recent decades.[1;6-10] Within the context of drug development, a new innovation is generally defined as the discovery, development and bringing to market of a new chemical entity (NCE);[11] 'an active ingredient that has never been marketed... in any form'.[12] These new entities may be relatively minor modifications of existing drugs or represent radical new breakthroughs.

Much of the evidence for an 'innovation dip' comes from North America. Data from the United States (US) Food & Drug Administration (FDA) show a downward trend in the number of NCEs introduced throughout the 1990s and at the start of the new millennium,[13,14] with the 18 new medicines approved in 2007 'the lowest figure in a quarter of a century'.[1] A decrease has also been noted in patented medicines granted market access in Canada between 1997 and 2008.[15] Worldwide data also indicate a decline in NCE introductions between 1982 and 2002/03;[16,17] however studies that include earlier decades suggest that this may be an artefact of a peak in 1996, with a return to historic levels thereafter.[5;18-20] More recent trends also show an increase in new biologic agents[5;13;16;18] and orphan products,[16] which suggests a shift in the focus of innovation. Papers focussing specifically on the United Kingdom (UK) report a decline in NCEs launched from 1960 to the late 1980s,[2;21,22] although the downward trend is considerably weakened by omitting the years 1960-63.[22] Numbers of NCEs authorised in the UK between 1972 and 1994 also show no consistent annual trend, although there was an increase in authorisations of new biological entities and products of biotechnology.[23] By contrast, numbers of all newly launched medicines, including new

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formulations of existing drugs and generic drugs, show no decline in new product introductions in the UK subsequent to the implementation of the Medicines Act 1968 in 1971, though there had been a fall in new drugs launched in the early 1960s following the thalidomide tragedy.[22] However, even though there is disagreement on the crude rate of drug launch, it does at least seem certain that the rate per R&D spend has declined. Scannell and colleagues calculated that the rate of new drugs per billion dollars spent on R&D (adjusted for inflation) has halved approximately every 9 years since the 1950s.[10]

We aimed to test the widely held belief that annual numbers of new drugs launched in the UK have declined or are declining. After the US, the UK is the next largest source of NCE development, accounting for 10.4% of pharmaceutical innovation worldwide.[24] It is recognised that prior to the implementation of the Medicines Act 1968 there was no formal licensing of medicines in the UK, other than those covered by the Therapeutic Substances Act 1956;[2] earlier evidence suggests that the Medicines Act 1968 would have slowed or even prevented some product introductions from the early 1970s onwards.[22] New drugs include both NCEs and new biologic agents, which are medicinal products created by biological processes rather than chemical synthesis. New biologics include vaccines, blood products, allergenic extracts, somatic cells, gene therapies, tissues, recombinant therapeutic proteins, or living cells used therapeutically.[25] We primarily considered the period from 1982 to 2011, but also incorporated existing published UK data[2;21,22] in order to consider the entire period from the implementation of the Medicines Act 1968 in 1971.

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METHODS

Data collection and classification of entries

We obtained data on the numbers of new drugs (NCEs and new biologic 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, not all of which are available on the National Health Service (NHS). Information on the active ingredient for every item in the 'new preparations' section of each edition of the BNF from edition 3 in 1982 to edition 62 in 2011 was obtained and entered onto a database. As the BNF also includes non-drug products, these were excluded (nutraceutical and medical foods, natural products, devices and diagnostic products – definitions are given in appendix 1) leaving only drugs (NCEs, existing chemical compounds, new salts or esters of existing chemical compounds, new biologic agents and existing biologic agents). Different dosages of the same product (e.g. 5mg and 10mg tablets) were counted once; different formulations of the same product, e.g. 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.

Definition of new drugs

Entries were classified as new (NCE or new biologic agent) by checking whether the drug substance appeared in previous editions of the BNF. New formulations, generic versions and new salts or esters of existing drugs were therefore not classified as new. Commercial pharmaceutical databases (PharmaProjects V5.2, Informa Healthcare. and Adis R&D Insight, Wolters Kluwer Pharma Solutions) were also used to determine whether a substance was a new drug at the date of UK launch. Where preparations could not be found in commercial

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pharmaceutical databases, we undertook internet searches for scientific articles or patents relating to the substances.

