New active substances authorized in the United Kingdom between 1972 and 1994

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Aims The study was undertaken to assemble a list of all new active medicinal substances authorised in the United Kingdom between 1972 and 1994; to assess whether the pattern of introductions had changed; and to examine withdrawal rates and the reasons for withdrawal.

Methods The identities of those new active substances whose manufacturers had obtained Product Licences between 1972 and 1994 were sought from the Medicines Control Agency's product data-base. For each substance relevant information was retrieved including the year of granting the Product Licence, its therapeutic class, whether currently authorised (and, if not, reason for withdrawal), and its nature (chemical, biological etc.).

Results The Medicines Control Agency's data-base was cross-checked against two other data-bases for completeness. A total of 583 new active substances (in 579 products) were found to have been authorised over the study period. The annual rates of authorisation varied widely (9 to 40 per year). Whilst there was no evidence for any overall change in the annual rates of authorising new chemical entities, there has been a trend for increasing numbers of new products of biological origin to be authorised in recent years. Fifty-nine of the 583 new active substances have been withdrawn (1 each for quality and efficacy, 22 for safety, and 35 for commercial reasons).

Conclusions For reasons that are unclear there is marked heterogeneity in the annual rates of authorisation of new active substances. Their 10 year survival is approximately 88% with withdrawals being, predominantly, for commercial or safety reasons. This confirms the provisional nature of assessments about safety at the time when a new active substance is introduced into routine clinical practice, and emphasises the importance of pharmacovigilance.

Keywords: new active substances, new chemical entities, new biological substances, new biotechnology agents, product licences, safety withdrawals

Introduction

Since 1972 the manufacturers of all medicines containing new active substances (NASs) have been required, prior to marketing their products in the UK, to submit comprehensive data to support their applications for a Product Licence. Several attempts have been made to identify NASs introduced into the UK over the period 1960 to 1993 [1–4]. None, however, has provided a full picture of recent and relevant licensing practice. First, these studies do not encompass the relevant period. Secondly, they have relied on identifying newly marketed NASs from sources that may not be comprehensive. They do not, therefore, include NASs which, though licensed in the UK, have never been commercialised. Thirdly, some have included active substances authorised after 1972 but which had been marketed in the UK before then.

The present study was undertaken with three objectives. First, an attempt has been made to assemble a complete list of all NASs whose manufacturers were granted Product Licences between 1972 and 1994. Secondly, we have tried to assess whether there has been a change in the pattern of NASs authorised during this time. Thirdly, we have investigated the fate of all fully authorised NASs in order to examine withdrawal rates, and the reasons for withdrawal. In particular, we sought to examine rates of withdrawal on grounds of either quality, efficacy or safety.

Methods

The definition of an NAS, used in this study, is an adaptation of the one approved by the European Commission [5]:-

'A new chemical, biological or pharmaceutical active substance includes:

- (i) a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product (in the UK),
- (ii) an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a

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medicinal product in (the UK) but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;

(iii) a biological substance previously authorised as a medicinal product in (the UK), but differing in molecular structure, nature of the source material, or manufacturing process;

(iv) a radiopharmaceutical substance which is a new radionuclide, or the ligand has a novel molecular structure, or the coupling mechanism to link the molecule and the radionuclide has not been previously authorised'.

This definition differs from that of the Commission only in so far as the words in parentheses ('the UK') have replaced 'the European Community'.

The identities of those NASs whose manufacturers had been granted a Product Licence between 1972 and 1994, were sought by scrutinising the Medicine Control Agency's (MCA) product data-base (PLUS) which contains details of over 77 000 products. Details of those Product Licences annotated as containing 'new actives', for the years 1972 to 1994, were retrieved. This primary source of authorised NASs, however, included products which had been available in the UK, according to the literature [6], before 1972. These were therefore excluded together with NASs in contact lens cleaning fluids.

For each relevant NAS the information recorded included:

Year of licensing This was the year in which the PL was granted for the first product containing the particular NAS.

