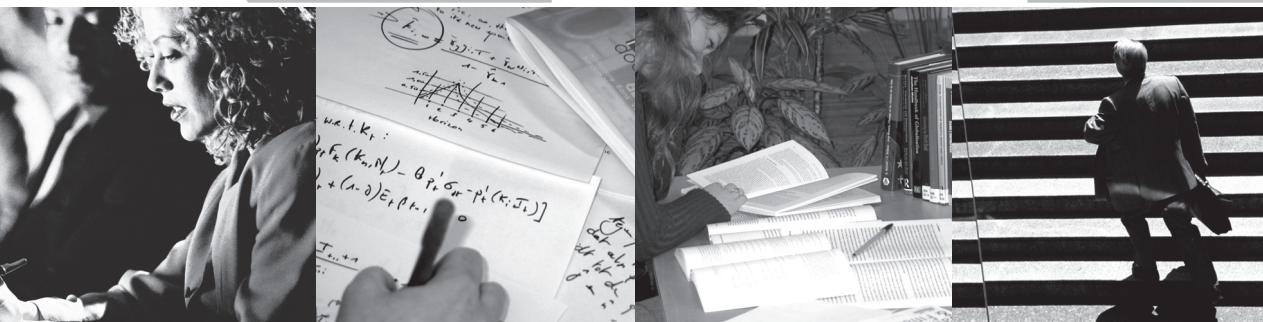


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R&D in the Belgian Pharmaceutical Sector

H. De Doncker



NATIONAL BANK OF BELGIUM

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R&D IN THE BELGIAN PHARMACEUTICAL SECTOR

Helga De Doncker (*)

The views expressed in this paper are those of the authors and do not necessarily reflect the views of the National Bank of Belgium.

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Abstract

The Belgian pharmaceutical sector has been accorded a leading role in the attainment of the R&D investment targets which the EU Member States set themselves as part of the Lisbon strategy. To gain a better insight into that sector's research activities, the NBB conducted an ad hoc survey in 2005, covering pharmaceutical companies active in Belgium in the field of research, production and distribution of drugs for human use. The analysis of the information obtained from that survey makes up the main body of this working paper.

The survey results do not only confirm the importance of the research activities conducted by Belgian establishments, but also indicate the frequent cooperation with other research centres and the crucial importance of expertise as a factor influencing the location of such activities in Belgium. The breakdown of the survey results by kind of establishment on the basis of the type of activities conducted in Belgium reveals further clear differences of emphasis in the nature of the R&D activities pursued in Belgium and divergences in the scale of the resources used.

The paper also comprises a number of annexes giving additional information on the sector. More particularly, they deal with added value and employment, the indirect effects and profitability of the pharmaceutical companies, and background information on reference reimbursement of drugs.

JEL-code : I18, L65, O3.

Keywords: pharmaceutical industry, R&D, reference reimbursement.

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1 INTRODUCTION

1.1 Aim of the research

At the Lisbon and Barcelona summits, the European Union countries set themselves the goal of becoming the most competitive, knowledge-based society in the world by 2010. In that connection, a leading role in Belgium is assigned to the drugs sector. That sector in fact invests heavily in research and development (R&D) in both absolute and relative terms¹, because there more than in any other branch, successful R&D activities are the key to commercial success. However, the current statistics and analyses still shed too little light on numerous aspects concerning the investment efforts of the drugs sector. In 2005 the NBB therefore conducted an ad hoc survey aimed at gaining a better insight into the R&D processes in the Belgian drugs sector. For the purposes of the survey, the sector was defined more specifically as pharmaceutical companies active in Belgium in the field of research, production and distribution of drugs for human use. In organising the survey, the NBB was assisted by the sector federation, pharma.be, in composing the population of firms concerned and formulating the questionnaire. However, the Bank alone was responsible for collecting, processing and interpreting the results.

The main body of this report deals with the analysis of the survey results. For the non-specialist reader, the annexes provide a brief explanation of the sector from an economic point of view. Apart from information on value added, employment, indirect effects and profitability, there is also background information on reference reimbursement of drugs.

1.2 Content of the survey form

The form presented to participants in the ad hoc survey contains different types of questions in terms of both content and design².

In terms of content, the information obtained by the survey can be divided into three broad subjects. The first concerns the general economic characteristics of the firm, such as turnover, exports and staff. These data can be used not only to assess the representativeness of the answers and determine the weighting coefficients for the (quantitative) questions, but also to ascertain the profile of the respondents involved in R&D. The other two subjects covered by the survey concern respectively the input and the output of the R&D efforts. In regard to input, the survey does not only look at traditional items such as expenditure, the staff deployed, location factors and sources of funding, but also tries to obtain a clearer view of the relative importance of the various R&D phases for projects developed in Belgium and cooperation with other research centres.

In the case of output, attention focuses both on the successful projects (patents and marketing) and on discontinued projects (reasons for discontinuation).

The questions were designed with the aim of minimising the items calling for precise figures, in order to ensure a representative response rate even for such a complex subject as R&D. A number of questions were therefore formulated in qualitative terms so that participants only needed to tick the items.

¹ For a general economic overview, see Annex 2.

² The full questionnaire and explanatory notes may be found in Annex 1.

The definitions to which the survey form refers are those devised by the Organisation for Economic Cooperation and Development (OECD) in the Frascati Manual for R&D surveys. The period covered by the survey runs from 2002 to 2004. However, in so far as the data for the three years considered are stable and no clear trends are apparent, the analysis which follows is based on averages for the period.

1.3 Sample

Altogether, letters were sent out to a total of 200 firms. More particularly, this concerned a population of firms composed by pharma.be – both members and non-members of the sector association - active in the development, production and distribution of drugs for human use in Belgium. The initial response rate was worryingly low; eventually, by the end of February 2006, after the sending of reminders and postponement of the cut-off date, 64 firms had responded to the request for participants, including 28 with R&D activities³. The analysis which follows will discuss only the survey results relating to the latter.

Although at first sight the response rate may still appear low, with a total of 64 response forms, and particularly just 28 firms active in R&D, the sample is nevertheless fairly representative.

Measured in terms of "turnover on the Belgian market", these 64 participants represent roughly 80 p.c. of the sector total published by pharma.be⁴; firms active in R&D account for around 67 percentage points of that figure. On the basis of employment, the sample represents on average 72 p.c. of all respondents and 65 p.c. of those active in R&D (table 1).

TABLE 1 REPRESENTATIVENESS OF THE SURVEY SAMPLE

	All firms (64 forms)				Firms active in R&D (28 forms)				
	2002	2003	2004	Average	2002	2003	2004	Average	
Belgian market turnover (billion €)	2.5	2.6	2.8	2.6	Belgian market turnover (billion €)	2.1	2.2	2.3	2.2
<i>Pc of sector total*</i>	82.3	79.0	79.2	80.1	<i>Pc of sector total*</i>	69.2	66.8	65.1	66.9
Employment (physical units 31/12)	18,522	18,995	19,186	18,901	Employment (physical units 31/12)	16,830	17,261	17,432	17,174
<i>Pc of sector total(*) (**)</i>	72.9	72.0	70.2	71.7	<i>Pc of sector total(*) (**)</i>	66.2	65.4	63.8	65.1

Sources: IMS, pharma.be, NBB.

* See footnote 4.

** The total sector employment figures relate to the situation on 30 June.

The Belgian pharmaceutical sector has a strong multinational profile. Although most of the pharmaceutical multinationals have a subsidiary in Belgium, they do not all engage in the same activities. The sample of firms active in R&D reflects that heterogeneity, as the participants' activities come under various activity codes (manufacture of pharmaceuticals (Nacebel code 24.4); wholesale

³ In the rest of the text the terms "branches/establishments" and "firms" are used as synonyms for participants/forms, although that is not entirely correct. For instance, there are cases in which a form relates to more than one establishment belonging to the same firm, while there are also cases where a form relates only to a firm's research department.

⁴ For completeness, it should be pointed out that the totals published by pharma.be are not confined to members of the sector association. Moreover, the sector concept is broader than that used for the survey, since – unlike the latter – it also concerns activities relating to veterinary medicines and in vitro diagnostics.

of pharmaceutical and chemical products (Nacebel codes 51.46 and 51.55 respectively) and research and experimental development on natural sciences and engineering (Nacebel 73.1)).

The type of principal activity – production or distribution – pursued by the Belgian branch of a pharmaceutical company has some influence on the scale and nature of the R&D activities which it conducts in Belgium⁵. The largest firms often prove to be the biggest R&D players, so that the average tendencies deduced from the survey results do not provide a representative picture for the majority of the participants. In discussing the results of the firms active in R&D it was therefore decided to calculate not only the general total, which might mask very divergent situations, but also the “peer group” results, thus adding to the usefulness of the survey. On the basis of the general economic characteristics (output, export, (basic) research, etc.) indicated by the firms on the survey form, and the typology of classes of firms used by the industry association, pharma.be, it is possible to identify a number of classes of “similar” firms.

TABLE 2 COMPOSITION OF THE R&D SAMPLE BY CLASS OF FIRMS

<u>Class</u>	<u>Description</u>	<u>Number in sample</u>	<u>Nacebel</u>
A			
1	Firms with production in Belgium destined for export and basic research in Belgium	3	24.4
2	Firms whose main activity consists of R&D	2	73.1
B	Firms with production in Belgium destined largely for export	2	24.4
C	Firms with production in Belgium (whether or not for own account), destined mainly for the Belgian market	2	24.4
D	Firms resorting mainly to outside processing in Belgium	0	
E	Firms which engage mainly in importing		
1	and to a lesser extent exporting	13	51.46+51.55
2	and not exporting	6	51.46+51.55
Total		28	

Sources: pharma.be, NBB.

The federation divides the pharmaceutical companies into five classes according to the activities which they pursue in Belgium. Classes A, B, C and D concern firms manufacturing the majority of their products in Belgium; firms in the first three classes produce the goods (largely) themselves, whereas those in class D resort (mainly) to subcontractors. Class C is different from A and B in that the production is destined primarily for the Belgian market, whereas most of the production in the last two classes mentioned is for export; firms in class A are different again in that they engage in basic research in Belgium, alongside their production activity. Finally, class E comprises firms which engage mainly in distribution in Belgium, and import most of their products.

Table 2 shows the composition of the R&D sample for these five different classes of firms. When discussing the survey results, it also proved useful to make a further distinction for some items in classes A and E, and this is indicated in the table by sub-classes A1 and A2, and E1 and E2 (table2).

⁵ In this connection, see 2.2.4 "Type of R&D activities".

However, it was not possible to analyse the survey results at a lower level of aggregation and/or at regional level because that would have breached the confidentiality of the information supplied by the individual firms.

2 SURVEY RESULTS FOR FIRMS ACTIVE IN R&D

2.1 Economic characteristics

2.1.1 Turnover

The total turnover of the R&D sample⁶ during the period considered averaged €5.9 billion. Although sales on the domestic market grew slightly faster than those on the foreign market during that period, domestic sales still represent a significantly smaller percentage of total turnover, averaging €2.2 billion⁷ (table 3).

TABLE 3 ECONOMIC CHARACTERISTICS OF THE R&D SAMPLE

	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>Average</u>
Turnover (billion €)	5.7	5.9	6.2	5.9
of which: Sales on the domestic market	2.1	2.2	2.3	2.2
Exports (billion €)	3.6	3.7	3.9	3.8
Employment (physical units 31/12)	16,830	17,261	17,432	17,174

Source: NBB

The uneven distribution of total turnover across the classes of firms reflects the heterogeneity of the Belgian pharmaceutical landscape. The firms producing in Belgium (classes A, B and C) account for just seven companies⁸ in the sample, but represent 69 p.c. of the turnover, while the distribution companies (E) account for the remaining 31 p.c.

Among the production companies, class A firms clearly predominate, while class C represents a virtually negligible percentage of turnover – at least where the sample is concerned (chart 1).

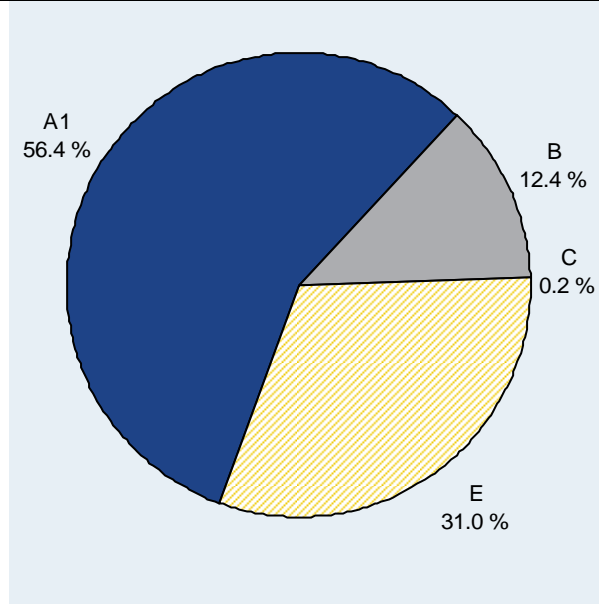
⁶ The sample also includes two firms whose main activity consists of R&D and which therefore have no turnover. They are, of course, disregarded in the figures concerning turnover and export calculated below.

⁷ For comparison: taking all respondents together, the total turnover averaged €6.5 billion, comprising 2.6 billion on the domestic market and 3.9 billion on the foreign market.

⁸ The total comes to nine if the two firms mentioned in footnote 6 are included.

CHART 1 SHARES OF THE CLASSES OF FIRMS* IN THE TOTAL TURNOVER

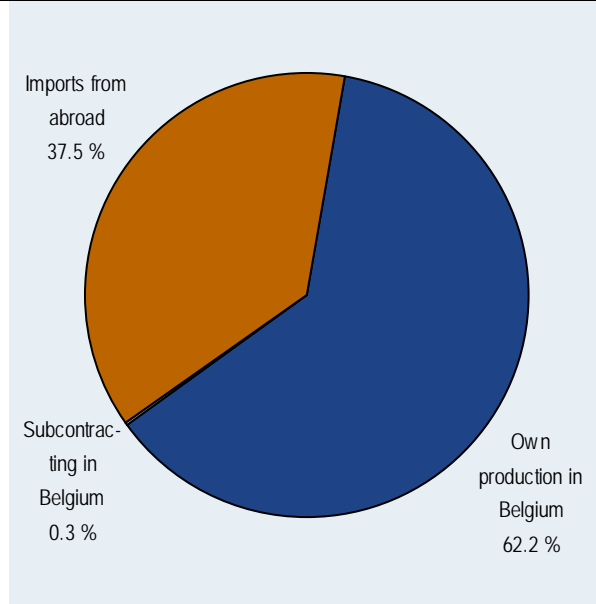
(percentages, averages 2002-2004)



Source: NBB

CHART 2 TURNOVER BY ORIGIN OF THE DRUGS

(percentages, averages 2002-2004)



Source: NBB

*For a description of the classes of firms, see table 2.

In view of the degree to which pharmaceutical companies producing in Belgium dominate the total turnover of the sample, it is not surprising that this turnover consisted mainly of drugs produced by the firms themselves in Belgium. Roughly speaking, almost two-thirds of the drugs sold for human use were actually produced in Belgium while over one-third were imported from abroad. Drugs produced by subcontractors in Belgium are of minor significance, at less than half of one per cent (chart 2).

TABLE 4 TURNOVER OF THE CLASSES OF FIRMS* BY ORIGIN OF THE DRUGS
(percentages of the total per class, averages 2002-2004)

Class*	Own production in Belgium	Subcontracting in Belgium	Imports from abroad
A (A1)	98	0	2
B	52	1	47
C	46	53	1
Production firms (A+B+C)	90	0.3	10
Distribution firms (E)	0	0.3	100
Total	62	0.3	37

Source: NBB.

* For a description of the classes of firms, see table 2.

The breakdown of the turnover of the classes of firms by origin of the drugs reveals wide variations⁹. Belgian produced drugs account for 0 p.c. in the case of the distribution firms as opposed to 90 p.c. for the production firms. Among the production firms, the proportion rises to over 98 p.c. in the case of class A, whereas for classes B and C it hovers around 50 p.c. For all classes except C, the rest of the turnover concerns drugs imported from abroad. In the case of class C, however, foreign imports are negligible at 1 p.c., but this is the only class that makes relatively significant use of subcontracting in Belgium, namely 53 p.c. (table 4).

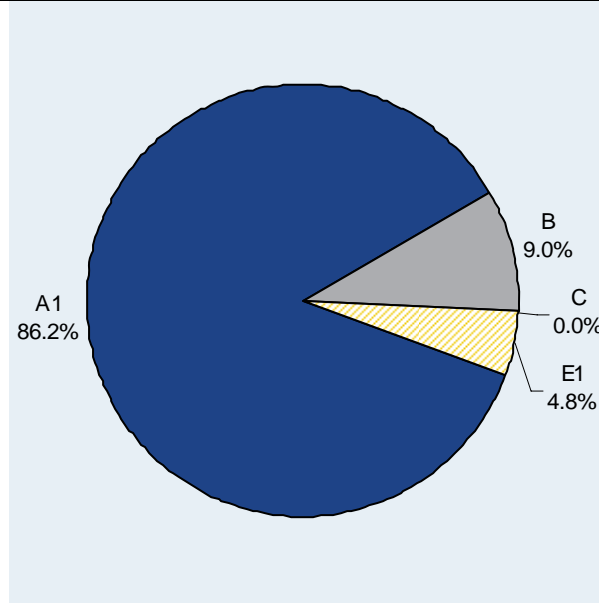
2.1.2 Export

During the period 2002-2004, the average annual exports of firms in the R&D sample came to 3.8 billion euro (table 3).

The distribution of those exports among the various classes of firms exhibits far wider divergences than in the case of turnover. The production firms account for over 95 p.c. of the total. Class A (A1) alone represents over 86 percentage points of that figure, while the remaining 9 percentage points come under class B. The relative contribution of class C to exports is consequently negligible. The distribution firms together account for barely 5 p.c. of total exports. Furthermore, a single firm is the source of three-quarters of that figure. Most of the distribution firms in the R&D sample therefore export little or nothing, and are local branches specifically geared to the Belgian market (chart 3).