Analysis

Time trends in the numbers of new drugs introduced in the UK were analysed using linear regression (SPSS v17.0, IBM). Year (1971 to 2011) was treated as a continuous variable. The primary analysis included all new drugs (NCEs and new biologics) added to the BNF from 1982 to 2011, with a sub-analysis of the 1997-2006 decade for comparison with the published literature on worldwide NCE launches.[16] Analysis of covariance (ANCOVA) was used to test for homogeneity of regression before and after the 1997 peak, with number of new drugs as the dependent variable and year as the covariate, grouped by the periods either side of the peak (1982-1997 and 1998-2011). The secondary analysis incorporated existing published UK data to include all new drug introductions from 1971 to 2011. Data on NCE launches were originally reported by Lis & Walker[2] using published sources including the BNF, the Monthly Index of Medical Specialties (MIMS; Haymarket Group) and Scrip (Informa), up to 1987; this was extended up to 1990 by the Centre for Medicines Research (CMR; now Centre for Medicines Research International, The Thomson Corporation, London).[21] Where there was overlap (1982 to 1990), we took the average of the two values.

RESULTS

Analysis 1: New drugs launched from 1982 to 2011

Figure 1 shows the number of new drugs launched annually in the UK from 1982 to 2011. The mean number of new drugs introduced each year was 23.9 (SE 1.16). The lowest was 11 in 1985, and the highest was 34 in 1997 and again in 2010. These data suggest only a minor

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upward linear trend in the annual numbers of new drugs launched, a result that was not statistically significant (new drugs launched: y = -291 + 0.16 x year, r = 0.22, p = 0.25).

[Insert Figure 1 here]

Figure 1: New drugs launched in the UK from 1982 to 2011.

A sub-analysis for the 1997-2006 decade (Figure 2) revealed a statistically significant downward trend (new drugs launched: y = 3047 - 1.51 x year, r = 0.89, p = 0.001). ANCOVA showed no significant interaction between year and period ($F_{1,26} = 2.68$, p = 0.11), indicating equality of regression slopes pre- and post-1997. There was significant positive first-order autocorrelation in the residuals (Durbin-Watson statistic = 1.09, $p < 0.01$).

[Insert Figure 2 here]

Figure 2: New drugs launched between 1997 and 2006.

Analysis 2: New drugs launched from 1971 to 2011

This analysis used new drug data collected for this study from the BNF and NCE data from the CMR to extend our timeline back to 1971 (Figure 3). The mean number of new drugs introduced each year was 22.7 (SD 6.0). The lowest was 9 in 1985, and the highest was 34 in 1997 and 2010. These data showed a modest upward linear trend in the annual numbers of new drugs launched between 1971 and 2011, a result that was statistically significant. In addition, the rate of annual increase was very similar to that seen in our data for the period 1982-2011 (new drugs launched: y = -296 + 0.16 x year, r = 0.32, p = 0.04). Again, ANCOVA revealed no interaction between year and period, indicating equality of regression slopes pre- and post-1997 ($F_{1,37} = 2.35$, p = 0.13). There was significant positive first-order autocorrelation in the residuals (Durbin-Watson statistic = 1.10, $p < 0.01$).

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[Insert Figure 3 here]

Figure 3: New drugs launched in the UK from 1971 to 2011.

DISCUSSION

This is the most complete study of the number of new drug introductions in the UK, with 30 years complete data on new products. The BNF includes all medicinal products available for dispensing in the UK and is updated every six months, providing an accurate and reliable account of new drugs launched in the UK each year. We found no statistically significant linear trend in new drug introductions between 1982 and 2011, however a statistically significant, though modest upward trend was observed after extending the data further to include the years 1971 to 1981,[21,22] contradicting the widely held view that the number of new medicines being launched is declining. Although there was indeed a dip in new drug introductions during the decade from 1997 to 2006, this was largely an artefact of a peak in 1997, which was itself preceded by an unusually low number of launches in 1985-87. Additionally, the peak number of new drugs added to the BNF in 1997 was matched in 2010.

The main limitation of the study is that it only describes trends in launch and cannot attribute causes to changes; nor do we here disaggregate the data to explore different trends for different treatments and different disease groups. There are nonetheless key events during the timeline that should be noted, as they may provide some insight into the observed trends. Despite the implementation of the Medicines Act 1968, it has been argued that the thalidomide crisis did not lead to more rigorous drug regulation; instead, there was a culture of 'reluctant regulation' which was linked to trust and optimism concerning the safety of new drugs, and avoiding potential conflicts with industry interest.[26,27] This arrangement was