British Approved Name

Therapeutic Class The classification adopted in the British National Formulary [7] was used but supplemented by an additional 'Diagnostics' category encompassing radiological contrast media, radiopharmaceuticals and other diagnostic agents. In some instances the same active substance is now included in more than one therapeutic class (e.g. timolol, prazosin). In such instances the therapeutic class relevant to the original indication has been used.

Currently Authorised Products were categorised as 'currently authorised' (as of August 1995) provided a contemporary Product Licence existed for them. Authorised products which are no longer promoted were therefore included.

Withdrawals The year that NASs were withdrawn from the market (either by voluntary surrender, or by involuntary suspension or revocation) were noted, together with the underlying reasons (i.e. on grounds of quality, safety, efficacy, or for commercial reasons). There are two instances where NASs have been withdrawn from the market (at the request of the CSM & MCA) but where the licence has not been formally surrendered. These are included as 'safety withdrawals'.

Innovative class Each NAS was categorised either as a new chemical entity (NCE), a new biological entity (NBE), or the product of biotechnology (BIOT). NBEs are therefore NASs where the active substances have been isolated from natural sources. BIOTs are those NASs synthesised from

microbiological sources, or mammalian cell lines, mainly by recombinant DNA techniques.

Total numbers of new product licences were calculated by year and the χ^2 test used to examine their homogeneity. Spearman's rank correlation (r_s) was used to test for monotonic increases or decreases in numbers with respect to time. The 23 years of the study from 1972 to 1994 were also divided into two 8-year periods (1972–79 and 1980–87) and one 7-year period (1988–94) and the results examined by period in order to highlight possible time related trends. The Kaplan-Meier estimate of the survival curve was used to illustrate the life of Product Licences, suitably adapted for the situation when only the years of licensing and withdrawal are available.

Results

Examination of the MCA's PLUS data-base revealed obvious omissions mainly arising from the period (before the inception of the MCA) when licensing records did not routinely include information about whether the 'active' substance was an NAS. The PLUS data-base was therefore cross-checked for completeness against two other sources. The first [1], an analysis of drug withdrawal (discontinuation) rates in the USA & UK and covering the period 1970 to 1988, yielded an additional 30 NASs not included in the primary data-base. The second, a data-base maintained by the Centre for Medicines Research [2], encompasses all products (including NASs) marketed between 1960 and 1988. A further 16 NASs, granted a full Product Licence between 1972 and 1988, were identified from this source. A total of 579 products, incorporating 583 NASs (four products each contained two NASs), were identified as having been authorised between 1972 and 1994. A copy of the full list can be obtained, on request, from the authors.

Licensing activities

The numbers of NASs authorised each year (Table 1) showed marked heterogeneity ($\chi^2_{22} = 61.2$, $2P < 0.001$) with a median of 26 (mean 25.3) per year and ranging from 9 (in 1984) to 40 (in 1989). The number of NCEs authorised each year (median 21 per annum) has also been very variable (Table 1). However, over the period 1972 to 1994 no consistent time-related trend was detected in the number of NASs ($r_s = 0.216$, $2P > 0.1$) or NCEs ($r_s = 0.030$, $2P > 0.1$) licensed annually. The median annual rates of NASs introduced for the periods 1972–79, 1980–87 and 1988–94 are 24, 17.5 and 34 per year respectively, indicating the more complex pattern of a fall and subsequent rise in these rates, which is partially responsible for the heterogeneity identified. Scrutiny of Table 1 indicates that the reduction in the numbers of authorised NASs was most substantial between 1983 and 1987. By contrast (Table 1) there has been an overall, and fairly consistent increase, in the annual rates of authorisation of both NBEs ($r_s = 0.392$, $2P = 0.065$) and BIOTs ($r_s = 0.875$, $2P < 0.002$).

The distribution of NASs between therapeutic classes is shown in Table 2. Products for the treatment of disorders of the cardiovascular system, the central nervous system, and

Table 1 Annual authorisations of new chemical entities (NCEs), new biological entities (NBEs) and products of biotechnology (BIOTs).