CHART 3 EXPORT SHARES OF THE CLASSES OF FIRMS*

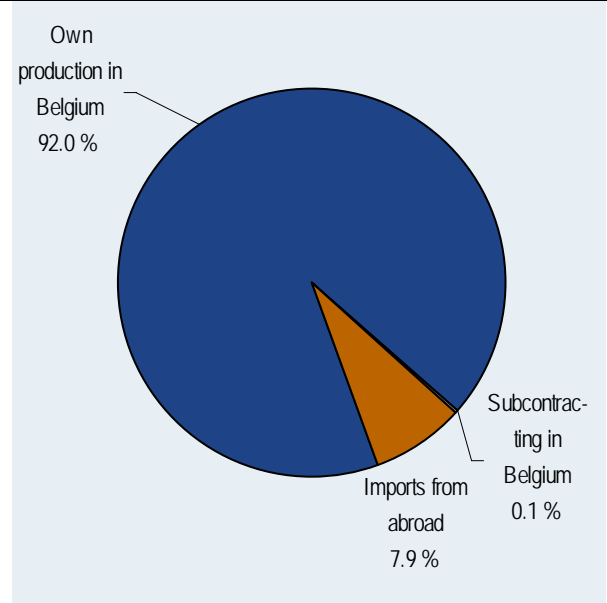
(percentages, averages 2002-2004)



Source: NBB

CHART 5 EXPORTS BY ORIGIN OF THE DRUGS

(percentages, averages 2002-2004)



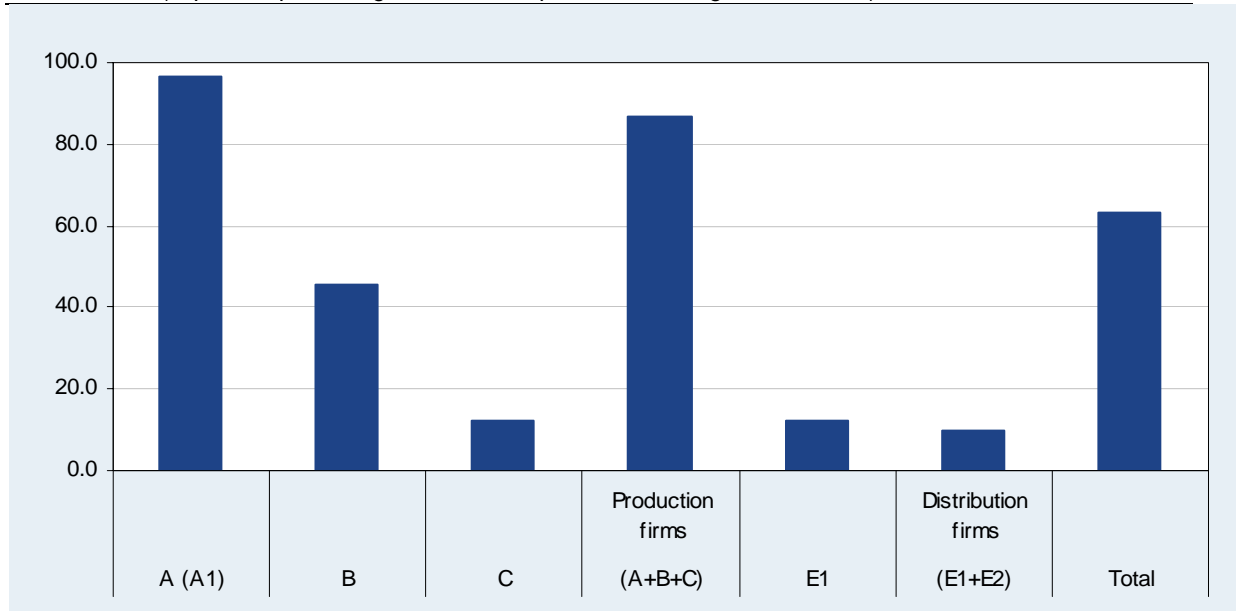
Source: NBB

* For a description of the classes of firms, see table 2.

The difference between the production and distribution firms in the R&D sample in terms of export orientation is very obvious from looking at the export/turnover ratio per class of firms. On the basis of that ratio, it is particularly apparent that the overall figure of 63 p.c. masks very different real-life situations.

⁹ The calculations naturally included only those firms which were able to supply data for this breakdown.

CHART 4 EXPORT ORIENTATION PER CLASS OF FIRMS*
 (exports in percentages of turnover per class, averages 2002-2004)



Source: NBB

* For a description of the classes of firms, see table 2.

The general picture is greatly influenced by the production firms: exports account for 87 p.c. of their turnover, whereas that figure is barely 10 p.c. for distribution firms. Once again, the export orientation of the production firms mainly reflects the situation for companies in class A, as that class achieves 96 p.c. of its turnover via exports, whereas for companies in class B that figure drops to 46 p.c. In terms of export orientation, with a figure of 12 p.c., production firms in class C are then on the same level as the exporting distribution firms in class E1 (chart 4).

The marked dominance of the production firms, and more particularly class A, in turnover and exports naturally explains why no less than 92 p.c. of exports by the R&D sample concern drugs produced by the companies themselves in Belgium. The rest of the sample's exports actually concern "transit" since almost all – namely 7.9 percentage points – consist of drugs imported from abroad. Drugs produced by subcontractors in Belgium account for a negligible share of exports, at 0.1 p.c., and that is of course due to the small share of the sector's total exports represented by class C, the only group of firms in the sample which commonly uses subcontractors for production in Belgium (chart 5 and table 5).

TABLE 5 EXPORTS PER CLASS OF FIRMS* BY ORIGIN OF THE DRUGS
(percentages of the total per class)

Class*	Own production in Belgium	Subcontracting in Belgium	Imports from abroad
A (A1)	98	0	2
B	88	1	11
C	54	47	0
Production firms (A+B+C)	97	0.1	3
Distribution firms E (E1)	0	0	100
Total	92	0.1	8

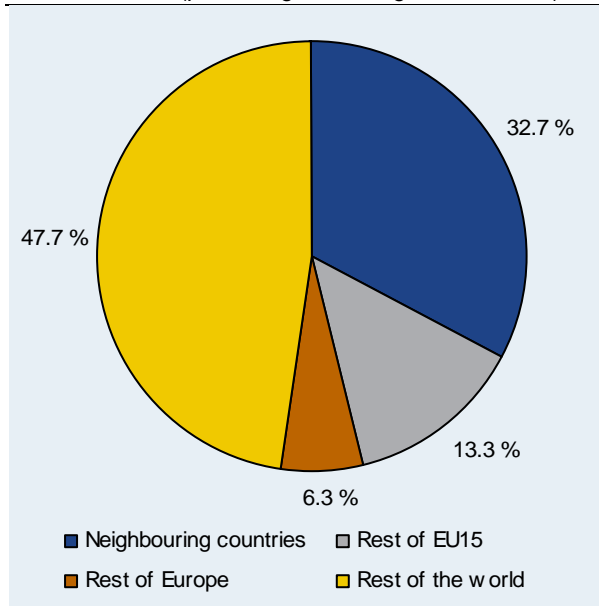
Source: NBB

* For a description of the classes of firms, see table 2.

2.1.3 Export destination

As regards the destination of the exports of the R&D sample, the "rest of the world" is in the lead with 47.7 p.c. of the total. "Neighbouring countries" are the second largest export destination, taking 32.7 p.c. of the drugs exported. Of the remaining exports, namely 19.6 p.c., 13.3 percentage points go to the "rest of EU15" and 6.3 percentage points to the "rest of Europe" (chart 6).

CHART 6 EXPORT DESTINATION
(percentages, averages 2002-2004)



Source: NBB

However, in terms of export destination it must once again be said that the overall percentages conceal wide variations in the results for the classes of firms. The overall picture again reflects the situation of the production companies, particularly those in class A.

TABLE 6 EXPORT DESTINATION PER CLASS OF FIRMS*
(percentages of the total per class, averages 2002-2004)

Class*	Neighbouring countries	Rest of EU15	Rest of Europe	Rest of the world
A (A1)	25	14	7	53
B	70	8	1	20
C	80	0	1	16
Production firms (A+B+C)	29	14	7	50
Distribution firms E (E1)	97	2	0	1
Total	33	13	6	48

Source: NBB

* For a description of the classes of firms, see table 2.

Generally speaking, it can be said that, for the individual classes of firms, there is a trade-off between the importance of "neighbouring countries" and the "rest of the world", while the "rest of the EU15" and the "rest of Europe" are less important. Thus, in the case of the production companies it can be said, in particular, that the more a class of firms focuses on exports, the more global its activities; conversely, the less a class of firms is geared to exports, the stronger its focus on neighbouring countries. In the case of the distribution firms, no less than 97 p.c. of exports are destined for neighbouring countries; the individual companies in the sample often even state that all their exports go to this group of countries. In view of the small percentage of their turnover represented by exports, the implication must be that "neighbouring countries" often means solely the Grand Duchy of Luxembourg (table 6). Finally, for all classes of firms the export destination remained decidedly constant over the three-year period considered.

TABLE 7 EXPORT MATRIX: SHARES OF THE CLASSES OF FIRMS* AND DESTINATIONS
(percentages of the overall total, averages 2002-2004)

Class*	Neighbouring countries	Rest of EU15	Rest of Europe	Rest of the world	Total
A (A1)	22	12	6	46	86
B	6	1	0	2	9
C	0	0	0	0	0
E (E1)	5	0	0	0	5
Total	33	13	6	48	100

Source: NBB

* For a description of the classes of firms, see table 2.

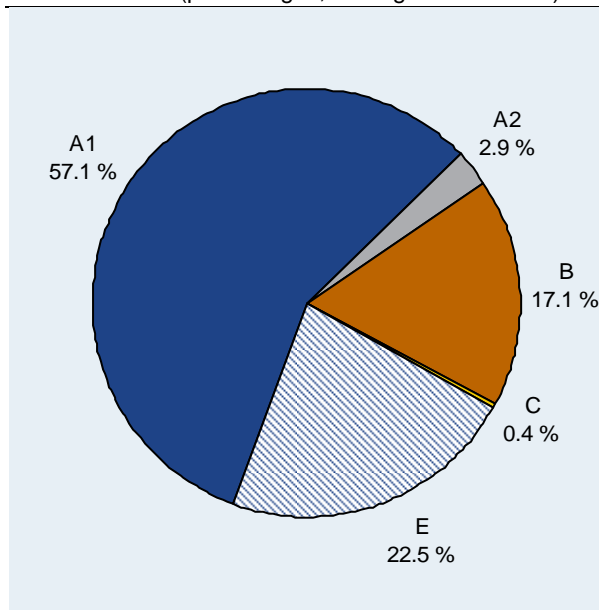
The data concerning the export volume and destination can be used to construct an overall export matrix for the sample by classes of firms and export destinations. This shows that, apart from exports by A to the various regions, only exports by classes B and E1 to neighbouring countries represent a share of 5 p.c. or more of the overall total (table 7).

2.1.4 Overall staff

The overall staff of the R&D sample averaged over 17 000 employees during the period 2002-2004, thus representing 65.1 p.c. of the total for the sector (tables 1 and 3).

During the three-year period considered, firms in the R&D sample recorded a continuous expansion in their overall staff, totalling an estimated 3.6 p.c. over the period as a whole. They therefore did significantly better than the sector in general, since employment declined by just over 4 p.c. during those years.

CHART 7 SHARES OF THE CLASSES OF FIRMS* IN THE OVERALL STAFF
(percentages, averages 2002-2004)



Source: NBB

* For a description of the classes of firms, see table 2.

The production firms account for 77.5 p.c. of the overall staff in the sample, with A1 firms alone representing 57.1 percentage points of that figure (chart 7).

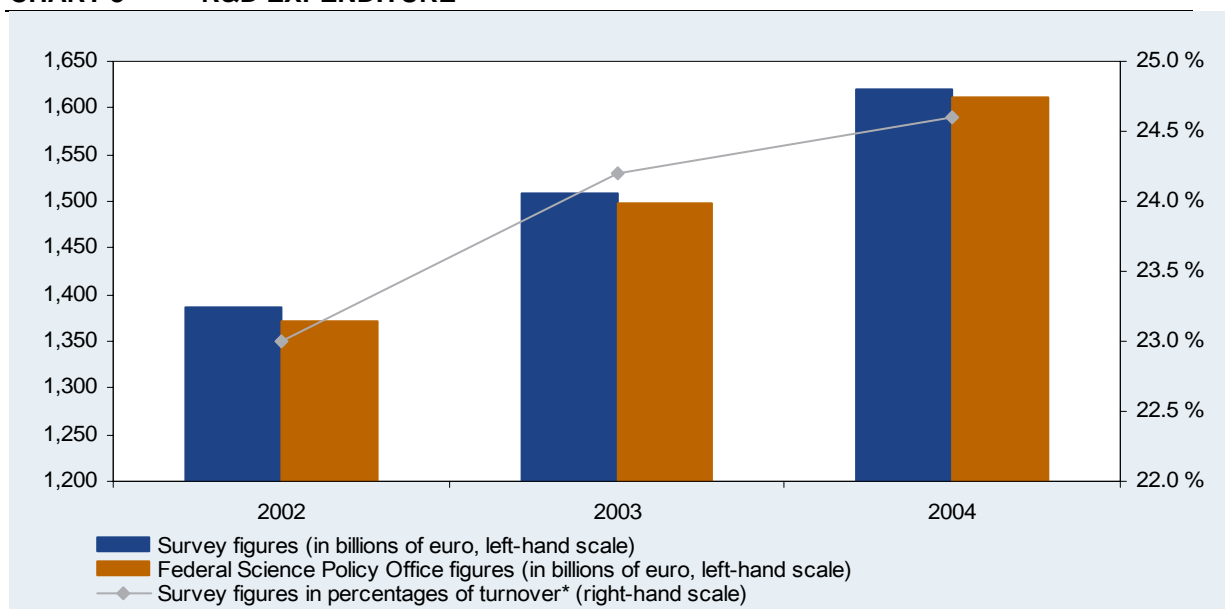
The expansion of the overall staff over the period 2002-2004 was a phenomenon common to virtually all classes of firms. However, the percentage increase was by far the largest in class A2, and to a lesser extent in class C, whereas class A1 recorded the bulk of the increase in absolute numbers.

2.2 Input data concerning the R&D activities of Belgian branches

2.2.1 R&D expenditure

The global figure for the R&D expenditure of the participating firms increased from € 1.4 billion in 2002 to € 1.6 billion in 2004, representing a rise of 16.7 p.c. These figures are of the same order of magnitude as the data compiled for Belgium by the Federal Science Policy Office, reported to Eurostat and the OECD for the purpose of international comparison¹⁰. Bearing in mind that the survey analysed here is confined to drugs for human use, whereas the data from the Federal Science Policy Office in principle concern all pharmaceutical sector disciplines, i.e. including in vitro diagnostics and veterinary medicines, then the R&D sample can be considered complete (chart 8).

CHART 8 R&D EXPENDITURE



Sources: NBB, Federal Science Policy Office

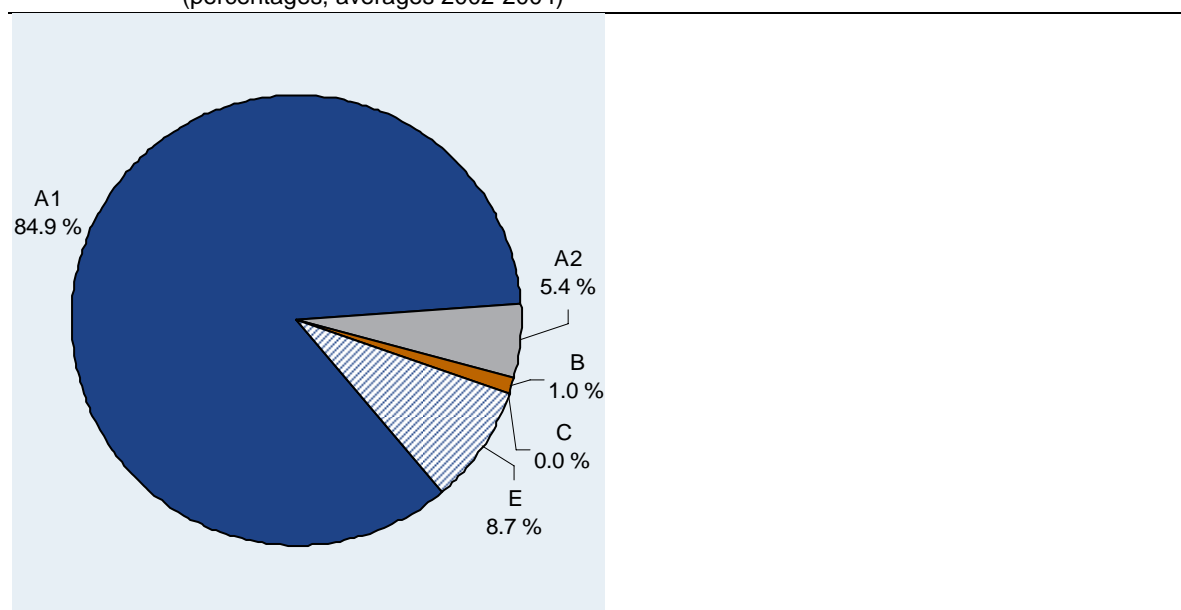
* Excluding expenditure by firms in class A2.

On average, the shares of the classes of firms in this total vary widely, as 90.3 p.c. of that expenditure is concentrated on the production firms in class A, while the remaining percentage consists almost exclusively of expenditure by distribution firms (chart 9).

¹⁰ The Federal Science Policy Office figures for R&D expenditure concern more particularly ANBERD (Analytical Business Enterprise Research and Development) data in which the sectoral allocation of the R&D figures is based on the product line level, and the industry-related R&D activities of the R&D service sector are allocated to the corresponding industry. In other words, this means that the figures referred to here include not only the R&D expenditure of the pharmaceutical firms in manufacturing industry, but also that of those firms in the wholesale trade and those belonging to the research and development sector. It should also be pointed out that the figures used here for comparison in fact represent the sum of intramural and extramural expenditure (for an explanation of these terms, see the explanatory notes to the survey form in Annex 1) by the Belgian pharmaceutical sector. This approximation is not entirely correct, since that sum theoretically leads to an overestimate of the sector total: external expenditure giving rise to activities by Belgian firms within the sector itself leads to double counting, because it is included in the (externally funded) intramural expenditure of the latter firms. However, the fact that the total obtained via the survey exceeds the figures from the Federal Science Policy Office appears to indicate that such double counting is negligible in practice for the pharmaceutical sector.

That dominance of class A is naturally connected with the fact that the type of primary activity – production or distribution – pursued by the Belgian branch of a pharmaceutical company is bound to affect the nature of its R&D activities in Belgium¹¹. In this connection, the industry federation explains that, owing to economies of scale, a multinational company will try to concentrate its R&D work and the preparation of active substances (plus the conversion to finished drugs) in one or a few branches, generally located in the company's country of origin. In Belgium, the establishments in which these two phases of the drugs process take place in fact belong to Belgian firms or firms of Belgian origin which have been taken over by foreign companies. However, some parts of the R&D process can be divided among various branches. This applies mainly to the clinical trials, especially those conducted simultaneously in various countries in phases II and III, but coordinated by the head office¹².

CHART 9 SHARES OF THE CLASSES OF FIRMS* IN R&D EXPENDITURE
(percentages, averages 2002-2004)



Source: NBB

* For a description of the classes of firms, see table 2.