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disrupted by the practolol disaster of the early 1980s, which resulted in approximately 2,450 reports of adverse reactions including 40 deaths,[26] and the withdrawal of four NCEs worldwide in 1983 due to safety concerns[2;28] and may partly explain the low number of new drugs launched during 1985-1987.[27] The European Agency for the Evaluation of Medicinal Products (European Medicines Agency [EMA] since 2004) was set up with funding from the European Union and the pharmaceutical industry to integrate the work of existing national medicine regulatory bodies, and may also have impacted upon new drug approvals and launches following its inception in 1995. Changes in drug review processes may partially account for the peak in new drugs launched in the mid-1990s, and the generally higher levels observed in the latter half of the timeline. For example, faster approval times by the FDA following the global AIDS epidemic[29] and the introduction of the Prescription Drug User Fee Acts from 1992[30] may have influenced worldwide marketing approaches, including decisions to seek new drug licenses; while in Europe, a new review system implemented by the EMA in 2006 attempted to reduce approval times for innovative drugs offering significant clinical benefit.[31] Increased innovation could also be driven by policy, such as the EU Regulation on orphan medicinal products, which exists to stimulate research and development into drugs for rare conditions.[31,32]

We included all new drugs in the analysis, but did not separate these into 'first-in-class' and 'me-too' drugs, which arguably represent different levels of innovation and significance. It has been asserted that the true 'innovation crisis' is due to the majority of new drugs being chemically similar to existing ones and offering few therapeutic gains.[19] Yet data from the FDA show that the percentage of priority products (i.e. those that appear to represent an advance over available therapies)[12] reached a 30-year high during 2005-09, at almost 50% of total new drug approvals.[20] We also excluded incremental innovation to existing drugs, such as new indications and formulations, which in some cases can be as important as new drug

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launches in terms of clinical and economic benefits.[33,34] Berndt and colleagues demonstrated an overall increase in the number of supplementary new drug approvals for new indications for three major drug classes (ACE inhibitors, histamine H_2-antagonists/proton-pump inhibitors, and selective serotonin/norepinephrine reuptake inhibitors) since the early 1990s, suggesting that the value of incremental innovation may be overlooked when assessing productivity trends for pharmaceutical R&D.[34] It should nevertheless be noted that there is no standard framework for assessing the therapeutic value of drugs developed over such a broad time frame and variety of classes.[24]

The findings are consistent with published reports of decreasing drug introductions, but only during the mid-1990s to early 2000s.[1;2;7;13;16,17;21] In particular, there was consistency with the CMR data for UK NCE launches up to 1990;[21] minor variations were likely to be due to differences in the data sources used. However, the data do not show a longer term decline, but instead support more recent analyses suggesting a return to historic levels following a peak around 1997.[5;18-20] Clearly the start and end dates included in analyses can influence the interpretation of time trends. Furthermore, the trend gradients for the present study data and the longer time trend are very similar, only reaching statistical significance with sufficient data points. Taken together they indicate a gradual increase in the annual number of new drug introductions (approximately 0.16 new drugs per year). This is in line with a recent forecasting analysis, which predicts an increase in new drug launches in the 2012-2016 period compared with the previous five years to 2011.[35]

Whilst the data do not show a reduction in absolute numbers of new drugs, it has been argued that the pharmaceutical industry has become less productive, as the number of new drugs launched has not increased relative to R&D time and expenditure or the availability of more advanced technology.[5;7;10;21;36] The cost per new drug produced is estimated to have grown at an annual compound rate of 13.4% since the 1950s; adjusting for inflation (3.7% per year)

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and other cost increases such as regulation (8.3% per year) increases the estimated cost per new drug considerably.[5] This may be a cause for concern, and certainly for disappointment in the pharmaceutical industry. Advances at the drug discovery stage (e.g. the introduction of high throughput screening in the late 1980s and early '90s) in theory means that more new compounds can be investigated more quickly and the introduction of target-based drug discovery in the mid-1990s was a further promising breakthrough. However, drug development times have been increasing; the time taken to bring a new drug to market rose from approximately 3 years in 1960[2] to 12 years at the start of the new millennium.[3] Notwithstanding the EMA's (and FDA's) attempts to accelerate approvals these may reflect more rigorous processes and requirements, and higher rejection rates in establishing the safety and efficacy of new drugs.[7] It has also been suggested that we are approaching the scientific and economic limits of innovation,[37] so there may be a ceiling limiting drug discovery.

The nature and context of pharmaceutical innovation have changed considerably over the last half century. We now need a further exploration of the detail of the nature of the drugs launched and of the events surrounding the innovation timeline to elucidate the factors underpinning the apparent steady state.