Year	Total*	NCE	NBE	BIOT
1972	33 (32)	31	2	0
1973	23 (23)	21	2	0
1974	30 (30)	29	1	0
1975	15 (15)	15	0	0
1976	19 (19)	18	1	0
1977	28 (28)	28	0	0
1978	25 (25)	25	0	0
1979	23 (23)	21	2	0
1980	26 (26)	26	0	0
1981	32 (32)	32	0	0
1982	32 (32)	28	2	2
1983	17 (17)	17	0	0
1984	9 (9)	9	0	0
1985	13 (13)	10	2	1
1986	18 (18)	15	1	2
1987	14 (14)	12	1	1
1988	29 (28)	27	0	2
1989	40 (40)	33	4	3
1990	37 (36)	31	3	3
1991	35 (35)	29	2	4
1992	28 (28)	21	3	4
1993	23 (23)	16	3	4
1994	34 (33)	31	1	2
Total	583 (579)	525	30	28

*Numbers in parentheses refer to products.

Table 2 Distribution between therapeutic classes of new active substances authorised between 1972 and 1994.

Therapeutic class	Total
Gastrointestinal	21
Cardiovascular	100
Respiratory	30
Central nervous	79
Infections	97
Endocrine	36
Obstetrics, gynaecology and urinary	18
Malignancy and immunosuppression	42
Nutrition and blood	16
Musculo-skeletal	32
Eye	7
Ear, nose and throat	5
Skin	35
Vaccines	15
Anaesthesia	19
Diagnostics	31

of infections predominate and together account for 47% of all NASs introduced during the period.

Withdrawals

Table 3 shows the 35 NASs whose manufacturers have surrendered their Product Licences for commercial reasons. Of these, nine were apparently never commercialised. The commercial withdrawals cover a wide range of therapeutic

classes but 10 were anti-infectives and seven cardiovascular agents.

The 24 NASs (23 products) withdrawn for reasons of quality, efficacy or safety are shown in Table 4. One NAS (each) was withdrawn for reasons of quality and efficacy. Twenty-two NASs (21 products) were withdrawn (Table 4) for safety reasons. The proportion of safety withdrawals thus represents 3.8% (22/583) of authorised NASs, or 3.6% (21/579) of authorised products. The median time between authorisation and removal from the market was 4 years (range less than 1 year to 13 years). Twenty NASs were withdrawn for reasons of clinical safety of which six involved nonsteroidal anti-inflammatory drugs (NSAIDs).

Discussion

This study aims to provide a comprehensive account of both the introduction, and the subsequent fate, of all NASs authorised with the grant of a Product Licence between 1972 and 1994. Our primary source of information, the MCA's PLUS data-base, in conjunction with two secondary sources, should have achieved this aim; if there are any omissions or errors they are unlikely to effect the picture presented and conclusions drawn.

The only analogous study [1] spanned the period (1970 to 1988) before, and after, the introduction of the statutory regulation of medicines in the UK. It included a number of products which were not NASs in 1972 and omits others which, according to our definition, should have been included; and it obviously could not take account of NASs introduced between 1989 and 1994. Our data on licensing are not strictly comparable with those of Tansey *et al.* [2]. First, the definition of an NAS used in the present study is slightly different. Secondly, the NAS data of Tansey *et al.* [2] are based on the year of marketing rather than the year of authorisation. Thirdly, our data-base includes NASs which, though licensed in the UK, were never commercialised. Nevertheless there is a very large measure of agreement between the two data-sets.

There is clear evidence that the annual rates of authorisation of new biological agents (both NBEs and BIOTs) have increased (Table 1) and, between 1989 and 1994, accounted for 19% of all licensed NASs. By contrast there has been no consistent change in the annual rate of licensing of NCEs. Table 1 shows, however, the marked decline in the numbers of NASs authorised annually between 1983 and 1987. A comparable decline, but delayed by 1 year, is discernible from the data of Tansey *et al.* [2]. There are, broadly, two possible explanations: either the Product Licence applications, submitted by manufacturers were reduced in number or quality; or the Committee on Safety of Medicines (CSM) adopted a more stringent approach in advising on the grant of Product Licences. The present study cannot distinguish between these possibilities.