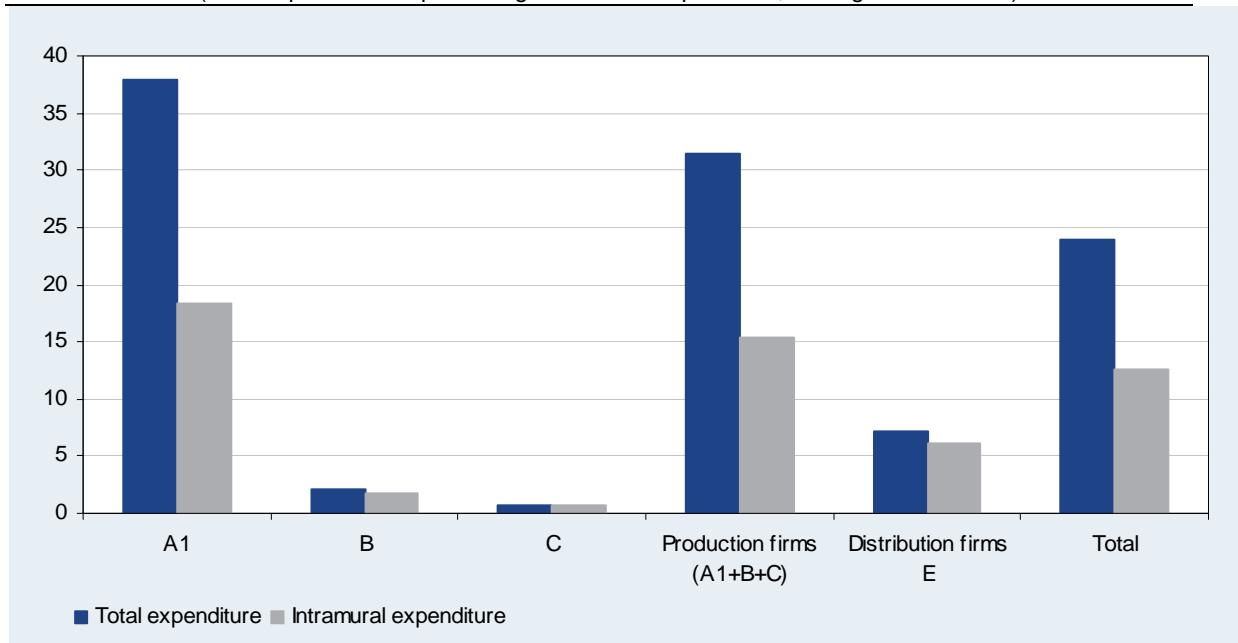
The intensiveness of the R&D efforts – a criterion for this was obtained by relating total R&D expenditure to turnover – therefore varies greatly from one class of firms to another. For the companies taken as a whole, that figure is just under 25 p.c., and increases slightly over the period considered, more precisely from 23.0 p.c. to 24.6 p.c.¹³ (chart 8). In the case of firms which also engage in basic research (class A), however, the expenditure increases to almost 40 p.c. of turnover, whereas that figure varies for the other groups from barely 1 p.c. to around 7 p.c. (chart 10).

¹¹ In this connection, see 2.2.4. "Type of R&D activities"

¹² pharma.be (2004).

¹³ The expenditure of research institutions in group A2 was excluded from this calculation since those institutions do not have any real turnover. However, if the R&D expenditure by class A2 is included, the percentage is more than 1 percentage point higher.

CHART 10 R&D INTENSIVENESS PER CLASS OF FIRMS*, MEASURED BY EXPENDITURE
(R&D expenditure in percentages of turnover per class, averages 2002-2004)

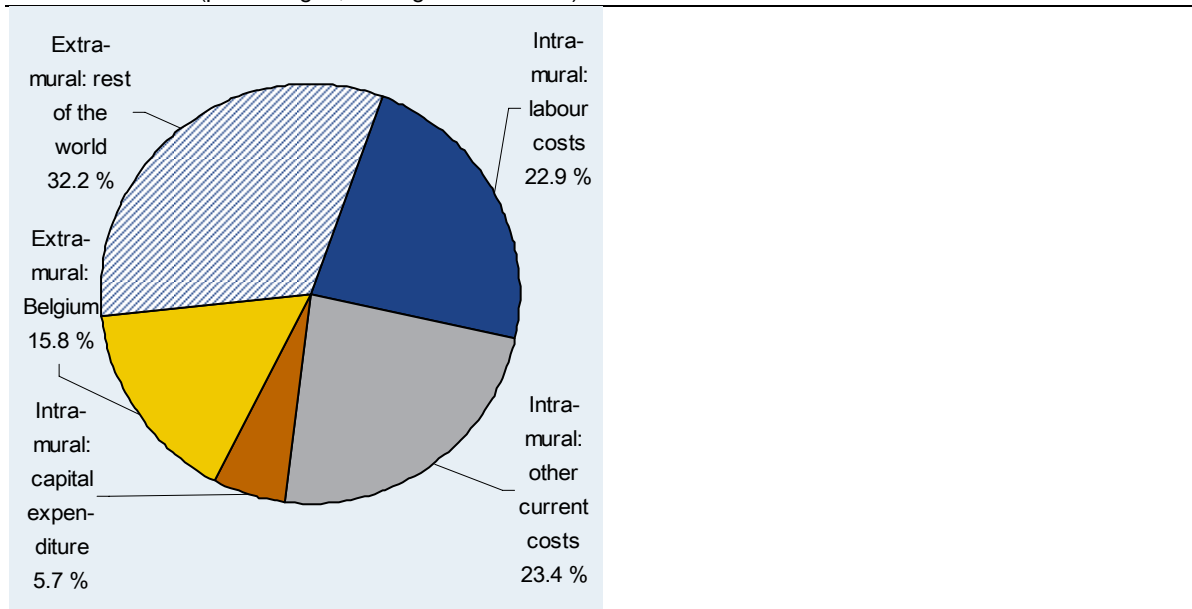


Source: NBB

* For a description of the classes of firms, see table 2.

The breakdown of R&D expenditure by type for the sample as a whole presents a very balanced distribution between intramural (52 p.c.) and extramural expenditure (48 p.c.)¹⁴ (chart 11).

CHART 11 R&D EXPENDITURE BY TYPE
(percentages, averages 2002-2004)



Source: NBB

¹⁴ For an explanation of these terms, see the explanatory notes to the survey form in Annex 1.

Within intramural expenditure, labour costs and other current costs account for roughly 44 and 45 p.c.; capital expenditure is therefore a less significant item, generally speaking, representing the remaining 11 p.c. Roughly one-third of the extramural expenditure is effected in Belgium and two-thirds in the rest of the world (chart 11).

TABLE 8 R&D EXPENDITURE PER CLASS OF FIRMS* BY TYPE
(percentages of the total per class, averages 2002-2004)

Class *	Intramural	In p.c. of intramural expenditure			Extra mural	In p.c. of extramural expenditure	
		Labour costs	Other current costs	Capital expenditure		Belgium	Rest of the world
A1	48	41	46	13	52	15	85
A2	54	64	27	10	46	66	34
A (A1+A2)	49	42	45	13	51	26	74
B	84	38	59	3	16	99	1
C	48	99	1	0	52	100	0
Production firms (A+B+C)	49	42	45	13	51	27	73
Distribution firms (E)	84	54	44	2	16	97	3
Total	52	44	45	11	48	33	67

Source: NBB

* For a description of the classes of firms, see table 2.

This general picture is also an accurate reflection of the relative importance of R&D expenditure by type for the production firms as a whole; however, in the case of the distribution firms the percentages diverge, because these firms spend a much higher percentage, over 80 p.c., on intramural research, and within that figure a markedly smaller proportion goes on capital expenditure. The production firms in class B, like the distribution firms, present an expenditure pattern dominated by intramural expenditure¹⁵ (table 8).

Within the different classes of firms, it is noticeable that labour costs represent a higher proportion in the case of type A2 research centres, but also for type C firms. However, this finding must be qualified by stating that the relative share of labour costs and other current costs varies very widely between individual firms: both range between 0 and 99-100 p.c., which implies that the dividing line between the two types of expenditure cannot perhaps always be clearly defined. Conversely, a point that emerges clearly from the figures is that the capital expenditure is higher for firms in class A, probably because of the higher costs of laboratory equipment for basic research.

As regards external expenditure on R&D, the differences between the individual classes of firms are clearer. For instance, distribution firms (class E) and production firms which do not conduct any basic research in Belgium (classes B and C), effect that expenditure almost exclusively in Belgium.

¹⁵ However, as will become apparent later (see 2.2.4 "Type of R&D activities" and 2.2.6 "Cooperation with other research centres", the dominance of intramural expenditure in R&D budgets for most firms concerned produces a distorted picture of the location of the R&D activities. For example, respondents pointed out that extramural expenditure by the Belgian establishment is paid for (in part) directly by the parent company, and that a high incidence of cooperation with other research centres does not always imply substantial investment volumes.

In contrast, class A firms spend decidedly more on external research in the rest of the world. Within group A, there is a further striking difference between A1 and A2 firms, the latter effecting “only” one-third of their external expenditure abroad, while the figure for the former is no less than 85 p.c.

Consequently, if the R&D intensiveness of the classes of firms is assessed on the basis of intramural rather than total expenditure, that results in only a very small downward adjustment for distribution firms and production firms outside class A. However, for this last class, and - in view of its dominance of the sector’s R&D activity- for both the production firms as a whole and the overall total, R&D intensiveness is roughly halved if those percentages are calculated only on the basis of intramural expenditure (chart 10).

Yet the assessment of the investment efforts of the pharmaceutical sector on the basis of intramural expenditure only – this approach being fairly common, particularly for international comparisons of R&D investments – does not necessarily give an accurate picture of the value of those investments for the domestic economy. On the one hand, external R&D expenditure effected abroad may have a pay-back for the local economy if there is a direct link with the local production set-up. Conversely, it is sometimes claimed that external R&D expenditure, e.g. with Belgian contract organisations (CROs¹⁶ etc.), without the intellectual property rights being retained in the country, creates little value for the Belgian economy. However, in that connection it can be said that, in practice, such expenditure on research conducted by universities, hospitals, etc. appears to be an important source of funding for those institutions, which they in turn can devote to research (especially basic research and post-graduate training). An additional social effect is that such research programmes enable Belgian patients to gain earlier access to potentially innovative drugs.

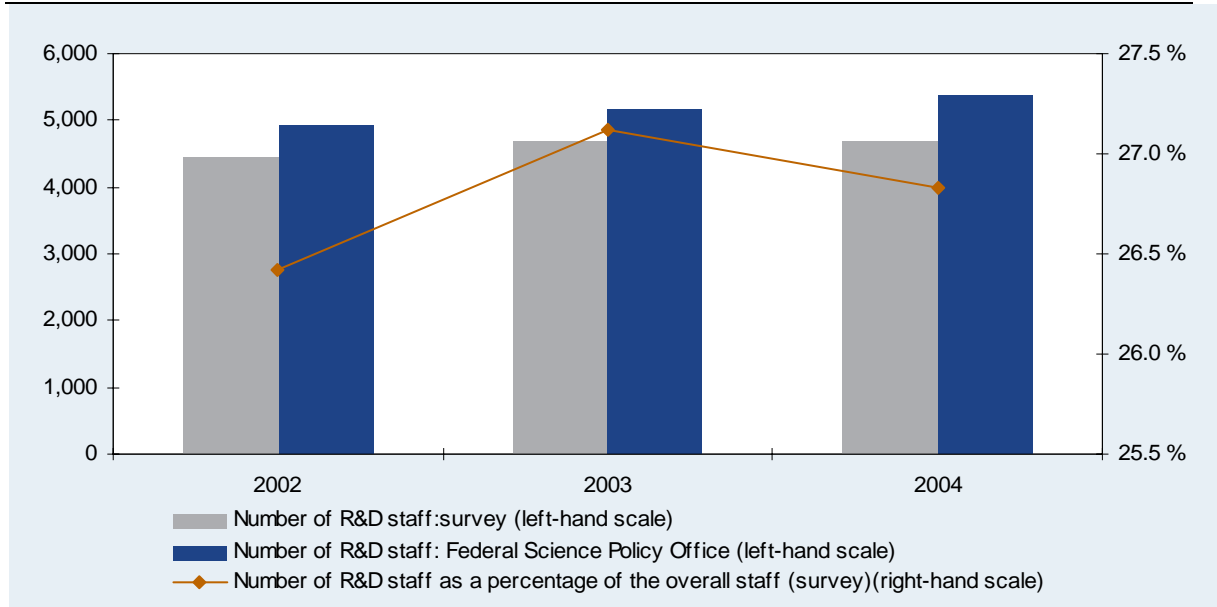
2.2.2 R&D staff

The total number of staff employed by survey participants for intramural research averaged around 4600 units during the period 2002-2004, which is about 500 fewer than the average number of units according to the Federal Science Policy Office figures¹⁷. In contrast to this last series, which indicates a gradual increase in the R&D staff, the changes in the research staff of the R&D sample did not exhibit any clear trend during the period considered: in 2003 the numbers were higher than the previous year, but in 2004 they remained more or less constant (chart 12).

¹⁶ Contract Research Organisations (CROs) are commercial firms which focus on setting up, conducting and analysing clinical studies for large pharmaceutical companies.

¹⁷ The figures relating to R&D staff obtained from the Federal Science Policy Office concern ANRSE (Analytical Researchers, Scientists and Engineers) data. These are compiled in a manner similar to that described for ANBERD data in footnote 10.

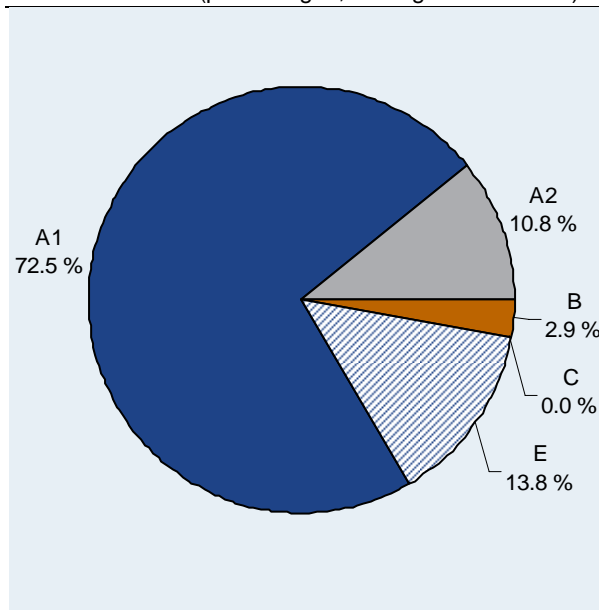
CHART 12 R&D STAFF



Sources: NBB, Federal Science Policy Office.

Most of the R&D staff in the sample are found in class A firms, which account for 83.3 p.c.; the other production firms represent only 2.9 p.c. while the distribution firms together employ 13.8 p.c. of that staff (chart 13).

CHART 13 SHARES OF THE CLASSES OF FIRMS* IN THE TOTAL R&D STAFF
(percentages, averages 2002-2004)



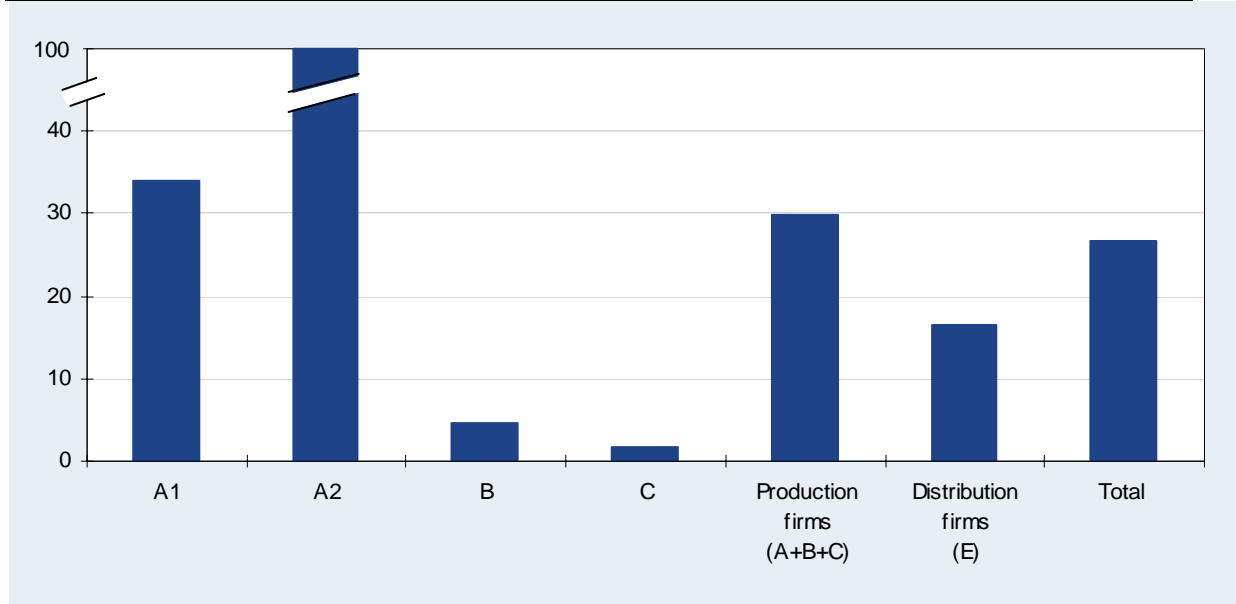
Source: NBB

* For a description of the classes of firms, see table 2.

The average number of staff employed on R&D in relation to the total overall staff provides an alternative way of measuring R&D intensiveness. For the survey sample as a whole, that figure is

around 27 p.c., and is thus at much the same level as the R&D intensiveness calculated earlier on the basis of expenditure, which came to around 24 p.c.¹⁸ (chart 12).

CHART 14 R&D INTENSIVENESS PER CLASS OF FIRMS*, MEASURED BY THE STAFF
(R&D staff as percentages of the overall staff per class, averages 2002-2004)



Source: NBB

* For a description of the classes of firms, see table 2.

The relative differences in R&D intensiveness for the individual classes of firms ascertained on the basis of expenditure are confirmed if the intensiveness is calculated on the basis of the R&D staff. According to this last criterion, however, the figures are somewhat closer together, as intensiveness comes to 37 p.c. for class A, while for the other classes it ranges between 2 and 16 p.c. (chart14).

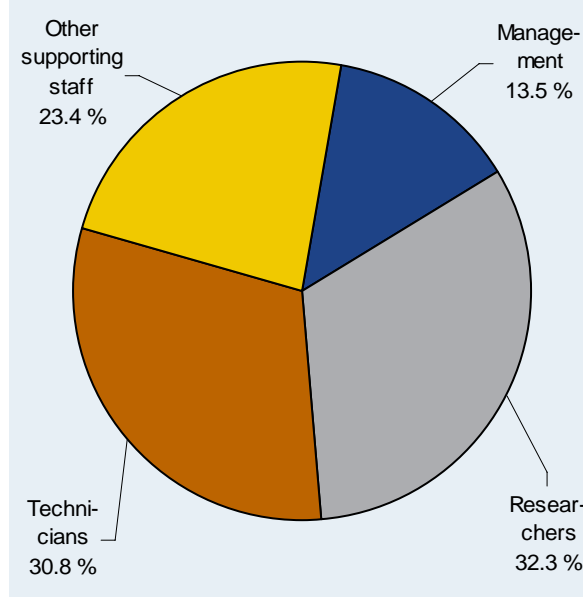
The human capital employed can be broken down from two angles, namely according to the function or type of work performed by the staff in the course of the R&D activities, and according to the highest level of qualification reached, though that approach has its limitations since no account can be taken of research experience and personal development¹⁹.

¹⁸ For the calculation of R&D intensiveness on the basis of expenditure, expenditure by firms in class A2 was disregarded (see footnote 13).

¹⁹ For a description of the various functions and levels of qualification identified in the survey, see the explanatory notes to the survey form in Annex 1.