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Contributors: All authors were involved in the study conception and design, contributed substantially to the interpretation of the data and to subsequent drafts of the paper, and approved the final version. OM collected and analysed the data, and produced the initial draft of the paper. All authors had full access to all of the study data (including statistical reports

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and tables), and can take responsibility for the integrity of the data and the accuracy of the analysis. DW is guarantor.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) DW, OM, SS and AS have support from the National Institute for Health Research for the submitted work; (2) DW, OM, SS and AS have no relationships that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) DW, OM, SS and AS have no non-financial interests that may be relevant to the submitted work.

Ethical approval: Not required.

Data sharing: Please contact the corresponding author: o.i.martino@bham.ac.uk

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ABSTRACT

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Setting and data source: Database of new preparations added annually to the British National Formulary (BNF).

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- Whilst there are dips and peaks during specific time periods, the longer-term trend contradicts the widely held view that pharmaceutical innovation is declining, suggesting that annual numbers of newly launched drugs may have increased since the early 1970s.
- It is important to take into account the start and end dates included in analyses when interpreting time trends.

Strengths and limitations of this study

- This is the most up-to-date study of trends in the launch of new drugs in the UK, using 30 years of complete data. The results are consistent with data on US and worldwide drug launches.
- Although numbers of NCEs and new biologic agents launched are a useful indicator of trends in pharmaceutical innovation, they are not the sole metric. Our data do not differentiate between varying degrees of novelty or clinical importance, which may represent different levels of innovation.

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INTRODUCTION

Despite increasing pharmaceutical research and development (R&D) times, costs and spending,[1-5] there are concerns that these increasing efforts are not being reflected in the numbers of new drugs being brought to market. Indeed, it is widely reported that there has been a decline or dip in the rate of development of new drugs over recent decades.[1;6-10] Within the context of drug development, a new innovation is generally defined as the discovery, development and bringing to market of a new chemical entity (NCE);[11] 'an active ingredient that has never been marketed... in any form'.[12] These new entities may be relatively minor modifications of existing drugs or represent radical new breakthroughs.

Much of the evidence for an 'innovation dip' comes from North America. Data from the United States (US) Food & Drug Administration (FDA) show a downward trend in the number of NCEs introduced throughout the 1990s and at the start of the new millennium,[13,14] with the 18 new medicines approved in 2007 'the lowest figure in a quarter of a century'.[1] A decrease has also been noted in patented medicines granted market access in Canada between 1997 and 2008.[15] Worldwide data also indicate a decline in NCE introductions between 1982 and 2002/03;[16,17] however studies that include earlier decades suggest that this may be an artefact of a peak in 1996, with a return to historic levels thereafter.[5;18-20] More recent trends also show an increase in new biologic agents[5;13;16;18] and orphan products,[16] which suggests a shift in the focus of innovation. Papers focussing specifically on the United Kingdom (UK) report a decline in NCEs launched from 1960 to the late 1980s,[2;21,22] although the downward trend is considerably weakened by omitting the years 1960-63.[22] Numbers of NCEs authorised in the UK between 1972 and 1994 also show no consistent annual trend, although there was an increase in authorisations of new biological entities and products of biotechnology.[23] By contrast, numbers of all newly launched medicines, including new

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formulations of existing drugs and generic drugs, show no decline in new product introductions in the UK subsequent to the implementation of the Medicines Act 1968 in 1971, though there had been a fall in new drugs launched in the early 1960s following the thalidomide tragedy.[22] However, even though there is disagreement on the crude rate of drug launch, it does at least seem certain that the rate per R&D spend has declined. Scannell and colleagues calculated that the rate of new drugs per billion dollars spent on R&D (adjusted for inflation) has halved approximately every 9 years since the 1950s.[10]

We aimed to test the widely held belief that annual numbers of new drugs launched in the UK have declined or are declining. After the US, the UK is the next largest source of NCE development, accounting for 10.4% of pharmaceutical innovation worldwide.[24] It is recognised that prior to the implementation of the Medicines Act 1968 there was no formal licensing of medicines in the UK, other than those covered by the Therapeutic Substances Act 1956;[2] earlier evidence suggests that the Medicines Act 1968 would have slowed or even prevented some product introductions from the early 1970s onwards.[22] New drugs include both NCEs and new biologic agents, which are medicinal products created by biological processes rather than chemical synthesis. New biologics include vaccines, blood products, allergenic extracts, somatic cells, gene therapies, tissues, recombinant therapeutic proteins, or living cells used therapeutically.[25] We primarily considered the period from 1982 to 2011, but also incorporated existing published UK data[2;21,22] in order to consider the entire period from the implementation of the Medicines Act 1968 in 1971.