The broad distribution (Table 2) of NASs, between therapeutic classes, is not surprising. Table 2 does not, however, indicate the many important advances within individual therapeutic classes that occurred during the period. There was also a notable fall in the introduction of new NSAIDs and β -adrenoceptor blockers presumably due to manufacturers' disinclination to invest in overcrowded

<i>British Approved Name</i>	<i>Therapeutic class</i>	<i>Year licenced</i>	<i>Year surrendered</i>
Azidocillin*	Infections	1972	1976
Amidephrine	Ear, nose and throat	1972	1976
Benapryzine	Central nervous	1973	1981
Meglumine iocarmate	Diagnostic	1973	1980
Butriptyline	Central nervous	1974	1988
Glibornuride	Endocrine	1975	1987
Fazadinium	Anaesthesia	1976	1984
Medigoxin	Cardiovascular	1976	1987
Carbuterol	Respiratory	1977	1992
Vidarabine	Infections	1977	1990
Metrizamide	Diagnostic	1977	1992
Lysine acetylsalicylate*	Musculo-skeletal	1978	1993
Mezlocillin	Infections	1979	1989
Sulphamoxole	Infections	1979	1985
Lidoflazine	Cardiovascular	1979	1989
Sissomycin	Infections	1979	1989
Diagnostic antigen	Diagnostic	1979	1989
Oxantel	Infections	1979	1989
Ciclobendazole*	Infections	1980	1989
Proquazone*	Musculo-skeletal	1980	1982
Difenoxin*	Gastro-intestinal	1980	1983
Idoxamic acid	Diagnostic	1980	1985
Latamoxef	Infections	1981	1991
Prenalterol	Cardiovascular	1981	1985
Glisoxepide	Endocrine	1981	1983
H-B Vax	Vaccine	1982	1992
Tetroxoprim*	Infections	1982	1991
Niceritrol*	Cardiovascular	1982	1982
Saralasin	Cardiovascular	1982	1992
Sulbenicillin	Infections	1984	1994
Xylose	Diagnostic	1984	1989
Dexbrompheniramine	Respiratory	1984	1989
Bentiromide (16.2.0)	Diagnostic	1985	1990
Guanfacine* (2.5.2)	Cardiovascular	1989	1991
Encainide* (2.3.2)	Cardiovascular	1990	1991

*Products apparently never commercialised.

therapeutic areas. The significant safety problems with the former, during the early 1980s, is likely to have been an important additional factor. By contrast, manufacturers' continued development of novel penicillins and cephalosporins, which are also heavily oversubscribed, has been followed by substantial commercial withdrawals presumably as a result of an inability to penetrate well-established markets.

A small number of products, though authorised, have never been commercialised in the UK. There appear to be several reasons for this. In one instance safety problems emerged between authorisation and marketing. In one case marketing was prevented by a patent dispute. In two other instances, the original dosage forms were never marketed but subsequently sustained release preparations were introduced in their place. In others a UK Product Licence was probably sought in order to encourage acceptance in other world markets, or to obtain export certification.

Overall surrender of Product Licences, for commercial reasons (Table 3), has involved a relatively small proportion (6.0%) of licensed NASs (35/583). Many appear to have occurred as a result of failure to achieve sufficient market penetration, or because they had become superseded. In

some instances manufacturers appear to have rationalised their portfolio of products, and company mergers may have contributed to this.

The 21 product safety withdrawals (involving 22 NASs), identified in the present study, have not previously been formally documented. The withdrawals (Table 4) fall into two categories. The two non-clinical withdrawals (polidexide and brotizolam) would not have occurred in the context of contemporary (1996) UK and European regulatory requirements. Polidexide's genotoxic impurities would now be identified at the time of authorisation and probably earlier. The carcinogenicity of brotizolam in rats would now, likewise, be known at the time of licensing. However, for a limited period during the early 1980s, licences for non-genotoxic NASs were granted subject to an agreement with the licence-holder that carcinogenicity studies had started and would be reported in due course. This approach would only be adopted, nowadays, under exceptional circumstances.