CHART 15 R&D STAFF BY FUNCTION*

(percentages, averages 2002-2004)

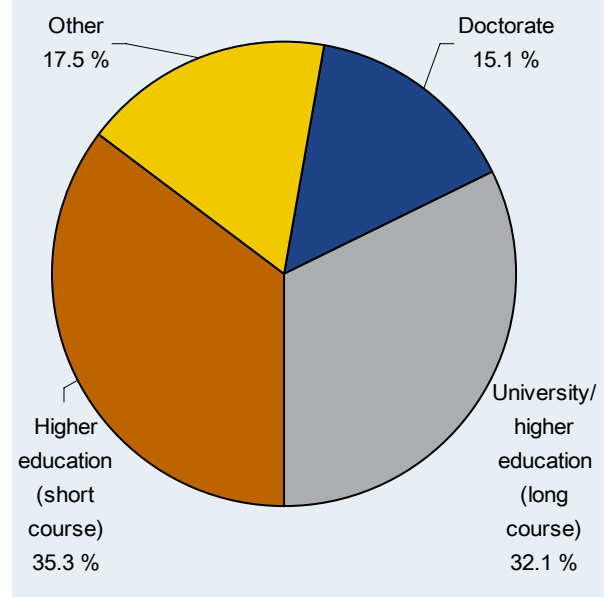


Source: NBB

* For a description of the functions, see the explanatory notes to the survey form in Annex 1.

CHART 16 R&D STAFF BY LEVEL OF QUALIFICATION*

(percentages, averages 2002-2004)



Source: NBB

* For a description of the levels of qualification, see the explanatory notes to the survey form in Annex 1.

The breakdown of R&D staff by functions shows that the categories "researchers" and "technicians" are best represented, with 32 and 31 p.c. respectively. The "other supporting staff" and "management" categories account for 23 p.c. and 14 p.c. in that order (chart 15).

TABLE 9 R&D STAFF PER CLASS OF FIRMS* BY FUNCTION AND LEVEL OF QUALIFICATION**

(percentages of the total per class, averages 2002-2004)

Class *	Function**				Level of qualification**			
	Management	Researchers	Technicians	Other supporting staff	Doctorate	Univ. / higher education (long course)	Higher education (short course)	Other
A1	11	33	37	18	16	26	39	19
A2	13	39	11	37	5	75	0	20
A (A1+A2)	11	34	34	21	15	28	37	19
B	13	66	2	20	13	36	48	4
C	100	0	0	0	0	100	0	0
Production firms (A+B+C)	12	35	33	21	15	29	38	19
Distribution firms (E)	33	7	10	50	15	63	13	8
Total	14	32	31	23	15	32	35	17

Source: NBB

* For a description of the classes of firms, see table 2.

** For a description of the functions and levels of qualification, see the explanatory notes to the survey form in Annex 1.

However, the relative importance of these four categories must be interpreted with due caution, as the variations in the individual answers appear to indicate that the distinction is subjective. There are also a number of clear deviations from the average pattern in the various classes of firms. In the distribution firms (class E) the job distribution is clearly dominated by "management" and "other supporting staff"- this covers mainly administrative personnel – while in the case of the production firms in A2 and B the "technicians" category gives way to "other staff" and "researchers" respectively. This is probably to do with the type of R&D activities conducted by the firms (themselves). The size of the firm is also a factor which can influence the job breakdown, as is illustrated by class C (table 9).

As regards the standard of education of the R&D staff, "university/higher education (long course)" and "higher education (short course)" are the ones which occur most frequently. These categories respectively account for 32 p.c. and 35 p.c. of the R&D staff, while 15 p.c. hold a doctorate (or the equivalent), and the remaining 17 p.c. have a different standard of education (chart 16).

The most striking deviations within the individual classes are a percentage of "university/higher education (long course)" which is almost twice as high in the distribution firms and research centres in class A2. In the case of the distribution firms, the corollary to that higher percentage is a smaller proportion of "higher education (short course)" and "other", while in the case of the research centres it is offset by both the "higher education (short course)" category and – somewhat contrary to expectations – the "doctorate" category (table 9).

2.2.3 Structural changes

Since the early 1990s the pharmaceutical sector worldwide has been undergoing a substantial wave of restructuring, particularly in the form of mergers and acquisitions. The main motives for the amalgamation of pharmaceutical companies are generally given as aspects relating to both expenditure and income. Apart from the hoped-for cost cutting by means of economies of scale and synergy gains, the effort to achieve a regular flow of income also plays a key role. By using mergers and acquisitions to extend the range of existing drugs and the pipeline of molecules in development, it is possible to fill gaps in pipeline and cater for the impending expiry of patents on existing drugs. That is particularly true if that is a way of achieving a degree of diversification in the market and the pipeline products, because pharmaceutical companies traditionally focus on only a small number of types of therapy, which naturally implies a risk.

In a study conducted for the European Commission on innovation in the pharmaceutical sector, the authors conclude on theoretical grounds that mergers and acquisitions in the drugs sector tend in the short term to result in lower expenditure on research and development; they see those assumptions borne out empirically and by case studies. One reason for the decline in R&D activities might be the elimination of marginal and overlapping research projects²⁰.

The results of the R&D survey of the Belgian market indicate that, during the period 2002-2004, 23 p.c. or roughly one-quarter of the respondents had undergone a significant structural change with a perceptible impact on their R&D activities. It is noticeable that these companies took a positive view of the effects on the R&D activities in the Belgian branches, as 83 p.c. of those who answered 'yes'

²⁰ Charles River Associates (2004).

reported an increase in expenditure – the impact on the R&D expenditure was still not entirely clear for one respondent at the time of the survey – and 100 p.c. reported an increase in their research staff (table 10). In so far as mergers and acquisitions may have negative consequences in the short term for the R&D activities of the group of firms as a whole, this therefore certainly does not appear to be at the expense of the Belgian branches²¹!

TABLE 10 STRUCTURAL CHANGES AND IMPACT ON R&D

	No	Yes	
Structural changes in 2002-2004 (p.c. of respondents)	77	23	
		<u>Reduction</u>	<u>Increase</u>
Impact on expenditure (p.c. of those answering 'yes')		*	83*
Impact on staff (p.c. of those answering 'yes')		0	100

Source: NBB

* In the case of one respondent answering 'yes', the effects on expenditure were not yet apparent at the time of the survey.

2.2.4 Type of R&D activities

The traditional, input-related R&D indicators, namely expenditure and staff, give only a rudimentary picture of the research efforts made by the Belgian pharmaceutical sector, because the R&D process in the pharmaceutical sector is highly complex, and the degree to which firms engage in such activities may vary widely. To gain a better idea of the research on drugs conducted in Belgium, the survey therefore zoomed in on various aspects concerning the type of R&D activities.

For a proper understanding of the survey results, it is recommended that readers unfamiliar with the typical pattern of the R&D process in the pharmaceutical sector should first study the box below, which gives a brief explanation of the principal stages in the R&D process relating to drugs.

²¹ In the middle of 2006 it emerged that one of the Belgian firms taking part in the R&D survey but not reporting any significant structural changes affecting its R&D activities during the three years of the survey was soon to be closed down as a result of restructuring within the company.

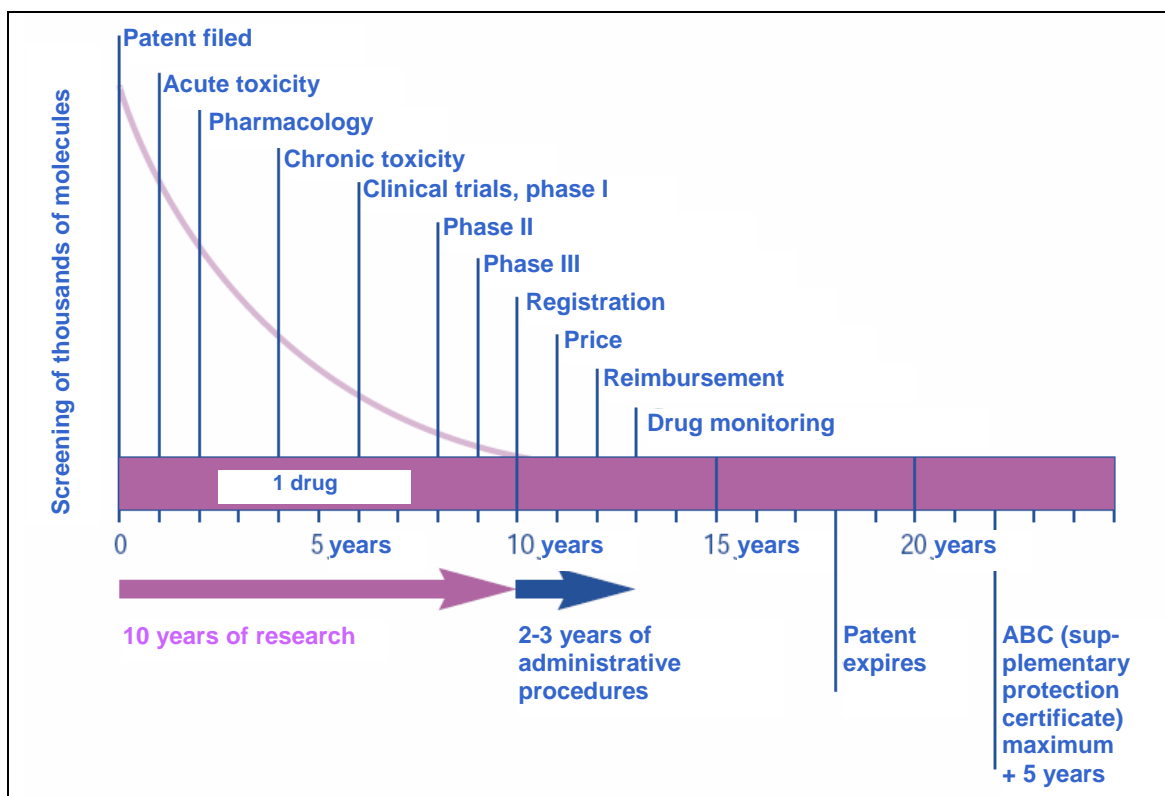
Box: The drug research and development process

The development of a new drug is a complex, lengthy, risky and expensive process.

COMPLEX

This R&D process comprises various stages, and is generally divided into the basic research phase and the pre-clinical and clinical phases²².

The research and development phases (R&D) required for a new drug



During the basic research phase, new molecules (new active substances) are produced and screened. Product development begins once such a new molecule looks promising, and will be subjected to further pre-clinical and clinical testing. At that point an application will already be submitted for a patent for the molecule in question²³.

The main object of the pre-clinical phase is to check the safety of the candidate drug by both in vitro testing and animal testing, before testing it on humans. This phase focuses in particular on the therapeutic effects of the substance (pharmacological testing), the physical side-effects (toxicological testing) and the metabolism (pharmakinetik testing).

During the clinical research and development, candidate drugs which have successfully passed the pre-clinical tests are tested on humans under strict medical supervision. These clinical studies are divided into various phases. In phase I the drug is administered to a small group of healthy

²² The various stages in the R&D process do not always follow one another as some stages run simultaneously.

²³ For completeness, it should be said that the "additional protection certificate" (ABC) makes it possible to extend the period of protection for a drug by a maximum of 5 years; the patent and the certificate must not be valid for more than 15 years from the date of the first registration in an EU country.

volunteers, the main aim being to check the safety of the product and to investigate the best dosage for administering the drug. The phase II trials are conducted on a small number of selected patients, and are intended in particular to evaluate the effectiveness of the candidate drug. The aim of the phase III tests is to compare the candidate drug with the standard treatment in terms of effectiveness and side effects on large groups of patients.

Finally, before the drug can be placed on the market there are still a number of administrative approval procedures to be completed: this concerns the submission of the registration papers followed by determination of the price, and possibly the transparency and reimbursement procedure.

Once the drugs are on the market, the “drug monitoring” begins, the main point being to check for any undesirable reactions²⁴.

LENGTHY

The time elapsing between the production of a new molecule and the licensing of a drug for market launch averages twelve to thirteen years. On average, ten years of that time is spent on the entire research and development process, and an average of two to three years on the administrative procedures (registration, pricing and reimbursement).

RISKY

According to the pharmaceutical sector, of the five to ten thousand molecules tested in the pre-clinical phase, only five proceed to the clinical trial phase; of those five, ultimately only one will be approved. Moreover, of the drugs placed on the market, only one in three will be profitable.

EXPENSIVE

Various attempts have already been made to calculate the cost of developing new drugs. The pharmaceutical sector itself refers in this connection to the latest study by J.A. DiMasi, which – for the year 2000 – arrived at a total cost of € 868 million for the development of a new drug (compared to € 149 million and 344 million at 2000 prices for the years 1975 and 1987 respectively). These costs take account of both failures and the opportunity costs of the capital invested. Because of this last element, and also because the calculations concern new molecules – the most expensive to develop – and no account is taken of the tax allowances for research budgets, some observers doubt this figure.

Sources: J.A DiMasi (2003), European Federation of Pharmaceutical Industries and Associations (EFPIA) and pharma.be.

The survey gathered data on the location and frequency of the activities in the period 2002-2004 for each type of drug research, more specifically basic research, and pre-clinical and clinical development. Since the questions were qualitative and the participants only had to tick the appropriate items, the results are given here in the form of percentages.

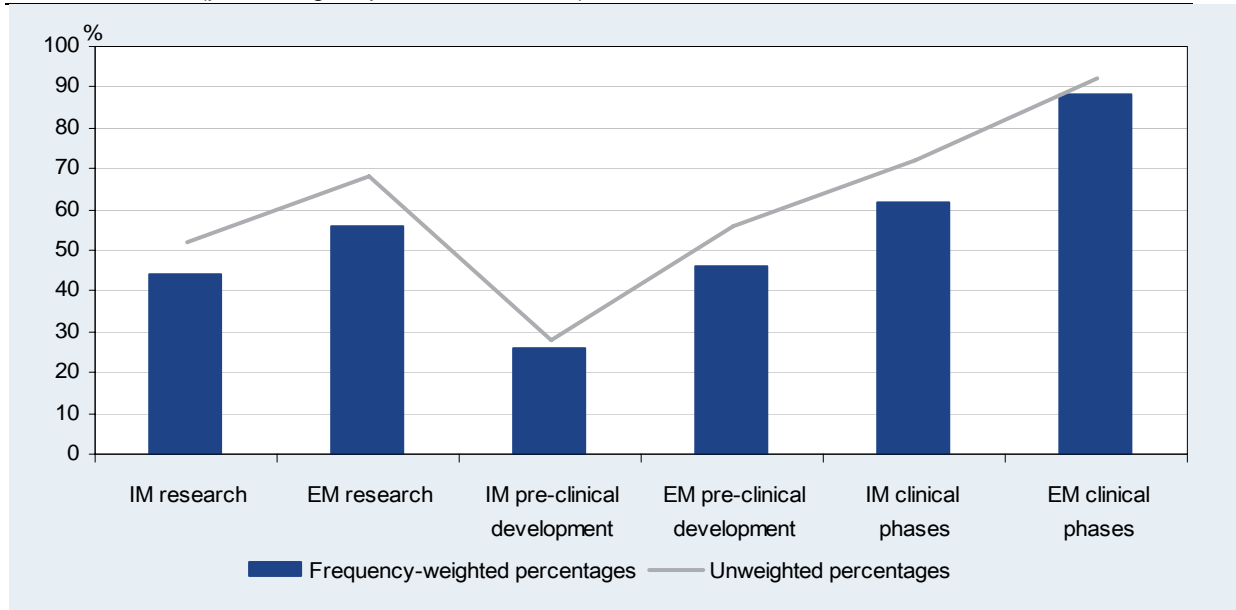
As regards the nature of pharmaceutical research in Belgium, the survey results clearly indicate the importance of the clinical development phases, as all participants state that they have been active in that R&D stage (100 pct.). Conversely, pre-clinical development was the stage in which the

²⁴ This is also known as phase IV of the clinical trials; by convention, however, this phase is not normally included under R&D (see Frascati OECD manual);

fewest Belgian firms were active, namely just 56 p.c., whereas 73 p.c. of the firms had engaged in research activities²⁵.

However, as was already apparent from the breakdown of R&D expenditure in section 2.1, the participants did not pursue all those activities internally. On the contrary, it is noticeable that for all stages the percentage of firms with extramural activities is higher than the percentage of firms with intramural activities (chart 17).

CHART 17 TYPE, FREQUENCY AND LOCATION OF THE R&D ACTIVITIES
(percentages, period 2002-2004)



Source: NBB

The survey results also reveal that if a participant is active in a particular research stage and location, that situation is generally permanent. This is apparent in chart 17 from the similarity between the unweighted and frequency-weighted percentages of participants. For the purpose of calculating this last figure, the percentage of participants ticking the option "permanent" was given twice the weight of those ticking the option "occasional" when the two were added together; consequently, the weighted series reflects not only the relative number of participants which were active for the type and location concerned, but also the frequency of that activity²⁶ (chart 17).

As expected, the breakdown of the survey results into individual classes of firms indicates a number of clear differences of emphasis between classes in the R&D activities conducted in Belgium. Thus, firms in class A are (almost) permanently active in all R&D stages, both intramurally and extramurally. The other production firms, particularly those in classes B and C, were all active in intramural and extramural research and clinical development phases, but less permanently so; however, pre-clinical development was only an occasional, and extramural occurrence. Finally, in the case of the distribution firms the emphasis is clearly on the clinical phases; the other stages

²⁵ The questionnaire made no distinction between basic and applied research.

²⁶ For completeness it should also be said that the weighted series underwent a further transformation which resulted in the figures theoretically ranging from zero – no-one engages in activities of the type and location concerned – to 100 – all firms are permanently engaged in activities of that type at that location.

involve only a minority of the firms. The distribution firms also exhibit a marked imbalance in favour of extramural activities at all stages (table 11).

TABLE 11 TYPE, FREQUENCY AND LOCATION OF THE R&D ACTIVITIES PER CLASS OF FIRMS*
(frequency-weighted percentages, period 2002-2004)

Class*	Research		Development			
	IM	EM	Pre-clinical		Clinical	
			IM	EM	IM	EM
A1	100	100	100	100	100	100
A2	50	50	75	100	75	100
A (A1+A2)	80	80	90	100	90	100
B	50	75	0	75	50	100
C	50	50	0	0	50	50
Production firms (A+B+C)	69	75	56	81	75	94
Distribution firms (E)	32	47	12	29	56	85
Total	44	56	26	46	62	88

Source: NBB

* For a description of the classes of firms, see table 2.

2.2.5 *Molecules and projects in development*

Apart from qualitative data on the nature of the R&D activities conducted in Belgium, the survey also attempted to obtain quantitative information on the importance of the Belgian component of the research pipeline. However, the quantitative information obtained by the survey must be treated with due caution, for two reasons: various respondents were unable/unwilling to provide the information requested, so that the aggregate figures must be regarded as a lower limit; also, the absolute figures must, of course, be related to a broader international reference point. But it must be emphasised in advance that the European and global data which we have in that connection provide only a very rough indication of the importance of drug research in Belgium, since the series are not entirely comparable in either conceptual or methodological terms.

At the time of the survey, i.e. during 2005, the number of new molecules being developed by the Belgian pharmaceutical sector was at least 478. That figure corresponds more particularly to the globalisation of the replies from only 24 respondents²⁷; if this figure is extrapolated on the basis of the company average of 20 molecules, then the total number developed in Belgium comes to over 500 molecules.