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METHODS

Data collection and classification of entries

We obtained data on the numbers of new drugs (NCEs and new biologic 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, not all of which are available on the National Health Service (NHS). Information on the active ingredient for every item in the 'new preparations' section of each edition of the BNF from edition 3 in 1982 to edition 62 in 2011 was obtained and entered onto a database. As the BNF also includes non-drug products, these were excluded (nutraceutical and medical foods, natural products, devices and diagnostic products – definitions are given in appendix 1) leaving only drugs (NCEs, existing chemical compounds, new salts or esters of existing chemical compounds, new biologic agents and existing biologic agents). Different dosages of the same product (e.g. 5mg and 10mg tablets) were counted once; different formulations of the same product, e.g. 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.

Definition of new drugs

Entries were classified as new (NCE or new biologic agent) by checking whether the drug substance appeared in previous editions of the BNF. New formulations, generic versions and new salts or esters of existing drugs were therefore not classified as new. Commercial pharmaceutical databases (PharmaProjects V5.2, Informa Healthcare. and Adis R&D Insight, Wolters Kluwer Pharma Solutions) were also used to determine whether a substance was a new drug at the date of UK launch. Where preparations could not be found in commercial

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pharmaceutical databases, we undertook internet searches for scientific articles or patents relating to the substances.

Analysis

Time trends in the numbers of new drugs introduced in the UK were analysed using linear regression (SPSS v17.0, IBM). Year (1971 to 2011) was treated as a continuous variable. The primary analysis included all new drugs (NCEs and new biologics) added to the BNF from 1982 to 2011, with a sub-analysis of the 1997-2006 decade for comparison with the published literature on worldwide NCE launches.[16] Analysis of covariance (ANCOVA) was used to test for homogeneity of regression before and after the 1997 peak, with number of new drugs as the dependent variable and year as the covariate, grouped by the periods either side of the peak (1982-1997 and 1998-2011). The secondary analysis incorporated existing published UK data to include all new drug introductions from 1971 to 2011. Data on NCE launches were originally reported by Lis & Walker[2] using published sources including the BNF, the Monthly Index of Medical Specialties (MIMS; Haymarket Group) and Scrip (Informa), up to 1987; this was extended up to 1990 by the Centre for Medicines Research (CMR; now Centre for Medicines Research International, The Thomson Corporation, London).[21] Where there was overlap (1982 to 1990), we took the average of the two values.

RESULTS

Analysis 1: New drugs launched from 1982 to 2011

Figure 1 shows the number of new drugs launched annually in the UK from 1982 to 2011. The mean number of new drugs introduced each year was 23.9 (SE 1.16). The lowest was 11 in 1985, and the highest was 34 in 1997 and again in 2010. These data suggest only a minor

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upward linear trend in the annual numbers of new drugs launched, a result that was not statistically significant (new drugs launched: y = -291 + 0.16 x year, r = 0.22, p = 0.25).

[Insert Figure 1 here]

Figure 1: New drugs launched in the UK from 1982 to 2011.

A sub-analysis for the 1997-2006 decade (Figure 2) revealed a statistically significant downward trend (new drugs launched: y = 3047 - 1.51 x year, r = 0.89, p = 0.001). ANCOVA showed no significant interaction between year and period ($F_{1,26} = 2.68$, p = 0.11), indicating equality of regression slopes pre- and post-1997. There was significant positive first-order autocorrelation in the residuals (Durbin-Watson statistic = 1.09, $p < 0.01$).

[Insert Figure 2 here]

Figure 2: New drugs launched between 1997 and 2006.

Analysis 2: New drugs launched from 1971 to 2011

This analysis used new drug data collected for this study from the BNF and NCE data from the CMR to extend our timeline back to 1971 (Figure 3). The mean number of new drugs introduced each year was 22.7 (SD 6.0). The lowest was 9 in 1985, and the highest was 34 in 1997 and 2010. These data showed a modest upward linear trend in the annual numbers of new drugs launched between 1971 and 2011, a result that was statistically significant. In addition, the rate of annual increase was very similar to that seen in our data for the period 1982-2011 (new drugs launched: y = -296 + 0.16 x year, r = 0.32, p = 0.04). Again, ANCOVA revealed no interaction between year and period, indicating equality of regression slopes pre- and post-1997 ($F_{1,37} = 2.35$, p = 0.13). There was significant positive first-order autocorrelation in the residuals (Durbin-Watson statistic = 1.10, $p < 0.01$).

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[Insert Figure 3 here]

Figure 3: New drugs launched in the UK from 1971 to 2011.