Several studies [1, 3, 4, 8] have attempted to compare safety withdrawal rates in the USA, UK and elsewhere. One [3] has concluded that there has been little difference. One

Table 3 Commercial withdrawals of new active substances authorised between 1972 and 1994.

Table 4 New active substances authorised between 1972 and 1994 and withdrawn for non-commercial reasons.

<i>Year licensed</i>	<i>Year withdrawn</i>	<i>British Approved Name</i>	<i>Therapeutic class</i>	<i>Reason</i>
1972	1984	Alphaxolone plus Alphadolone	Anaesthetic	Safety (anaphylaxis)
1974	1979	Oxolinic acid	Infections	Efficacy (resistance)
1974	1975	Polidexide	Cardiovascular	Safety (impurities)
1974	1985	Perhexilene	Cardiovascular	Safety (neurotoxicity and hepatotoxicity)
1976	1986	Nomifensine	Central nervous	Safety (haemolytic anaemia)
1977	1982	Clomacron	Central nervous	Safety (hepatotoxicity)
1978	1991	Triazolam	Central nervous	Safety (psychiatric reactions)
1978	1984	Fenclofenac	Musculo-skeletal	Safety (Lyell's syndrome)
1978	1984	Feprazone	Musculo-skeletal	Safety (multi-system toxicity)
1980	1983	Zomepirac	Musculo-skeletal	Safety (anaphylaxis)
1980	1986	Suprofen	Musculo-skeletal	Safety (nephrotoxicity)
1980	1982	Benoxaprofen	Musculo-skeletal	Safety (multi-system toxicity)
1981	1987	Penbutolol	Cardiovascular	Quality (stability)
1981	1983	Zimeldine	Central nervous	Safety (neurotoxicity)
1982	1989	Brotizolam	Central nervous	Safety (rodent carcinogenicity)
1982	1982	Indoprofen	Musculo-skeletal	Safety (gastrointestinal toxicity)
1986	1991	Terodiline	Urinary	Safety (arrhythmias)
1986	1990	Metipranolol	Eye	Safety (uveitis)
1990	1990	Dilevalol	Cardiovascular	Safety (hepatotoxicity)
1990	1994	Remoxipride	Central nervous	Safety (aplastic anaemia)
1991	1992	Temafloxacin	Infections	Safety (multi-system toxicity)
1991	1993	Nebacumab	Infections	Safety (mortality)
1992	1993	Flosequinan	Cardiovascular	Safety (mortality)

*Never commercialised.

[8] has claimed that the (reputedly) more stringent regulatory requirements in the US have resulted in a lower proportion of safety withdrawals compared with those in the UK. No study, however, provides valid comparisons of experience in the UK and US. Only Bakke *et al.* [4] confined their analysis to a period when there were statutory controls, in

the UK, on the introduction and marketing of medicines. All included either products that have never been licensed in the UK (e.g. natural growth hormone), or ones that have not been withdrawn for safety reasons (e.g. desensitising vaccines). Furthermore, no study has been able to enumerate the totality of NASs authorised during relevant and

Table 5 Life-table analysis of all withdrawals of new active substances (1972 to 1993).

<i>Years</i>	<i>Total licensed</i>	<i>Number reaching end of follow up</i>	<i>Withdrawn</i>	<i>Cumulative percentage remaining licensed</i>
0	583	34	3	99.5
1	546	23	4	98.8
2	519	27	6	97.6
3	486	33	2	97.2
4	451	34	5	96.1
5	412	39	7	94.5
6	366	29	5	93.2
7	332	14	2	92.6
8	316	16	2	92.1
9	298	12	2	91.4
10	284	6	10	88.2
11	268	17	2	87.6
12	249	26	3	86.5
13	220	27	2	85.7
14	191	19	1	85.3
15	171	17	3	83.8
16	151	21	0	83.8
17	130	24	0	83.8
18	106	16	0	83.8
19	90	14	0	83.8
20	76	26	0	83.8
21	50	21	0	83.8
22	29	29	0	83.8

comparable periods. Overall there is no evidence of markedly different risk-benefit withdrawal rates between the two countries, when valid comparisons are made.