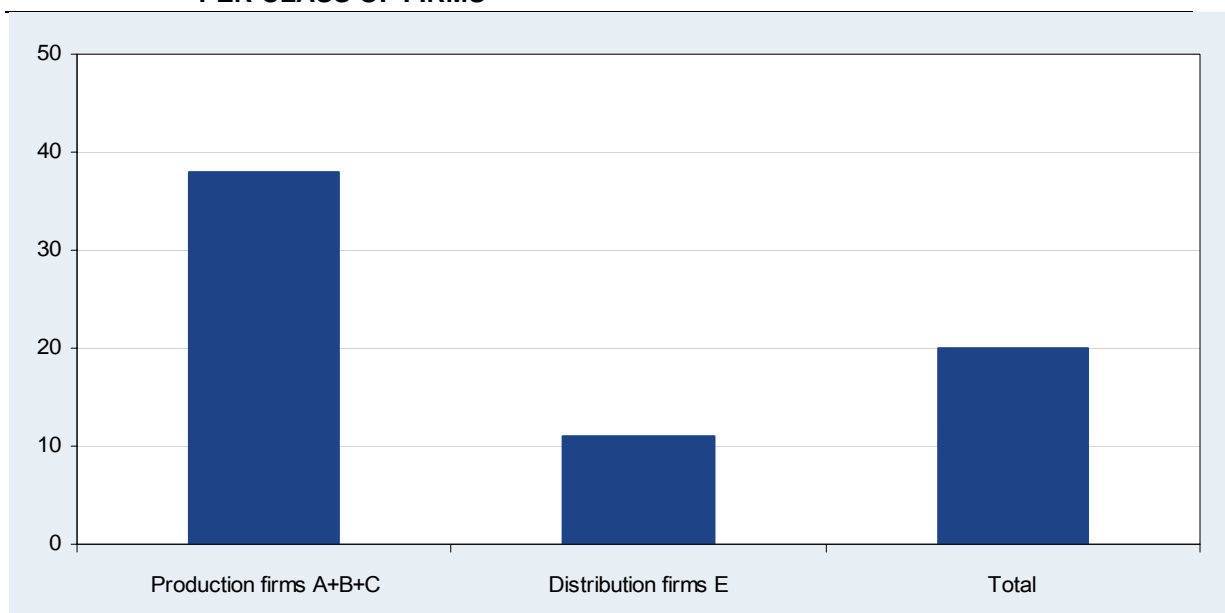
An average of 20 new molecules per Belgian firm seems fairly high when considered in the international context, as the Centre for Medicines Research International (CMR) calculated that – taking all sizes of firms together – the average size of the (global) development pipeline in the period 2000-2004 totalled around 25 to 30 new active substances²⁸.

²⁷ In calculating the figures a distinction was made between respondents answering "0" and those leaving a blank; unlike the former, the latter were naturally not included for calculating averages, for example.

²⁸ CMR (2005).

Of course, that general average of 20 molecules for the Belgian firms masks variations between individual firms. The production firms had, on average²⁹, a pipeline of 38 molecules, while the average for the distribution firms came to 11.

CHART 18 **AVERAGE NUMBER OF MOLECULES IN DEVELOPMENT IN 2005**
PER CLASS OF FIRMS*



Source: NBB

* For a description of the classes of firms, see table 2.

One result of these differences is that production firms account for 64 p.c. of the total number of molecules in the Belgian segment of the pipeline, while the remaining 36 p.c. of molecules are being developed by distribution firms.

As regards the allocation of those molecules across the various R&D phases, the survey results reveal a number of striking points about Belgian drug research.

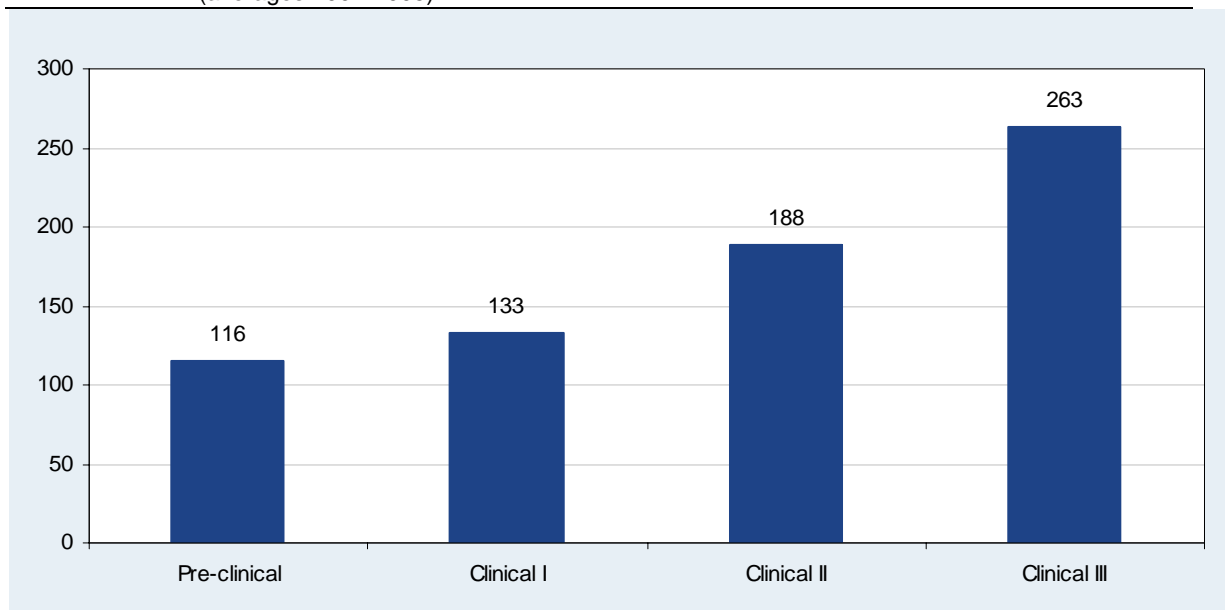
For instance, the distribution of the average number of projects in development³⁰ across the various development phases in 2004-2005³¹ indicates that the numbers are higher for the later R&D phases: in particular, there were 116 projects in the pre-clinical phases, compared to 133, 188 and 263 projects in the respective clinical phases (chart 20).

²⁹ It is not possible to provide any further breakdown by classes within the production firms without impairing the confidentiality of the figures.

³⁰ A "project in development" means the development of a molecule for a medical indication and form of administration. The number of projects in development therefore need not correspond to the number of new molecules in development, since the latter may give rise to multiple projects (e.g. various forms of administration). However, double counting of the total number of projects in development cannot be entirely ruled out, since studies may proceed simultaneously in various phases.

³¹ In view of the low response rate for the years 2002 and 2003, no data are published for those years.

CHART 19 NUMBER OF PROJECTS IN DEVELOPMENT IN THE VARIOUS R&D PHASES
(averages 2004-2005)



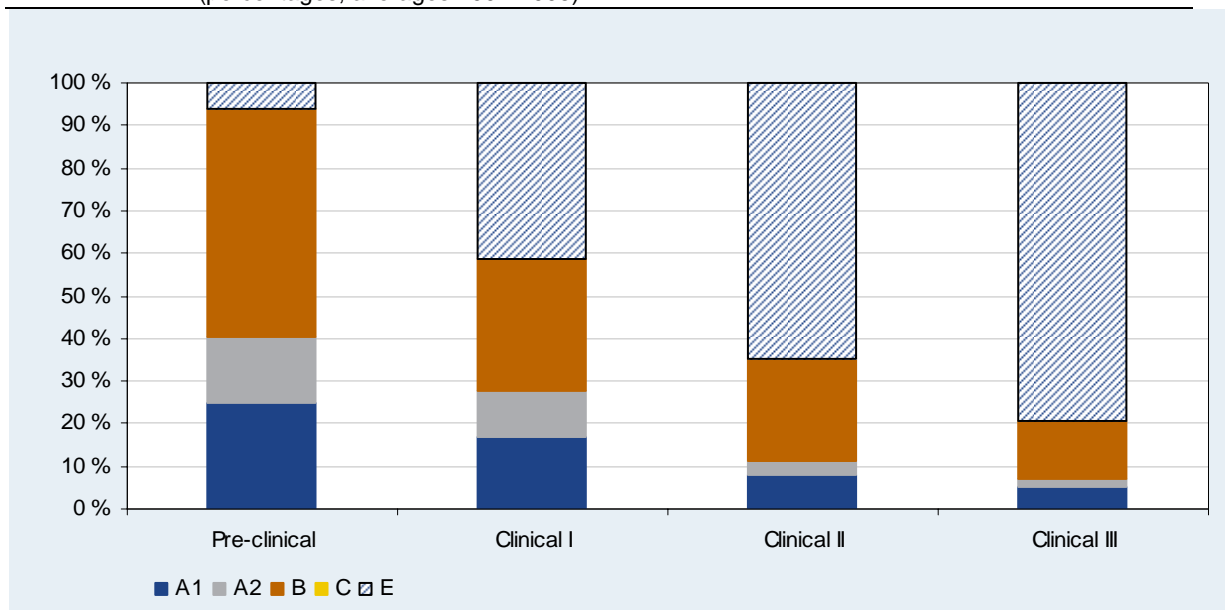
Source: NBB.

Such a distribution appears atypical for the sector. The international data on the phase distribution available to us, namely the products in development in the European countries, and the worldwide data (though the latter concern only the number of new molecules in development) indicate that phase III of the clinical research actually comprises the smallest number of products or new molecules³². Another striking point emerges if the figures from the survey are compared with the European data (by referring to "products in development", these appear to use a broader definition which is more appropriate to the survey concept): the pre-clinical research conducted here is not very significant, in accordance with the survey's findings in section 2.2.4 "Type of R&D activities". The number of projects in phases I and II of the clinical research in Belgium roughly corresponds to one-third of the number of products for Europe, but in the case of phase III the Belgian figures are slightly above those for Europe. Although attention must be drawn to the precarious character of this comparison³³, it does point to the relative importance of clinical research in Belgium, especially in the case of phase III.

³² These data were obtained from IMS and Pharmaprojects, being cited in CRA(2004) and CMR(2005) respectively.

³³ The figures for Europe concern the year 2003, while the survey results refer to the average for 2004 and 2005. There is also a methodological difference in that each "product" is counted only once for the European data, namely in the latest phase of the studies, while in the survey results double counting cannot be entirely ruled out. There could also be some conceptual differences between the two series.

CHART 20 SHARES OF THE CLASSES OF FIRMS* IN PROJECTS IN DEVELOPMENT
(percentages, averages 2004-2005)



Source: NBB

* For a description of the classes of firms, see table 2.

The atypical phase distribution for Belgium is of course connected with the fact that not all Belgian firms are active in every R&D phase. The total number of projects in development in Belgium therefore conceals a marked difference between the production firms and the distribution firms. In the case of the former, the total number of projects in development declines the later the stage in the development process, whereas for the latter the situation is precisely the reverse. This phenomenon is, of course, reflected in the shares represented by the various groups in the number of projects in the various development phases (chart 20).

According to the survey results, the overall number of clinical tests conducted on test subjects in Belgium in connection with projects in development averaged 495 per annum in the period 2004-2005. However, this figure must once again be interpreted as a lower limit, because in reality the total number of tests in Belgium is probably a great deal higher than could be ascertained by the survey³⁴. Various participants state that the figures on clinical testing could not be given in full. For instance, it is quite common for the R&D activities to be organised by the foreign head office for the whole European region; for example, if the Belgian branch is not involved in the use of contract organisations (CROs, etc.) in Belgium, it will often not have precise information on the tests carried out.

The distribution firms accounted for the majority of the total number of tests, at 71.5 p.c. That share is due purely to their numerical dominance, as the average number of tests conducted remained fairly constant across almost all classes of firms, totalling around 27 tests per year.

The total number of test subjects involved in these clinical tests in Belgium can be estimated at a minimum of 100,000 per annum, according to the survey results; on average, this represents

³⁴ The total of 495 tests is the aggregate for "only" 18 respondents. If this figure is extrapolated on the assumption that the other participants represent an average of around 27 tests, the actual total could be as high as 700 to 750.

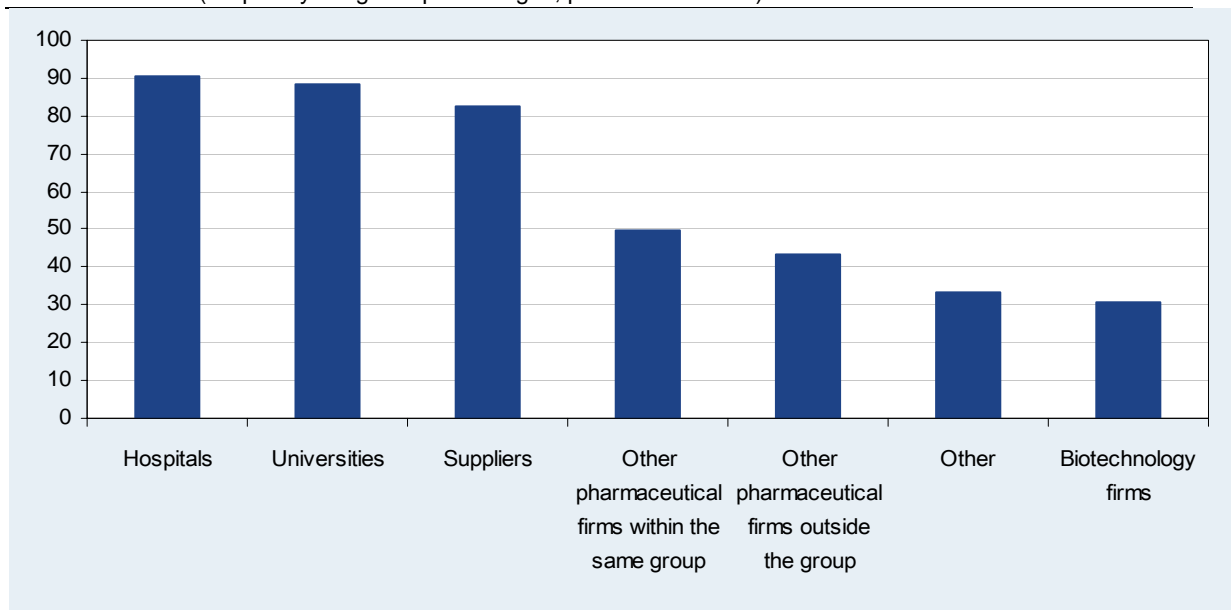
around 200 persons per test. That average masks considerable diversity within the individual responses, ranging from a few dozen to several hundred or thousands per test. The number of test subjects involved in any clinical test naturally depends on the specific clinical phase in which the test is conducted. However, the survey contained no details on this.

2.2.6 Cooperation with other research centres

Much of the drug research by Belgian branches in the period 2002-2004 was conducted extra muros. The survey ascertained the types of research centres involved in such cooperation and the frequency with which it occurred. In addition, a distinction was made between Belgian and foreign research centres, in order to detect any differences in the patterns of cooperation.

The participants' replies to this qualitative question revealed that those using other research centres addressed themselves to various types of partners, and did generally not confine themselves to partners in Belgium. However, some variation was apparent in the frequency of cooperation. For ease of analysis and to permit a ranking of the types of research centres, the participants' qualitative responses were therefore processed into weighted percentages, in the same way as described above for the answers concerning the type of research and development activities conducted in Belgium³⁵.

CHART 21 COOPERATION WITH OTHER RESEARCH CENTRES IN BELGIUM
(frequency-weighted percentages, period 2002-2004)



Source: NBB

The Belgian research centres with which the pharmaceutical sector collaborates can be divided into two groups. First there are the hospitals, universities and suppliers (contract research institutions): not only do the majority of the participants work jointly with these³⁶, the cooperation is generally also frequent. The fact that these types of research centres clearly rank first is due to the importance of

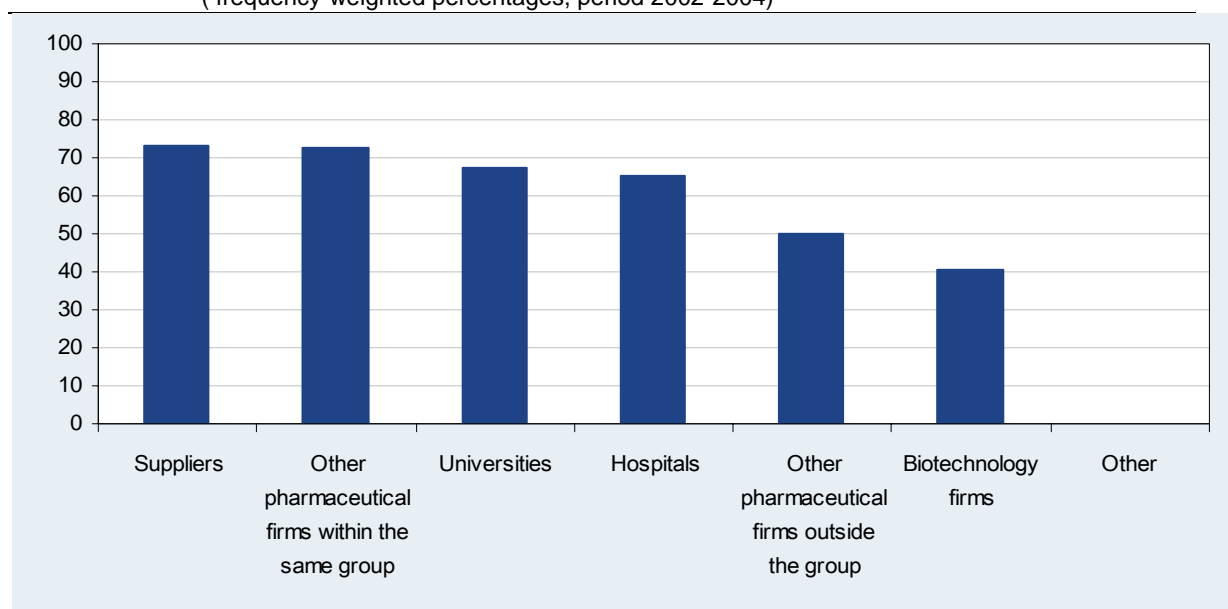
³⁵ In this connection, see 2.2.4 "Type of R&D activities".

³⁶ It is worth mentioning that all 26 participants responding to this survey question ticked cooperation with universities.

clinical development in the R&D activities undertaken by Belgian branches, although the cooperation with universities naturally also occurs in the case of basic research. Conversely, far fewer respondents ticked “other pharmaceutical firms” – either within the same group or from another group – and biotechnology firms, and the cooperation with these types of research centre tended to be occasional. “Other” research centres also appeared to belong to this second group of less widespread and less frequent partners. One respondent specified that this cooperation took place in the field of data management (chart 21).

In the case of cooperation with foreign research centres, the picture is slightly different, as the percentages for suppliers, universities and hospitals are a little lower than for joint projects conducted in Belgium. In contrast, in the case of international cooperation, pharmaceutical firms, particularly those from within the same group (contact with research departments located elsewhere), and to a lesser extent pharmaceutical firms from other groups and biotechnology firms come to the fore. There was no cooperation at all with “other” foreign partners (chart 22).

CHART 22 COOPERATION WITH OTHER RESEARCH CENTRES ABROAD
(frequency-weighted percentages, period 2002-2004)



Source: NBB

The advance of biotechnology in research methods has led to a worldwide trend towards increasing numbers of joint R&D projects in the pharmaceutical sector, e.g. in the form of licensing agreements between the pharmaceutical and the biotech sectors. For firms in the pharmaceutical sector, this cooperation is part of a new strategy for developing a pipeline of new products. However, the importance of such development in global research on drugs³⁷ is not, at first sight, fully reflected in the survey results. There are various possible reasons for this. Cooperation with biotech firms was perhaps not always classified as such in the survey. On the one hand, a number of major (Belgian) biotech firms are part of their own group of companies and were perhaps regarded as such, while on the other hand various biotech firms are set up as spin-offs of university research³⁸ and may be counted among “universities”. Moreover, cooperation with biotech firms may be organised and

³⁷ According to data from EFPIA, around one-fifth of the new molecules launched on the world market each year and half of all the drugs in development now come from biotechnology.