DISCUSSION

This is the most complete study of the number of new drug introductions in the UK, with 30 years complete data on new products. The BNF includes all medicinal products available for dispensing in the UK and is updated every six months, providing an accurate and reliable account of new drugs launched in the UK each year. We found no statistically significant linear trend in new drug introductions between 1982 and 2011, however a statistically significant, though modest upward trend was observed after extending the data further to include the years 1971 to 1981,[21,22] contradicting the widely held view that the number of new medicines being launched is declining. Although there was indeed a dip in new drug introductions during the decade from 1997 to 2006, this was largely an artefact of a peak in 1997, which was itself preceded by an unusually low number of launches in 1985-87. Additionally, the peak number of new drugs added to the BNF in 1997 was matched in 2010.

The main limitation of the study is that it only describes trends in launch and cannot attribute causes to changes; nor do we here disaggregate the data to explore different trends for different treatments and different disease groups. There are nonetheless key events during the timeline that should be noted, as they may provide some insight into the observed trends. Despite the implementation of the Medicines Act 1968, it has been argued that the thalidomide crisis did not lead to more rigorous drug regulation; instead, there was a culture of 'reluctant regulation' which was linked to trust and optimism concerning the safety of new drugs, and avoiding potential conflicts with industry interest.[26,27] This arrangement was

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disrupted by the practolol disaster of the early 1980s, which resulted in approximately 2,450 reports of adverse reactions including 40 deaths,[26] and the withdrawal of four NCEs worldwide in 1983 due to safety concerns[2;28] and may partly explain the low number of new drugs launched during 1985-1987.[27] The European Agency for the Evaluation of Medicinal Products (European Medicines Agency [EMA] since 2004) was set up with funding from the European Union and the pharmaceutical industry to integrate the work of existing national medicine regulatory bodies, and may also have impacted upon new drug approvals and launches following its inception in 1995. Changes in drug review processes may partially account for the peak in new drugs launched in the mid-1990s, and the generally higher levels observed in the latter half of the timeline. For example, faster approval times by the FDA following the global AIDS epidemic[29] and the introduction of the Prescription Drug User Fee Acts from 1992[30] may have influenced worldwide marketing approaches, including decisions to seek new drug licenses; while in Europe, a new review system implemented by the EMA in 2006 attempted to reduce approval times for innovative drugs offering significant clinical benefit.[31] Increased innovation could also be driven by policy, such as the EU Regulation on orphan medicinal products, which exists to stimulate research and development into drugs for rare conditions.[31,32]

We included all new drugs in the analysis, but did not separate these into 'first-in-class' and 'me-too' drugs, which arguably represent different levels of innovation and significance. It has been asserted that the true 'innovation crisis' is due to the majority of new drugs being chemically similar to existing ones and offering few therapeutic gains.[19] Yet data from the FDA show that the percentage of priority products (i.e. those that appear to represent an advance over available therapies)[12] reached a 30-year high during 2005-09, at almost 50% of total new drug approvals.[20] We also excluded incremental innovation to existing drugs, such as new indications and formulations, which in some cases can be as important as new drug

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launches in terms of clinical and economic benefits.[33,34] Berndt and colleagues demonstrated an overall increase in the number of supplementary new drug approvals for new indications for three major drug classes (ACE inhibitors, histamine H_2-antagonists/proton-pump inhibitors, and selective serotonin/norepinephrine reuptake inhibitors) since the early 1990s, suggesting that the value of incremental innovation may be overlooked when assessing productivity trends for pharmaceutical R&D.[34] It should nevertheless be noted that there is no standard framework for assessing the therapeutic value of drugs developed over such a broad time frame and variety of classes.[24]

The findings are consistent with published reports of decreasing drug introductions, but only during the mid-1990s to early 2000s.[1;2;7;13;16,17;21] In particular, there was consistency with the CMR data for UK NCE launches up to 1990;[21] minor variations were likely to be due to differences in the data sources used. However, the data do not show a longer term decline, but instead support more recent analyses suggesting a return to historic levels following a peak around 1997.[5;18-20] Clearly the start and end dates included in analyses can influence the interpretation of time trends. Furthermore, the trend gradients for the present study data and the longer time trend are very similar, only reaching statistical significance with sufficient data points. Taken together they indicate a gradual increase in the annual number of new drug introductions (approximately 0.16 new drugs per year). This is in line with a recent forecasting analysis, which predicts an increase in new drug launches in the 2012-2016 period compared with the previous five years to 2011.[35]