The need for withdrawal of any pharmaceutical product on grounds of either quality, efficacy or safety might be regarded as a failure of drug regulation. The data for those NASs, authorised in the UK under the provisions of the Medicines Act (1968), suggest that withdrawal for reasons of quality and efficacy are exceptional with only one example of each over 23 years. Risk-benefit withdrawals have, however, been more frequent and a detailed analysis will be undertaken later. For reasons discussed elsewhere [9] it is impossible to guarantee a product's safety at the time of authorisation; at this point in time only provisional risk-benefit judgements can be made. This report thus underlines, once more, the need for pharmacovigilance [9]. The report does not, however, address the frequency with which safety issues arise after marketing but which lead to regulatory action short of market withdrawal (e.g. restrictions on indications, reduced dosages etc). This issue is important because it is possible that such regulatory action could be rendered unnecessary either by more rigorous evaluation during the premarketing period, or by better scrutiny during licensing. This, too, will be the subject of a separate study.

Finally, a life-table analysis of withdrawals of NASs is shown in Table 5. This summates withdrawals for commercial and non-commercial (i.e. quality, efficacy and safety) reasons. The 10 year survival of all NASs, since 1972, is approximately 88%. By comparison with other consumer products this is probably a relatively low attrition rate.

References

- 1 Hass AE, Coppinger PL. Introductions and discontinuations of new drugs in the United States and the United Kingdom 1970–88. Food & Drug Administration: Rockville, 1989.
- 2 Tansey IP, Armstrong NA, Walker SR. Trends in pharmaceutical innovation. The introduction of products on to the UK market 1960–89. *J Pharm Med* 1994; **4**: 85–100.
- 3 Bakke OM, Wardell WM, Lasagna L. Drug discontinuations in the United Kingdom & the United States; 1964–83: Issues of safety. *Clin Pharmacol Ther* 1994; **35**: 559–567.
- 4 Bakke OM, Manocchia M, de Abajo F, Kaitin KI, Lasagna L. Drug discontinuations for safety reasons: an update with comparison of UK, US & Spain 1974–93. *Clin Pharmacol Ther* 1995; **58**: 108–117.
- 5 Commission of the European Communities. The Rules Governing Medicinal Products in the European Community. Volume II Notice to Applicants, 1994.

- 6 Martindale. The Extra Pharmacopoeia. Twenty-sixth Edition. Pharmaceutical Press: London, 1992.
- 7 British National Formulary. British Medical Association and Royal Pharmaceutical Society of Great Britain, 1995.
- 8 Public Citizen Health Research Group. Differences in the number of drug safety withdrawals United States, United Kingdom, Germany and France. Public Citizen Health Research Group: Washington, 1995.
- 9 Rawlins MD. Pharmacovigilance: Paradise Lost, Regained or Postponed? *J Roy Coll Phys* 1995; **29**: 41–49.

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Glossary

Active Substances The ingredient of a medicinal product that produces its therapeutic effects.

Committee on Safety of Medicines The independent advisory committee established under the Medicines Act. By custom and practice all product licence application relating to new active substances are referred to the Committee for their advice. If after an appeal the CSM advises against the grant of a licence the company has a further right of appeal to the Medicines Commission.

Licensing Authority The UK Health Ministers empowered under the Medicines Act to issue licences relating to medicinal products.

Medicines Act (1968) The primary legislation forming the basis of the regulation of medicines in the UK. Significant parts of the 1968 Act are now incorporated into the 1994 Free Standing Regulations which also bring into force the Single Instrument and the relevant EC Directives relating to the regulation of medicines.

Medicines Control Agency The executive arm of the Licensing Authority, and an agency of the Department of Health which is responsible for administering the relevant legislation on medicinal products.

Product Licence The licence (or marketing authorisation) issued by the Medicines Control Agency on behalf of the Licensing Authority that permits the holder to promote, for sale or supply, a particular medicinal product.