³⁸ In this connection, see FPS Economy (2006) for Belgium.

coordinated from the head office and/or the central R&D department, so that the Belgian branches of most companies are not directly involved. The higher percentage for foreign biotech partners than for Belgian partners could reflect the continuing lead maintained by the US in this sphere.

Finally, although the survey results indicate that cooperation with other research centres is a widespread phenomenon, and those joint projects are often frequent, one respondent pointed out that in terms of the investment volume or the number of staff involved in such cooperation, those contacts are not always equally significant. Moreover, joint projects do not always come under the actual outsourcing of pharmaceutical R&D activities, but also concern a joint search for technological solutions with specialist suppliers.

2.2.7 Location factors

Although the Belgian pharmaceutical sector did not escape the general shift in pharmaceutical R&D activities from Europe to the US, it still puts in a decidedly substantial R&D effort in regard to other European countries, compared to both national production and the size of the national market (turnover)³⁹.

Not only do a number of firms in Belgium pursue significant activities in the field of basic research, the Belgian pharmaceutical sector has also built up a worldwide reputation for clinical research. However, the opportunities for Belgian corporate subsidiaries in attracting/retaining those research activities depend on the Belgian investment climate.

That climate is influenced by many different factors; apart from government incentives, aspects which may play a role are among others the location of experts, including networks of scientists, laboratories, universities and R&D suppliers, and price regulation. Various authors⁴⁰ also mention the strong interaction between the location of R&D and the drug reimbursement system. They argue that more investment can be expected in countries where drugs gain quicker access to the market and where there are fewer price restrictions (the price in the country of development being taken as the reference price), so that higher profits can be achieved.

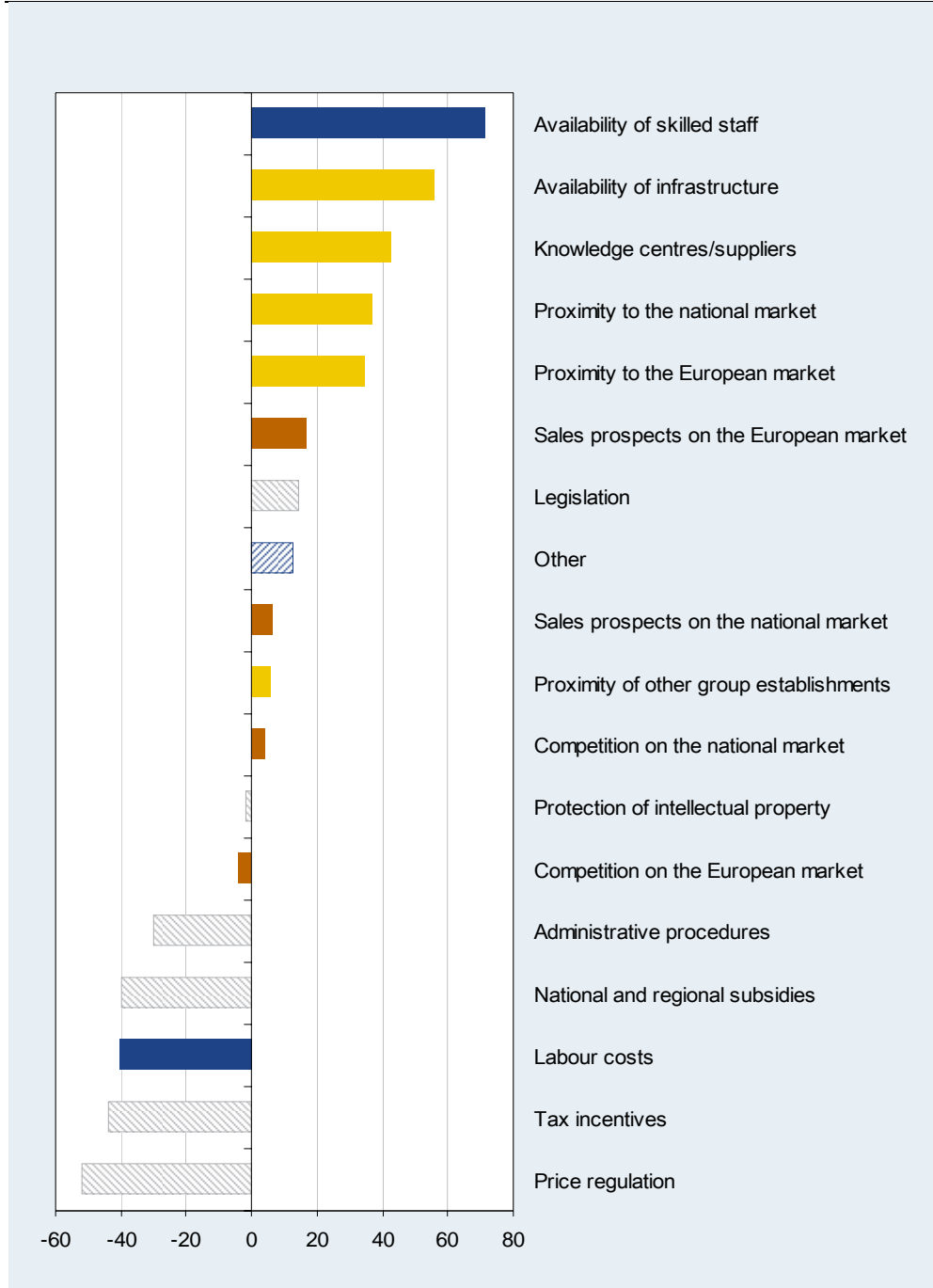
The survey attempted to provide an idea of the importance of various factors for the location of pharmaceutical research in Belgium. The possible factors were ranked under the headings Human Resources (■ in chart 23), geographical location (■), government (■), market situation (■) and "other" to be defined in more detail (■). Taking account of the degrees of importance assigned to each factor by the respondents, the results for each item were summarised in the form of an index which may range, in theory, from -100 (all respondents assess the factor as highly negative) to +100 (all respondents assess the factor as highly positive)⁴¹ (chart 23).

³⁹ In this connection, see Annex 2.

⁴⁰ e.g. Charles River Associates (2004).

⁴¹ More specifically, the percentage of replies for each degree of importance was taken as the basis for each sub-heading. A net percentage was calculated for each factor – i.e. the "negative" percentages were deducted from the "positive" percentages, the "highly positive" and "highly negative" percentages being given twice the weighting in the total compared to the "moderately positive" and "moderately negative". For ease of interpretation, care was taken to ensure that the net percentage obtained could range in theory from – 100 (all firms assess the factor concerned as highly negative) to + 100 (all firms assess the factor concerned as highly positive), in the same way as described in section 2.2.4 "Type of R&D activities".

CHART 23 ASSESSMENT OF LOCATION FACTORS
 (balances of the weighted percentages of "positive" and "negative")



Source: NBB

The item which stands out as the most important in the ranking of the location factors is the availability of skilled staff; that factor was not assessed as negative by any of the firms. However, some participants did specify that the calibre of the staff was an advantage, but the availability or quantity was sometimes inadequate.

Conversely, the HR factor "labour costs" was assessed as decidedly negative. The trend towards relocation in the pharmaceutical sector, by means of contract organisations, transferring clinical trials to low wage countries such as Eastern Europe and India therefore represents a genuine threat

to Belgium's leading position here, especially as those countries have other advantages as well⁴². As implied by the index figures calculated, however, this factor – taking all firms together⁴³ - does not currently entirely outweigh the first factor, namely the knowledge and expertise available here.

Belgium's geographical location is regarded as an advantage, as all factors under this heading were assessed as positive. However, it is noticeable that, for the pharmaceutical sector, it is not so much the central location in Europe that matters – as half of the individual firms gave a neutral response on this – but mainly the availability of the infrastructure and the proximity of knowledge centres and suppliers. Conversely, the proximity of other group branches is a far less important factor in the location of research activities, a result which is in line with the findings concerning cooperation with other research centres in Belgium, discussed earlier in section 2.2.6 "Cooperation with other research centres".

The "other" factors⁴⁴ and elements connected with the market situation are assessed as the most neutral, though it can be said that within this last group of factors, sales prospects are assessed somewhat more favourably than competition conditions.

The survey results also indicate a number of clear points for policymakers, as the factors relating to the government are almost all assessed as decidedly negative. The only exception to that adverse appraisal applies to the factor "legislation concerning research and pre-clinical trials". The fact is that the Belgian legislature, aware of Belgium's key position as a host country for clinical trials, endeavoured to safeguard Belgium's competitive position when transposing the European directive on clinical trials into Belgian law, by creating an attractive framework. Thus, the periods for granting a licence to conduct such tests – 15 and 18 days respectively for mono-centre and multi-centre testing – are among the shortest in Europe⁴⁵. However, it appears that the law is still not being implemented efficiently. In practice, the deadlines for granting approval for testing are not always respected; for example, objections are often not raised until after expiry of the statutory time limit, which of course leads to confusion and legal uncertainty.

The negative assessment of the factor "administrative procedures" is perhaps equally to do with the effective deadlines. Although maximum periods of time are laid down within the EU in regard to the registration of drugs, pricing and possible reimbursement, not only are those periods exceeded in practice in Belgium, the time taken also seems to be very long compared with that in other countries⁴⁶. The decision to set up the Federal Agency for Drugs and Health Products, which will supervise the entire drugs process from research to usage, may be a step in the right direction.

The subsidy policy and the fiscal policy pursued by the government directly and indirectly in regard to R&D is also assessed as negative by the participants⁴⁷. Nevertheless, in the past both the federal

⁴² For these countries, their larger population is an advantage, especially in the case of the rarer disorders. Moreover, patients in these countries tend to be "under medicated", which reduces the risk of interactions between different drugs and distortion of the research results.

⁴³ For completeness, it should be pointed out that the replies of the individual firms were not weighted for the purpose of calculating the total.

⁴⁴ The item "other" was seldom ticked, and only specified in exceptional cases ("historical links"). The individual assessments range from moderately negative to highly positive. When answering the question, the firms may have had a variety of factors in view, so that the overall balance is difficult to interpret.

⁴⁵ Trouet (2004).

⁴⁶ Cambridge Pharma Consultancy (Dec 2002) remarks in this connection: "Patients in Belgium on average wait 2 years longer to receive new medicines than patients in the UK and Germany (...). These delays are usually attributable to extended reimbursement negotiations".

⁴⁷ It should be remembered that the survey was conducted during 2005, i.e. before there was any more selective levy on the turnover of pharmaceutical firms, a measure which was welcomed by the production firms engaging in many R&D activities in Belgium.

and regional governments have already taken various measures aimed specifically at R&D and innovation or financing, and more generally in regard to taxation and employment. However, one participant makes the point that the lack of a coherent policy (coherence between federal and regional policy and coherence at federal level) is highly negative for Belgium. On the one hand, the sector receives support (education, academic research, tax concessions, science policy) while on the other hand the results of that research are seriously discouraged at the level of social affairs, the budget and public health.

Finally, price regulation emerges as the most negative factor according to the findings. Measures that depress prices clearly reduce the incentive for R&D, via lower revenues⁴⁸ and hence lower investment returns. The price comparisons produced by the pharmaceutical sector indicate that, in that connection, Belgian prices for innovative drugs are the second lowest in Europe, after Greece^{49 50}. However, it must also be said that, during the period of the survey, debate was raging in Belgium over the introduction of the Kiwi model for drugs. That element may have exacerbated the negative assessment of this factor: price regulation/low prices in itself plays a role in that context, but the pharmaceutical sector also regarded the possible introduction of a tendering system and the associated uncertainty as a deterioration in the Belgian investment climate⁵¹.

The assessment of the location factors varies somewhat according to the class of firms. For instance, the production firms, which have a larger staff, on average, take a more negative view of labour costs than the distribution firms. The latter naturally attach more importance to the proximity of the national and European markets than do the production firms, which export much of their output, some of it to the rest of the world. In view of the nature of the activities pursued in Belgium, the production firms are also more interested in such factors as the availability of infrastructure and expertise. Finally, although the proximity of group branches is not generally regarded as very significant, that is not so in the case of research centres in class A2.

2.2.8 Funding sources

The lengthy process facing candidate drugs proceeding through the various stages of development and marketing, and the high percentage dropped during the successive research phases, make the development of a new drug an expensive and risky business. Investments in pharmaceutical R&D therefore entail significant financial risks. Moreover, external funding is often complicated by the significant, asymmetric information problems w.r.t. this sector.

It is therefore not surprising that the survey results⁵² indicate that the R&D activities conducted by the Belgian pharmaceutical sector during the period 2002-2004 were funded almost exclusively internally, i.e. by the sale of drugs. Roughly three-quarters of the funds came from the parent company or the rest of the group of companies, and one-quarter from the Belgian branches themselves. The funding provided by the national government was relatively minimal, amounting to

⁴⁸ Owing to parallel imports and external reference pricing, these low prices are not confined to Belgium, their effects being extended to sales on foreign markets.

⁴⁹ A low price level for innovative drugs naturally does not necessarily mean that the general price level for drugs is lower, since the product mix also plays a role. In that connection, EFPIA data indicate that the cheaper, generic drugs with a market share of around 6 p.c. in Belgium in 2004 have a much lower market penetration than in most other European countries.

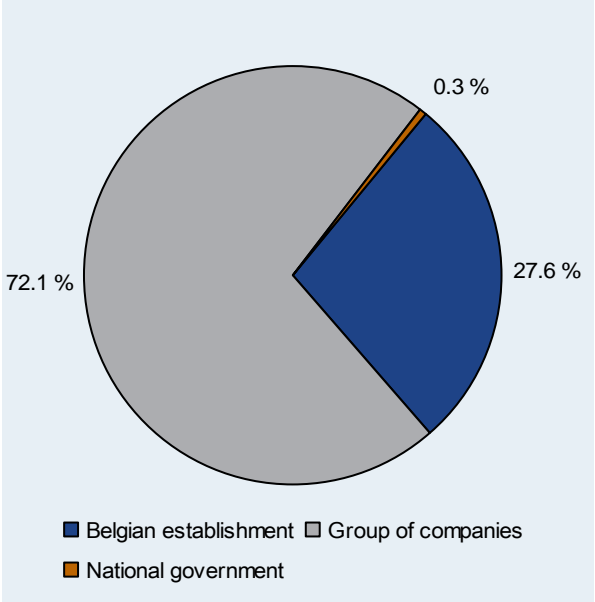
⁵⁰ Other interest groups recently came to the opposite conclusion on the basis of their own calculations. Some people consider that these divergent results are attributable to the drugs selected.

⁵¹ The possible effects of reference reimbursement and the "kiwi model" are discussed in more detail in Annex 4.

⁵² The answers were weighted according to R&D expenditure.

less than 3 tenths of one per cent of the total resources⁵³. Analysis by classes of firms also shows that this government funding only went to class A production firms, so that it may have been specifically aimed at basic research (chart 24).

CHART 24 SOURCES OF FUNDING FOR R&D ACTIVITIES
(percentages, averages 2002-2004)



Source: NBB

For the production firms and the distribution firms, the relative importance of the parent company and the Belgian branch(es) as funding sources proved to be very similar. However, a number of individual (production) firms deviate to some extent from this funding pattern: on the one hand, the activities of the class A2 research centres (which do not engage in production themselves) are wholly funded by the parent company/group of companies, while on the other hand, in the case of a number of production companies, almost all the R&D activities are financed by the Belgian branches themselves. This naturally applies to independent firms, but some of the production firms belonging to a multinational group are also in that situation (table 12).

⁵³ These figures may take no account of the various indirect support measures – which are more difficult to estimate – granted by different governments (tax measures in favour of R&D staff and encouraging R&D investment).

TABLE 12 FUNDING OF THE R&D ACTIVITIES PER CLASS OF FIRMS*
(percentages, averages 2002-2004)

Class*	Belgian branch	Group of companies	National government	Regional authorities	Supranational authorities	Other	Total
A1	29	71	0.4	0	0	0	100
A2	0	100	0	0	0	0	100
A (A1+A2)	27	72	0.4	0	0	0	100
B	85	15	0	0	0	0	100
C	100	0	0	0	0	0	100
Production firms (A+B+C)	28	72	0.4	0	0	0	100
Distribution firms (E)	25	75	0	0	0	0	100
Total	28	72	0.3	0	0	0	100

Source: NBB

*For a description of the classes of firms, see table 2.

2.3 Output data for the R&D activities of Belgian branches

The Belgian pharmaceutical sector puts substantial efforts into R&D in terms of both expenditure and personnel, and projects. However, in view of the high failure percentage – not all projects actually produce a positive result – regarded as inherent in drug research, these efforts are no guarantee of success.

Yet the output of the R&D activities is not so simple to measure. That is particularly true when it comes to estimating the specific output of Belgian branches within multinational groups where R&D is decentralised and controlled from above. That may be the reason why the response rate in the part of the survey devoted to output-related indicators was much lower for most items than for the first two sections of the survey, namely the general economic characteristics and the input-related indicators. Some of the results concerning the output of the R&D activities therefore need to be treated with due caution, since they may not give a totally representative picture of the overall situation⁵⁴.

Since innovative R&D output is difficult to measure and there is no criterion available which can give an adequate picture, the survey used various indicators, such as the number of patent applications, and the number of new drugs launched on the market and their impact⁵⁵.

2.3.1 Patent applications

Patent figures are commonly used as a yardstick for R&D output, since they offer an indication of the innovative output that firms are trying to protect. However, in the case of the pharmaceutical industry, it should be remembered that – owing to its specifically time character – this indicator provides only a partial picture, and should really be regarded as an intermediate product. In contrast

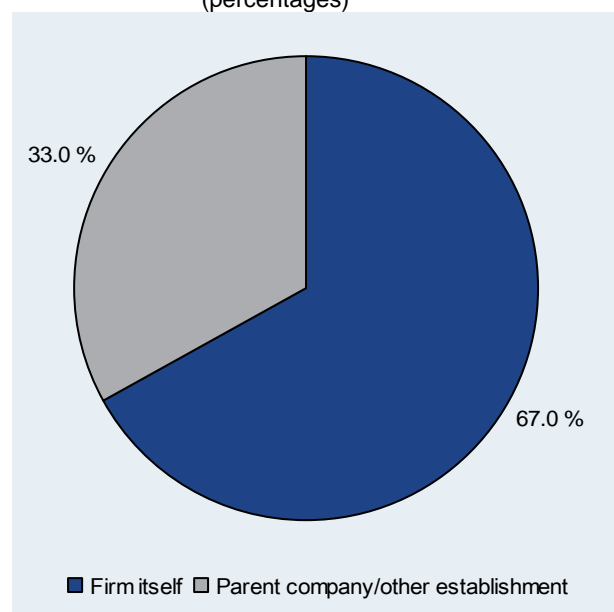
⁵⁴ For the same reason, details are not reported per class of firms for all questions.