Whilst the data do not show a reduction in absolute numbers of new drugs, it has been argued that the pharmaceutical industry has become less productive, as the number of new drugs launched has not increased relative to R&D time and expenditure or the availability of more advanced technology.[5;7;10;21;36] The cost per new drug produced is estimated to have grown at an annual compound rate of 13.4% since the 1950s; adjusting for inflation (3.7% per year)

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and other cost increases such as regulation (8.3% per year) increases the estimated cost per new drug considerably.[5] This may be a cause for concern, and certainly for disappointment in the pharmaceutical industry. Advances at the drug discovery stage (e.g. the introduction of high throughput screening in the late 1980s and early '90s) in theory means that more new compounds can be investigated more quickly and the introduction of target-based drug discovery in the mid-1990s was a further promising breakthrough. However, drug development times have been increasing; the time taken to bring a new drug to market rose from approximately 3 years in 1960[2] to 12 years at the start of the new millennium.[3] Notwithstanding the EMA's (and FDA's) attempts to accelerate approvals these may reflect more rigorous processes and requirements, and higher rejection rates in establishing the safety and efficacy of new drugs.[7] It has also been suggested that we are approaching the scientific and economic limits of innovation,[37] so there may be a ceiling limiting drug discovery.

The nature and context of pharmaceutical innovation have changed considerably over the last half century. We now need a further exploration of the detail of the nature of the drugs launched and of the events surrounding the innovation timeline to elucidate the factors underpinning the apparent steady state.

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and tables), and can take responsibility for the integrity of the data and the accuracy of the analysis. DW is guarantor.

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Ethical approval: Not required.

Data sharing: Please contact the corresponding author: o.i.martino@bham.ac.uk

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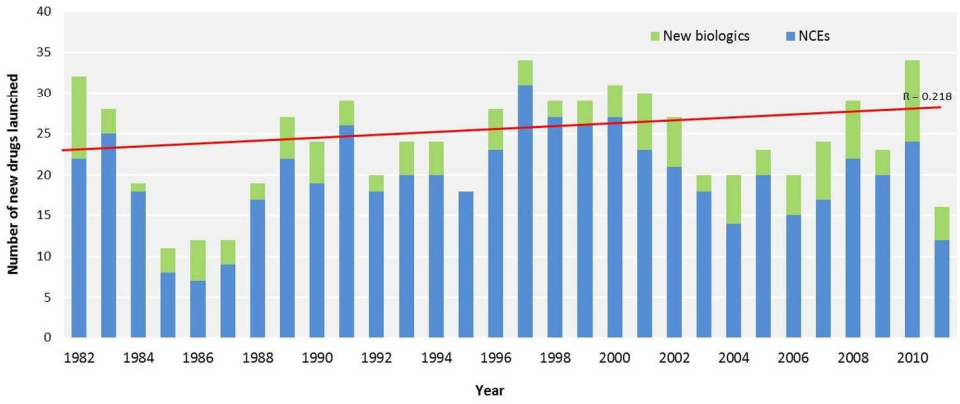

Figure 1: New drugs launched in the UK from 1982 to 2011.
211x90mm (300 x 300 DPI)

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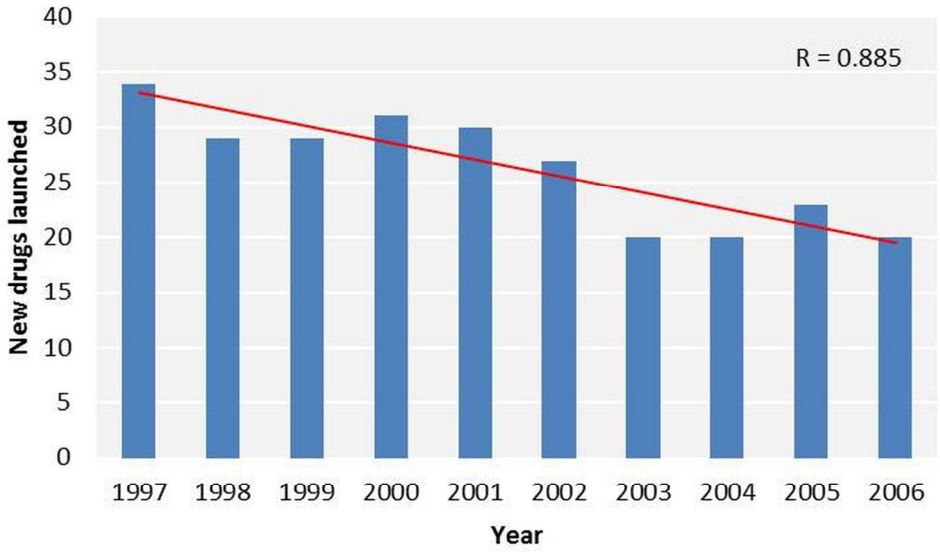