⁵⁵ It is implicitly assumed, as in the survey as a whole, that the innovations primarily concern products rather than processes.

to most sectors, the patenting of a pharmaceutical innovation⁵⁶ - a molecule which screening has shown to be promising - occurs very early on in the R&D process; following granting of the patent, the rest of the research process takes another 12 years or so, on average⁵⁷. The number of patent applications at the start of the research pipeline is therefore much greater than the number of drugs that will eventually be put on the market. This is not only because most of the molecules fail to survive the various phases of drug research, but is also due to strategic decisions on the part of pharmaceutical firms. Defensive patent applications are also filed for molecules on which no further research will be undertaken, purely because they are related to a molecule on which research will proceed and it might be possible for a competitor to model them⁵⁸.

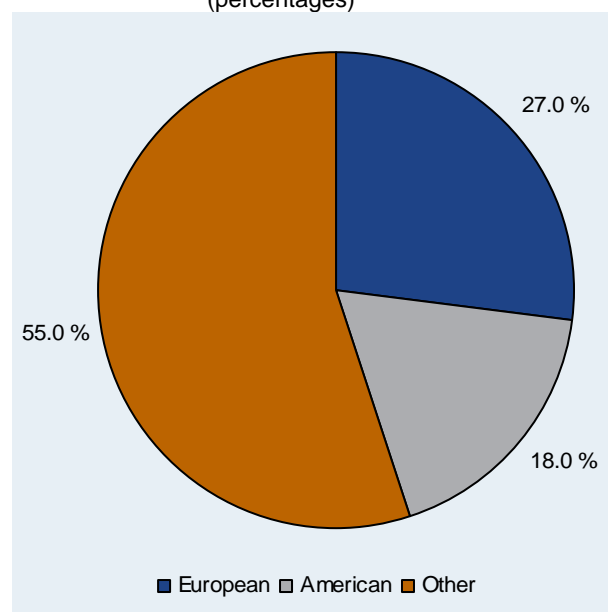
On the basis of the replies from 12 respondents, research activities in Belgium (and elsewhere) in the period 2002-2004 resulted in 961 patent applications. Although the response rate to this question was low, the global figure for the replies may give a fairly complete picture of the situation, because in practice, the applications were filed only by the production firms engaging in basic research in Belgium, and the response was complete for firms in the class concerned. However, it is noticeable that a good 71 p.c. of the total number of patent applications originated from a single participant.

CHART 25 PATENT APPLICATIONS IN 2002-2004 BY APPLICANT
(percentages)



Source: NBB

CHART 26 PATENT APPLICATIONS IN 2002-2004 BY PATENT OFFICE
(percentages)



Source: NBB

Most of the patent applications were filed by the Belgian branches themselves, and only in a minority of cases by another group company or branch: of the total number of applications, 67 p.c.

⁵⁶ For completeness, it should be mentioned that patents in the pharmaceutical industry do not only concern new active substances but may also concern other aspects of a drug (treatment, form of administration, etc.), so that a single drug may form the basis of multiple patents.

⁵⁷ Owing to the lapse of time between the R&D expenditure and the patent applications, there is little point in calculating the "patent intensiveness" of the R&D expenditure on the basis of the survey data, since those only cover a three-year period.

⁵⁸ Van Ex (2001).

or roughly two-thirds were filed by the Belgian branches (chart 25). If the patent applications originating from the firm which represents 71 p.c. of the total are disregarded, then that percentage is a great deal higher, namely 96.4 p.c.

The breakdown by patent office indicates that only a minority of patent applications were filed with the two leading world agencies in that field, namely 27 p.c. with the EPO (European Patent Office) and 18 pct. with the USPTO (US Patent and Trademark Office). Conversely, almost 55 p.c. were filed with "other" – i.e. national – patent offices, although there appear to be very wide variations in practice, depending on the firm (chart 26). The high percentage of "other" is due mainly to a single respondent, who specified that this concerned the national offices of several dozen countries worldwide: the high absolute number of applications submitted by that particular firm, together with the high number of different national offices to which those applications were submitted, would seem to indicate that those patent applications largely related to the same underlying "invention". In contrast, the other participants demonstrated a degree of "home bias", applying mainly to the EPO (73.4 p.c.) and to a lesser extent the USPTO (24.4 p.c.), while the applications filed with "other", more specifically European national offices represent only a few percentage points (2.2 p.c.) of the applications.

Not all firms appear to file their patent applications systematically with multiple (global) offices; the patents for which this is done are therefore likely to be "high value" patents.

2.3.2 *Drugs put on the market and their impact*

A second output-related indicator polled by the survey concerned the number of drugs put on the market as a result of R&D in Belgium (and elsewhere) in the period 2002-2004.

The question here was not confined to new active substances (NAS), an important, traditional yardstick for measuring the degree of innovation of the pharmaceutical sector, but referred to all types of product innovation, as various sources point out that research on the extension of existing product lines – be it by new forms of administration or new indications for existing products – is a growing trend. According to data published by the American trade association, the Pharmaceutical Research and Manufacturers Association (PhRMA), 80 p.c. of pharmaceutical R&D relates to fundamentally new molecules and 20 p.c. to new applications for existing molecules. Furthermore, the difference between new and existing molecules need not also reflect differences in the innovative value of the drugs, as a frequent criticism is that much of the R&D in the pharmaceutical sector is devoted to imitation or duplication of pharmaceutical innovations ("me-too" drugs), rather than innovation. Most pharmaceutical innovations are therefore incremental: ground-breaking innovations leading to treatment of previously incurable diseases are rare.

In order to cater for market launches and the impact of drugs with varying degrees of innovation, it was therefore decided that the survey should make the - admittedly subjective – distinction between "new" and "(significantly) improved" products for the market.

TABLE 13 DRUGS MARKETED AS A RESULT OF R&D ACTIVITIES: NUMBER AND IMPACT

	Average number of products per respondent	Average contribution to turnover* (p.c.)	GTT** (years)	Effect on employment (p.c. of firms)		
				None	Modest increase	Strong increase
New*** products	2.9	7.2	5	23	62	15
Significantly improved*** products	1.4	6.4	4	55	45	0

Source: NBB

* average per product.

** average (assumed) investment payback period.

*** for the market.

The findings in regard to marketing as a result of R&D activities in Belgian branches reveal that, during the period 2002-2004, each respondent launched on average 2.9 new products and 1.4 improved products⁵⁹ (table 13).

These averages are entirely consistent with the figures regarded as normal in the sector, since a pharmaceutical firm typically launches 1 to 3 important new drugs on the market each year, though the chances of success are small.

It is interesting that the survey results also indicate some variations in impact depending on whether the products in question are new or improved. For instance, the contribution to turnover is estimated as somewhat higher for a new product, at an average of 7.2 pct.⁶⁰ as opposed to 6.4 p.c. for a significantly improved product (table 13).

As regards the profitability of pharmaceutical R&D, the sector often mentions that, owing to constantly rising research costs combined with downward pressure on prices, it is becoming increasingly difficult to recoup the investment costs (plus reasonable recompense for the innovative work) with the short effective patent period⁶¹ of 7 to 8 years.

According to the pharmaceutical sector, only 1 in 3 of the drugs placed on the market will be profitable. As already stated, the survey results – particularly the output data – need to be treated with great caution, but they do present a more favourable picture. The average assumed investment payback time (GTT) appears to be shorter than the effective period of the patent. In the case of improved products it averages roughly 4 years, while in the case of new products it is estimated at 5 years. The fact that it takes a year longer to recoup the investment on a new product than on an improved product is doubtless due to the higher research costs entailed in the former case.

Finally, the employment effects are significantly greater in the case of new products: a good 77 p.c. of firms reported an increase in employment, with a strong increase in the case of 15 percentage

⁵⁹ The global figures calculated on the basis of the replies from 16 and 15 respondents respectively totalled 46 new and 21 improved products. In both cases, the respondents concerned were not always the same ones.

For comparison, according to data published by the European trade association, EFPIA, during the three years covered by the survey 93 new active substances were launched on the world market.

⁶⁰ Averages calculated on the basis of replies by 13 and 10 firms respectively. However, those averages conceal divergent percentages for the individual firms, ranging from less than 1 p.c. to over 30 p.c.

⁶¹ The effective period of the patent is the period between the market launch of the drug and the expiry of the patent protection.

points. Conversely, in the case of improved products, fewer than half – namely 45 p.c. – of firms recorded a (modest) increase in employment (table 12).

2.3.3 Discontinuation of R&D projects

Not all R&D projects actually produce a positive result. According to the pharmaceutical sector, only 1 in every 5 to 10 thousand screened molecules will actually reach the market as a drug. Although the chance of success increases with every hurdle that a molecule passes in the various research phases, the risk percentage remains considerable right up to the very last research phase (see the box on p. 22).

In the survey, 80 p.c. of respondents stated that they had discontinued projects during the period 2002-2004. However, the respondents who themselves stated that they were constantly setting up R&D activities in a particular phase⁶² all had to discontinue research projects prematurely.

The fact that most firms, namely 50 to 60 p.c., took that decision during the clinical research phases must, of course, be viewed in the light of the fact that most Belgian branches are active in that particular development phase (table 14).

The drug's ineffectiveness and/or unacceptable side effects were by far the principal reason for discontinuing the projects: 80 to 100 p.c. of firms which stopped a project in a particular phase indicated those reasons. Corporate strategy, unfavourable sales prospects and the lack of government support also appeared to play a role, though to a lesser extent, in both the research and development phases (table 14).

TABLE 14 PHASES AND REASONS FOR DISCONTINUATION OF THE PROJECT
(percentages of firms deciding to discontinue the project in the particular phase)

	Research	Pre-clinical	Clinical I	Clinical II	Clinical III
a) ineffective drug and/or unacceptable side effects	80	100	78	85	82
b) poor commercial prospects for the drug concerned	20	0	11	23	18
c) lack of skilled staff	0	0	0	0	0
d) high research costs	40	40	0	0	0
e) relocation	0	0	0	0	0
within the group of companies	0	0	0	15	18
outside the group of companies	0	0	0	0	0
f) lack of tax incentives	0	0	11	8	9
g) lack of government support	20	40	11	8	18
h) corporate strategy	20	40	11	15	9
i) other (specify)	0	20	0	0	0
pm: number of firms deciding to discontinue in this phase as p.c. of the total number of firms deciding to discontinue R&D projects	25	25	45	65	55

Source: NBB

⁶² In this connection, see the results for question 2.5, analysed in 2.2.4 "Type of R&D activities".

In contrast, the importance of the other reasons appears to vary according to the research phase. For instance, high research costs are a factor which only applied in the research and pre-clinical phases, as none of the firms ticked this reason in the clinical phases. Conversely, in these final research phases relocation (within the group) was indicated as a factor on several occasions, as was the lack of tax incentives. "Other" reasons prompting discontinuation in the pre-clinical phases included the rearrangement of priorities (table 14).

3 CONCLUSION

In 2005 the NBB carried out a survey of the R&D activities conducted in 2002-2004 by pharmaceutical firms active in Belgium in the field of research, production and distribution of drugs for human use.

In a sector dominated by multinationals, it was not always easy to quantify the exact contribution made by the Belgian branches to drug research. The survey results which, on the basis of a comparison with the existing (official) sectoral R&D data for Belgium can be regarded as virtually exhaustive, nonetheless reveal a number of clear trends.

The Belgian pharmaceutical sector puts a substantial effort into R&D in terms of both the amounts invested and the personnel used. The number of projects developed in Belgium is even high according to international standards, and confirms Belgium's leading position in global pharmaceutical research. According to the survey findings, more than one new drug launched by each firm per year is (partly) the result of R&D conducted by Belgian establishments.

The fact that these research activities may give rise to externalities (relating to expertise) is evident from the frequency with which they are outsourced. More generally, Belgian pharmaceutical firms engage in many cooperative projects with other research centres both at home and abroad; this primarily concerns hospitals, universities and suppliers (contract organisations), but there is also significant cooperation with foreign establishments belonging to the same group of companies.

The expertise available in Belgium, not only in the form of skilled staff but also more specifically in the form of knowledge centres, together with the availability of the infrastructure, were cited by the pharmaceutical firms as the main reasons for locating their R&D activities in Belgium. Most probably, this expertise factor was therefore one of the key advantages for the Belgian establishments at the time of the structural changes taking place in the firms in 2002-2004, for the survey respondents were unanimous in assessing the effects of those changes as positive for the research activities of their own establishment. Factors such as labour costs and government intervention in regard to various aspects (price regulation, tax incentives, subsidies and administrative procedures) were considered by the participants to have a decidedly negative impact on the location of such activities in Belgium .

As well as indicating the importance of Belgian pharmaceutical research, however, the survey findings also point to a fragility, which is of course significant with a view to the creation of a knowledge economy in accordance with the Lisbon objective.

The breakdown of the answers by type of firm on the basis of type of activities (production, export, etc.) conducted in Belgium reveals namely clear differences of emphasis in the type of research activities pursued and, consequently, wide variations in the amount of resources devoted to R&D.

In the case of distribution firms, the emphasis is clearly on the final phases of drug research, namely the clinical phases. In view of the numerical predominance of those firms, that therefore leads to an atypical phase distribution for Belgium in regard to projects in development, with the number of projects increasing the later the development phase concerned. The government has tried to consolidate Belgium's position as a host country for clinical trials by creating an attractive

legal framework for this type of research. However, the question is whether Belgium will have sufficient advantages to escape the trend towards relocation of clinical trials to low-wage countries; in the survey, at least, "relocation (within the group)" was ticked a number of times as the reason for discontinuating projects in these research phases in Belgium.

Conversely, the production firms are active in the various stages of drug research, and therefore have more molecules, on average, in the Belgian segment of their pipeline. Nonetheless, there are only three large production firms permanently active in all R&D phases in Belgium. These firms, which all belong to a Belgian company or a company of Belgian origin which was taken over by a foreign company, in fact appear to dominate pharmaceutical R&D activities in Belgium, as together they account for no less than 85 p.c. of R&D expenditure and 73 p.c. of research staff in the sector as a whole.

Abbreviations

ANBERD	Analytical Business Enterprise Research and Development (database)
ANRSE	Analytical Researchers, Scientists and Engineers (database)
CMR	Centre for Medicines Research International
EFPIA	European Federation of Pharmaceutical Industries and Associations
EM	extra muros (extramural)
EPO	European Patent Office
EUROSTAT	Statistical Office of the European Communities
HOKT	Hoger onderwijs van het korte type/ Higher education, short course
HOLT	Hoger onderwijs van het lange type/ Higher education, long course
IM	intra muros (intramural)
IMS-Health	Intercontinental Marketing Services-Health
NAI	National Accounts Institute
NAS	New Active Substance
NBB	National Bank of Belgium
OECD	Organisation for Economic Cooperation and Development
pharma.be	General association of the drugs industry
Pharmac	Pharmaceutical Management Agency Limited (New Zealand)
PhrMA	Pharmaceutical Research and Manufacturers Association (US)
R&D	Research and Development
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering / National Institute for sickness and disability insurance
SMEs	Small and medium-sized enterprises
USPTO	US Patent and Trademark Office
VA	Value Added
VOS	Voorschrift op stofnaam / Prescribing by substance name

Annex 1

Survey of R&D in the pharmaceutical sector in Belgium

Preliminary remark: This survey is collecting data on the R&D activities of the pharmaceutical sector in Belgium. Therefore, when answering the questions, please take account only of activities relating to **drugs for human use** pursued by (all) the **Belgian branches** of your company.

If none of the Belgian branches of your company engages in any R&D activities in that field, it is sufficient to complete items 1 to 2.1.

Explanatory notes are attached.

Particulars

Contact:

Telephone or e-mail:

Belgian branch(es):

1. General economic particulars concerning (all) Belgian branches

	2002 (x 1000 €)	2003 (x 1000 €)	2004 (x 1000 €)
1.1 Total turnover (<i>amounts in thousand euro</i>)			
of which (<i>approximate</i>) percentage share represented by:	%	%	%
a) drugs produced by the company itself in Belgium			
b) drugs produced by subcontractors in Belgium			
c) drugs imported from abroad			

	2002 (x 1000 €)	2003 (x 1000 €)	2004 (x 1000 €)
1.2 Total exports of drugs (<i>amounts in thousand euro</i>)			
of which (<i>approximate</i>) percentage share represented by:	%	%	%
a) drugs produced by the company itself in Belgium			
b) drugs produced by subcontractors in Belgium			
c) drugs imported from abroad			

	2002 %	2003 %	2004 %
1.3 Export destination (<i>approximate percentage shares</i>)			
a) neighbouring countries (France, Germany, Netherlands, Luxembourg, UK)			
b) rest of EU15			
c) rest of Europe (including the new EU Member States)			
d) rest of the world			

	2002	2003	2004
1.4 Overall staff as at 31 December according to your RSZ [social security] return (<i>in physical units</i>)			

2. Input data concerning the R&D activities of (all) Belgian branches

	2002 (x 1000 €)	2003 (x 1000 €)	2004 (x 1000 €)
2.1 Total expenditure on R&D (<i>amounts in thousand euro</i>)			
of which			
a) intramural or internal expenditure on R&D (<i>thousand euro</i>)			
of which (<i>approximate</i>) percentage shares of	%	%	%
1) labour costs			
2) other current costs			
3) capital expenditure			

	2002 %	2003 %	2004 %
b) extramural or external expenditure on R&D for (all) Belgian branches (<i>thousand euro</i>)			
of which (<i>approximate</i>) percentage shares	%	%	%
1) in Belgium			
2) in the rest of the world			

	2002	2003	2004
2.2 Staff used for intramural R&D (<i>in physical units as at 31 December</i>)			

2.2.1 by function (approximate percentage shares)

- a) managers
- b) researchers
- c) technicians
- d) other supporting staff

	%	%
	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>

2.2.2 by level of qualification (approximate percentage shares)

- a) holders of a doctorate (or equivalent)
- b) holders of a university degree or HOLT diploma
- c) holders of a HOKT diploma
- d) other

	%	%
	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>

2.3 In the past 3 years, have there been any significant structural changes (acquisition, merger, demerger, sale or department closure) in your company which have had a noticeable effect on the R&D activities?

yes no

2.3.1 if yes, indicate the effects on

- a) total R&D expenditure of all Belgian branches increase decrease
- b) R&D staff: increase decrease

2.4.a Total number of molecules currently in development

	Number of projects in development				Number of clinical tests on subjects in Belgium	Average number of persons per test in the case of subjects in Belgium
	Pre-clinical	I	II	III		
2002 (optional)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2003 (optional)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2004	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2005 (estimate)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

2.5 Tick the type, frequency and location of the R&D activities conducted by your firm over the past 3 years:

Frequency of R&D activities	Location of R&D activities					
	Research		Development			
	Intra muros	Extra muros	Pre-clinical		Clinical phases	
Intra muros			Extra muros	Intra muros	Extra muros	
Continuous	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Occasional	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Never	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2.6 For the whole of your R&D activities, tick the frequency of cooperation (including outsourcing) with other types of research centres during the past 3 years

	frequent	occasional	never
a) in Belgium:			
- other pharmaceutical firms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- within your own group of companies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- from another group of companies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- biotechnology firms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- universities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- hospitals	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- suppliers (SME, CRO, CTSO, ...)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- other (specify):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	frequent	occasional	never
b) abroad:			
- other pharmaceutical firms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- within your own group of companies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- from another group of companies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- biotechnology firms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- universities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- hospitals	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- suppliers (SME, CRO, CTSO, ...)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- other (specify):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2.7 Why did your firm locate the R&D activities in Belgium?

Tick the importance of the following determinants.