Figure 2: New drugs launched between 1997 and 2006.
150x90mm (300 x 300 DPI)

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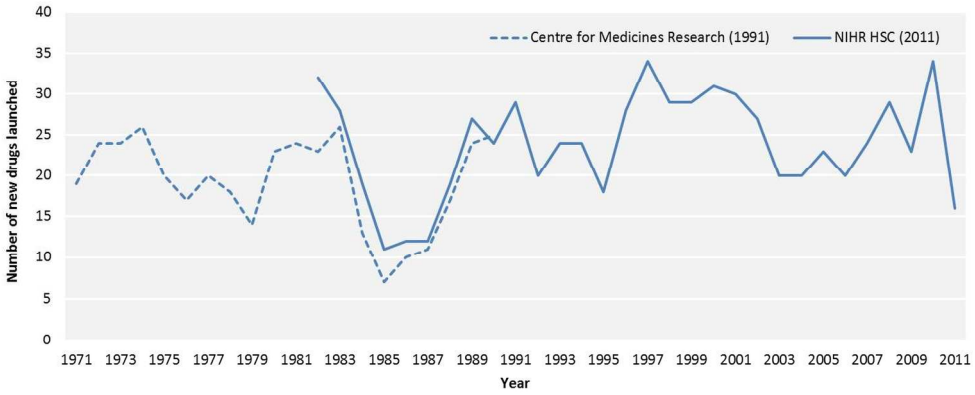

Figure 3: New drugs launched in the UK from 1971 to 2011.
209x90mm (300 x 300 DPI)

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Appendix 1: Definitions and frequencies of new products by category, 1982 to 2011.

Category		No. (%)	Definition
New drugs & biologics	NCEs	589 (21.1)	a) Appears in BNF for the first time and b) confirmed as being launched in the UK for the first time that year, or defined as NCE on commercial pharmaceutical databases. Includes new drug substances intended for therapeutic use; diagnostic agents are excluded (see 'Diagnostic products' below. May include new isomers of existing drugs.
	New biologics	127 (4.6)	Appears in BNF for the first time. Includes biologic drugs; blood products; vaccines e.g. first appearance for a particular disease; different strain of existing vaccine; new preparation technique for existing vaccine; and insulins e.g. new source of insulin; new type; new preparation technique.
Existing drugs & biologics	New salts/esters	31 (1.1)	Appears in BNF for the first time in that form, where previous forms of the compound have already been entered.
	Existing compounds	1,622 (58.2)	A drug substance that a) already appears in an earlier edition of the BNF, or b) is defined as *not* being a new chemical entity on commercial pharmaceutical databases at date of first launch.
	Existing biologics	217 (7.8)	Appears in earlier edition of BNF. Includes combinations of existing vaccines; and combinations of existing types of insulin.
Other substances	Nutraceuticals & medical foods	135 (4.8)	Includes vitamins, dietary supplements, foods for special diets, nutritionally complete or incomplete formulas for intravenous nutrition, and oral rehydration products.
	Natural products	22 (0.8)	A substance that occurs naturally and has not been chemically manipulated – although mechanical manipulation may have taken place.
	Devices	34 (1.2)	E.g. spacer devices, bandages. These have not been separated into new and existing technologies, as genuine innovation is more difficult to define with devices.
	Diagnostic products	4 (0.1)	E.g. tests for helicobacter pylori. These are products used for the detection and/or diagnosis of diseases rather than therapeutically. Does not include imaging agents as they do not appear in the BNF.
	Uncoded	7 (0.3)	An entry where no specific substances (active or otherwise) have been named, e.g. 'cleansing solution'.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **PP.1-2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **P.2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **PP.4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **P.5**
Methods		
Study design	4	Present key elements of study design early in the paper **P.5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants **N/A**	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **PP.6-7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **PP.6-7**
Bias	9	Describe any efforts to address potential sources of bias **N/A**
Study size	10	Explain how the study size was arrived at **PP.6-7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **P.7**
Statistical methods **P.7**	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants **N/A**	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data **PP.7-8**	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data **PP.7-8**	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results **PP.7-8**	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses **P.8**	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **P.9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **PP.9-11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **PP.11-12**
Generalisability	21	Discuss the generalisability (external validity) of the study results **P.11-12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **P.13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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