(--) *highly negative*, (-) *moderately negative*, (0) *neutral*, (+) *moderately positive*, (++) *highly positive*

	--	-	0	+	++
a) Human resources					
- availability of skilled staff	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- labour costs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Geographical location					
- proximity to sales markets: national market	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
European market	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- availability of infrastructure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- proximity of other knowledge centres/suppliers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- proximity of other group branches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Government					
- tax incentives	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- national and regional subsidies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- protection of intellectual property	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- price regulation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- administrative procedures (registration, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- legislation on research and (pre)clinical trials	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Market situation					
- competition					
- on the national market	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- on the European market	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- sales prospects for your product range					
- on the national market	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- on the European market	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Other: (specify).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2.8 Sources of funding for R&D activities over the past 3 years

(approximate average percentages)

a) all the Belgian branches themselves	<input type="text"/>
b) parent company or rest of the group of companies	<input type="text"/>
c) national government	<input type="text"/>
d) regional authorities	<input type="text"/>
e) supranational authorities	<input type="text"/>
f) other (specify):.....	<input type="text"/>
Total	<input type="text"/>

3. Output data concerning the R&D activities of all the Belgian branches

3.1 Average number of projects in phase I (determining the initial human dosage) leading to approval for the marketing of a drug over the past 3 years

3.2 Total number of patent applications filed in the past 3 years

- a) of which
 - filed by your firm itself
 - filed by another group company/branch

- b) of which
 - filed with the European Patent Office
 - filed with the US Patent Office
 - filed with other patent offices
 namely (specify):

3.3 Impact of the products launched on the market in the past 3 years as a result of R&D by type of innovation (*approximate figures*):

number	contribution to turnover (e) (%)	APP ¹ (years)	effect on employment (e) (please tick)		
			none	mode-rate increase	strong in-crease

- a) new products for the market
 b) (significantly) improved products for the market

			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

¹ APP= average assumed investment payback period (in years)

3.4 In the past 3 years, did your firm discontinue R&D - projects?

- yes no

3.4.1 If yes, tick the phase and reason for the discontinuation decision:

reason	phase	research	development			
			pre-clinical	clinical phases		
				I	II	III
a) ineffective drug and/or unacceptable side effects		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) poor sales prospects for the drug in question		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) shortage of skilled staff		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) high research costs		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) relocation		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	within the group of companies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	outside the of companies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f) lack of tax incentives		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) lack of government support		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h) corporate strategy		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) other: (specify).....		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

EXPLANATORY NOTES

General remark: This questionnaire uses definitions formulated by the OECD (Organisation for Economic Cooperation and Development) in the Frascati manual for R&D surveys. The terms used in section 2 of the questionnaire are explained below in order of occurrence.

QUESTION 2.1

Research and experimental development (R&D) comprises creative work undertaken on a systematic basis to increase the stock of knowledge and the use of this stock of knowledge to devise new applications. R&D concerns the following three activities:

Basic research: experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view.

Applied research: research work undertaken in order to acquire new knowledge, directed primarily towards a specific practical aim.

Experimental development: systematic work drawing on existing knowledge gained from research and/or practical experience, directed to producing new materials, products or devices, to installing new processes, systems and services, or to improving substantially those already produced or installed.

By convention, phases I, II and III of the clinical trials are regarded as R&D; conversely, phase IV is only regarded as R&D if it gives rise to further scientific or technological progress. However, marketing and process development activities conducted after phase III and before permission to launch a drug on the market must all be excluded from R&D.

NB: the questionnaire makes no distinction between basic and applied research.

Total expenditures for R&D: all expenditure for R&D activities conducted in Belgium and/or controlled or coordinated from Belgium.

Intramural R&D: Intramural or internal expenditure is all expenditure for R&D within the firm, whatever the source of funds.

Extramural R&D: Extramural or external expenditure is all expenditure for R&D activities conducted by third parties for the account of the firm (joint ventures or outsourcing).

Labour costs comprise all wages and salaries on an annual basis and all associated costs or fringe benefits. The labour costs of persons providing support services (e.g. security, maintenance and computer services) which are not included in the R&D staff data should be excluded; they should be recorded under the heading "other current costs".

Other current costs comprise all costs for purchases of material, supplies and equipment to support R&D activities performed by the statistical unit in a given year and not included under "capital expenditure". They include (pro rata, if necessary): water and fuel; books, journals, reference materials, subscriptions to libraries and scientific societies; materials for laboratories; administrative and other overhead costs (post, insurance, telecommunications, etc.); support services (security, maintenance and computer services).

Capital expenditures are the annual gross expenditures on tangible fixed assets used in the R&D activities of the statistical unit. They relate more specifically to land and buildings (land for building laboratories, construction or purchase of buildings, including improvements, alterations or maintenance work, etc.); instruments and equipment (purchase of major instruments and equipment used for R&D activities).

QUESTION 2.2

Overall staff: All persons employed directly on R&D should be counted, as well as those providing direct support services, such as managers, administrators and clerical staff.

Management: Managers and administrators responsible for planning and directing the scientific and technical aspects of R&D.

Researchers: Professionals engaged in the conception or creation of knowledge, products, processes, methods and systems and also in the management of the projects concerned.

Technicians: Persons whose main tasks require technical expertise and experience in one or more scientific or technical fields.

Others: Skilled and unskilled craftsmen, secretarial and clerical staff participating in R&D projects or directly associated with such projects.

HOLT: Hoger onderwijs van het lange type/ Higher education, long course

HOKT: Higher education, short course

QUESTION 2.4b

Projects in development: development of a molecule in regard to medical indication and form of administration

QUESTION 2.6

SMO: site management organisation

CRO: contract research organisation

CTSO: clinical trials supply organisation

Annex 2

The importance of the pharmaceutical sector in the Belgian economy: some data on value added, employment and R&D expenditure.

Value added and employment⁶³

Measured in terms of value added and employment, the pharmaceutical manufacturing industry has a relatively minor place in manufacturing industry in general and the economy as a whole. During the period 2002-2004, the pharmaceutical industry accounted for an average of 5.4 p.c. of the value added of manufacturing industry, and 0.9 p.c. of that of the economy as a whole in terms of GDP. As regards employment, the percentages during that period were somewhat lower, at 3.4 p.c. for employees in manufacturing industry and 0.6 p.c. of total employees; however, the pharmaceutical industry was one of the few industrial sectors which succeeded in maintaining its relative position in terms of employment.

TABLE 1 VALUE ADDED AND EMPLOYMENT

	<i>(in percentages of the total for manufacturing industry)</i>							
	<u>Value added</u>				<u>Employment</u>			
	<u>2002</u>	<u>2003</u>	<u>2004</u>	Average <u>2002- 2004</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	Average <u>2002- 2004</u>
Manufacturing industry	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Food	13.1	13.7	13.8	13.5	14.3	14.7	15.1	14.7
Textiles, clothing, footwear	5.3	4.6	4.4	4.8	7.9	7.7	7.4	7.7
Wood, paper, printing	9.5	9.7	9.0	9.4	9.8	9.7	9.8	9.8
Chemicals*	23.9	23.5	22.9	23.4	15.9	16.2	16.3	16.1
of which: Pharmaceutical industry	5.6	5.6	5.1	5.4	3.2	3.5	3.4	3.4
Iron and steel	14.1	14.3	15.6	14.6	16.3	16.6	16.6	16.5
Metalworking	22.8	22.7	21.8	22.5	25.0	24.3	24.1	24.5
of which: Audio, video and telecommunications	2.7	2.7	2.3	2.6	2.7	2.4	2.2	2.5
Other	11.4	11.5	12.5	11.8	10.8	10.7	10.7	10.8

	<i>(in percentages of the total for the economy)</i>							
	<u>Value added</u>				<u>Employment</u>			
	<u>2002</u>	<u>2003</u>	<u>2004</u>	Average <u>2002- 2004</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	Average <u>2002- 2004</u>
Manufacturing industry	16.2	15.6	15.5	15.7	17.7	17.2	16.7	17.2
Food	2.1	2.1	2.1	2.1	2.5	2.5	2.5	2.5
Textiles, clothing, footwear	0.9	0.7	0.7	0.8	1.4	1.3	1.2	1.3
Wood, paper, printing	1.5	1.5	1.4	1.5	1.7	1.7	1.6	1.7
Chemicals*	3.9	3.7	3.5	3.7	2.8	2.8	2.7	2.8
of which: Pharmaceutical industry	0.9	0.9	0.8	0.9	0.6	0.6	0.6	0.6
Iron and steel	2.3	2.2	2.4	2.3	2.9	2.8	2.8	2.8
Metalworking	3.7	3.5	3.4	3.5	4.4	4.2	4.0	4.2
of which: Audio, video and telecommunications	0.4	0.4	0.4	0.4	0.5	0.4	0.4	0.4
Other	1.8	1.8	1.9	1.9	1.9	1.8	1.8	1.8

Source: NAI

*including rubber and plastics

⁶³ In contrast to the rest of the text, owing to the lack of detailed data for the "wholesale" and "research and development activities" branches, this part of the paper relates only to pharmaceutical companies which come under manufacturing industry.

However, the above data on value added and employment give an incomplete picture of the importance of the pharmaceutical sector in the Belgian economy, since they confine that sector strictly to Nacebel code 24.4, or in other words the pharmaceutical manufacturing industry; apart from a number of establishments focusing entirely on pharmaceutical R&D activities (Nacebel code 73), there are numerous branches of multinationals which do not engage in any production activities in Belgium, but are involved purely in selling and therefore come under the wholesale sector (Nacebel code 51).

To obtain a more complete picture of the impact of the pharmaceutical sector on the Belgian economy, account must also be taken of the indirect effects – i.e. the effects entailed for suppliers in Belgium.

On the basis of the data obtained from the National Accounts Institute (NAI), using a methodology developed by the Bank and based on the input-output tables⁶⁴, the indirect effects generated in 2003 by all the firms registered for the survey were estimated⁶⁵. That estimate is not confined to first-line suppliers, but extends back indefinitely through the entire supply chain.

TABLE 2 INDIRECT EFFECTS ON VALUE ADDED AND EMPLOYMENT GENERATED BY THE PHARMACEUTICAL SECTOR
(ratio of indirect to direct effects)

	Employment		Value added	
	Total firms	Of which production firms	Total firms	Of which production firms
Total indirect effects	1.0	1.1	0.6	0.6
of which: first level	0.6	0.7	0.4	0.4

Source: NBB

The calculations reveal that the indirect effects generated by the drugs (for human use) sector on the Belgian economy are depressed by the sector's high import content. The ratio of total indirect effects on value added to the direct effects is 0.6; for employment that ratio is slightly higher, namely 1.0⁶⁶. For the production firms, which for both economic variables account for around half of the population surveyed, the ratio between the indirect effects and the direct effects is not significantly different from these overall figures.

⁶⁴ This methodology is described in detail in Coppens(2005).

⁶⁵ In this connection, see 1.3 "Sample" in the main text of this paper. Since it is not possible to distinguish in the input-output tables between trade in pharmaceutical products and wholesale in other types of products, the methodology used may be slightly less accurate for the distribution firms than for the production firms.

⁶⁶ For comparison: in the sector studies, the NBB has already calculated the indirect effects of the motor vehicle and ICT sectors. For these sectors, the ratios between indirect and direct effects were 2.3 and 0.5 respectively.

"Business services" is the branch of activity which experiences the most indirect effects, at almost 60 p.c.⁶⁷. More specifically, this primarily concerns coordination centres, consultancies, and enterprises involved in legal services and personnel selection.

After that, the indirect effects are perceptible in the wholesale sector (10 p.c.) and manufacturing industry (6 p.c.), within which they are particularly apparent in printing, the preparation of other chemicals and, of course, the pharmaceutical manufacturing industry. The remaining effects are spread more or less across all the other branches of activity, such as transport, construction, and the production and supply of energy and water.

R&D expenditure⁶⁸

However, the importance of the pharmaceutical sector in the Belgian economy is reflected much more prominently and obviously in the R&D expenditure of the Belgian firms. More so than in other branches of activity, successful R&D is crucial to the pharmaceutical sector: the importance of this sector in terms of the total research efforts of Belgian firms therefore far exceeds the share of the pharmaceutical manufacturing industry in purely productive terms (direct value added and employment). In view of the considerable extramural R&D activities of the pharmaceutical sector, including in Belgium, it can also be assumed that those activities have a significant (indirect) impact on certain areas of the Belgian economy. However, this cannot be estimated from the information available in the input-output tables.

TABLE 3 R&D EXPENDITURE (INTRAMURAL AND TOTAL)
(percentages of the total for the firms)

	Intramural expenditure				Total expenditure (intramural+extramural)			
	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>Average</u> <u>2002-2004</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>Average</u> <u>2002-2004</u>
	Total firms	100	100	100	100.0	100	100	100
Manufacturing industry	79.1	78.6	78.4	78.7	79.2	79.3	79.0	79.2
Food	2.8	2.9	2.9	2.9	2.6	2.7	2.8	2.7
Textiles, clothing, footwear	1.0	1.0	1.1	1.0	0.8	0.9	0.9	0.9
Wood, paper, printing	0.5	0.6	0.5	0.5	0.4	0.5	0.4	0.4
Chemicals*	34.6	37.4	38.1	36.7	40.6	43.7	44.3	42.9
of which: Pharmaceutical firms	19.2	21.6	22.6	21.1	28.0	30.7	31.7	30.2
Iron and steel	5.6	5.6	5.8	5.7	5.5	5.5	5.5	5.5
Metalworking	31.4	27.6	26.6	28.5	26.4	23.0	22.2	23.8
of which: Audio, video and telecommunications	16.2	12.6	11.5	13.4	13.5	10.2	9.4	11.0

Source: FPS Science Policy
* including rubber and plastics

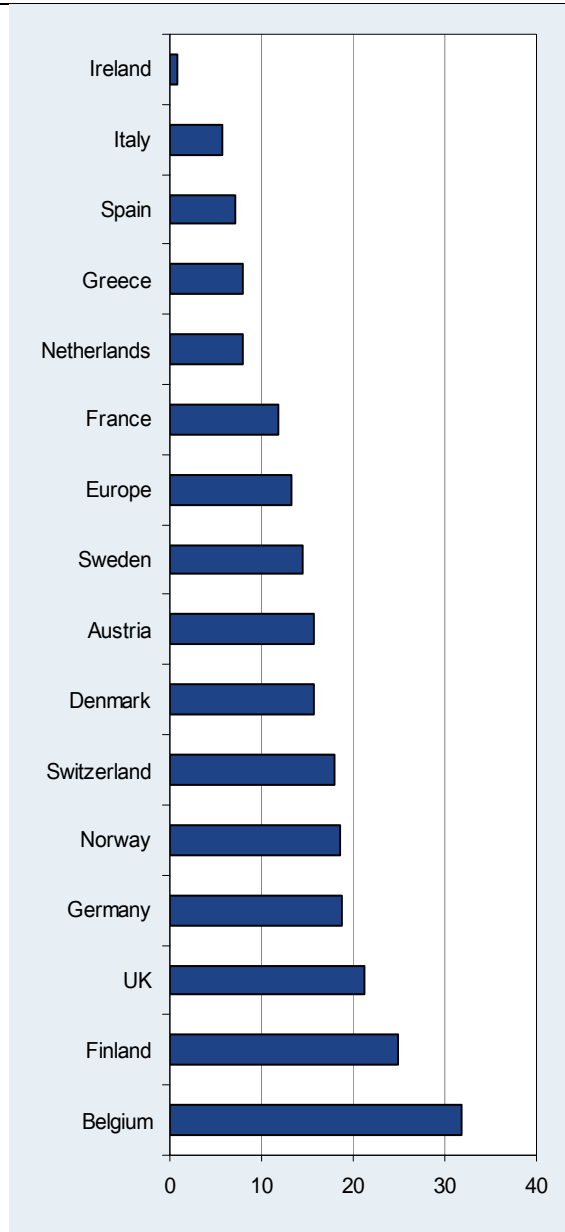
The Belgian pharmaceutical sector appears to spend substantial amounts on R&D, not only according to comparisons between sectors but also in international (European) terms. According to

⁶⁷ For completeness, it should be mentioned that, in the national accounts, some firms are assigned to sector classes which do not always correspond to the sector classes in which they submit their annual accounts.

⁶⁸ For a proper understanding, it should be remembered that the sectoral data on R&D expenditure are ANBERD-estimations; the data for the manufacturing industry thus in fact concern a broader aggregate. More specifically for pharmaceutical firms, this implies - contrary to the previous section of this annex where the data on value added and employment only concerned the pharmaceutical manufacturing- that the data in this section also incorporate R&D expenditure by pharmaceutical distribution firms and research centres. In this connection, see also footnote 10.

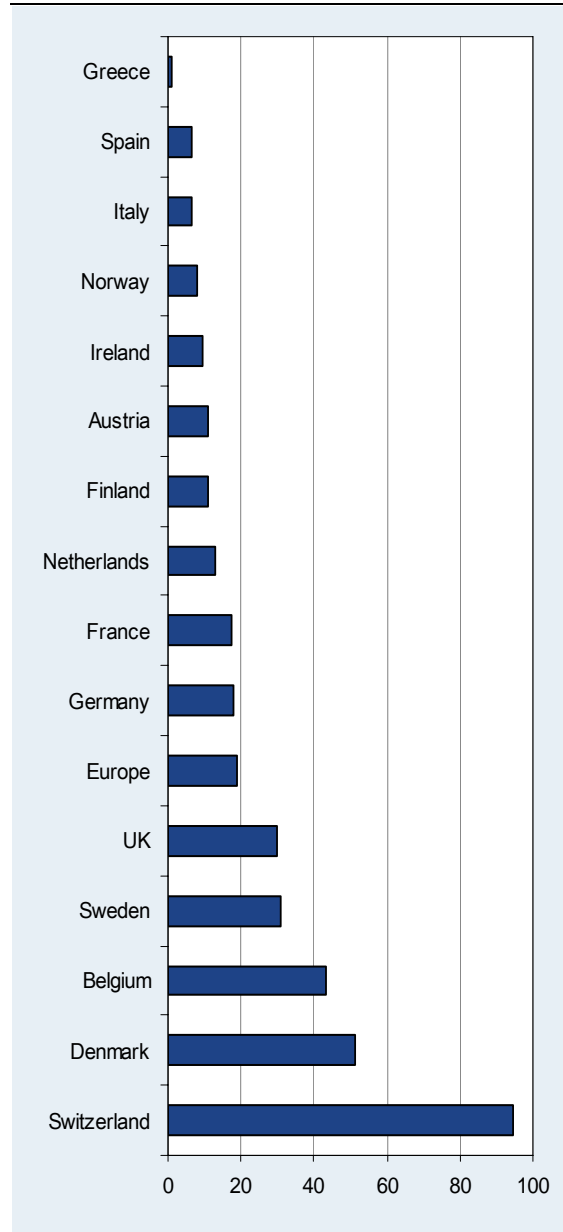
figures for 2004 supplied by the European umbrella organisation of the pharmaceutical sector associations, EFPIA, Belgium put significant efforts into research not only in relative terms – i.e. in comparison with output and the size of the national market – but also in absolute terms, as there were only some large countries such as the UK, France, Germany and Switzerland that preceded Belgium in the ranking of R&D expenditure.

CHART 1 R&D EXPENDITURE OF THE PHARMACEUTICAL SECTOR IN PERCENTAGES OF OUTPUT



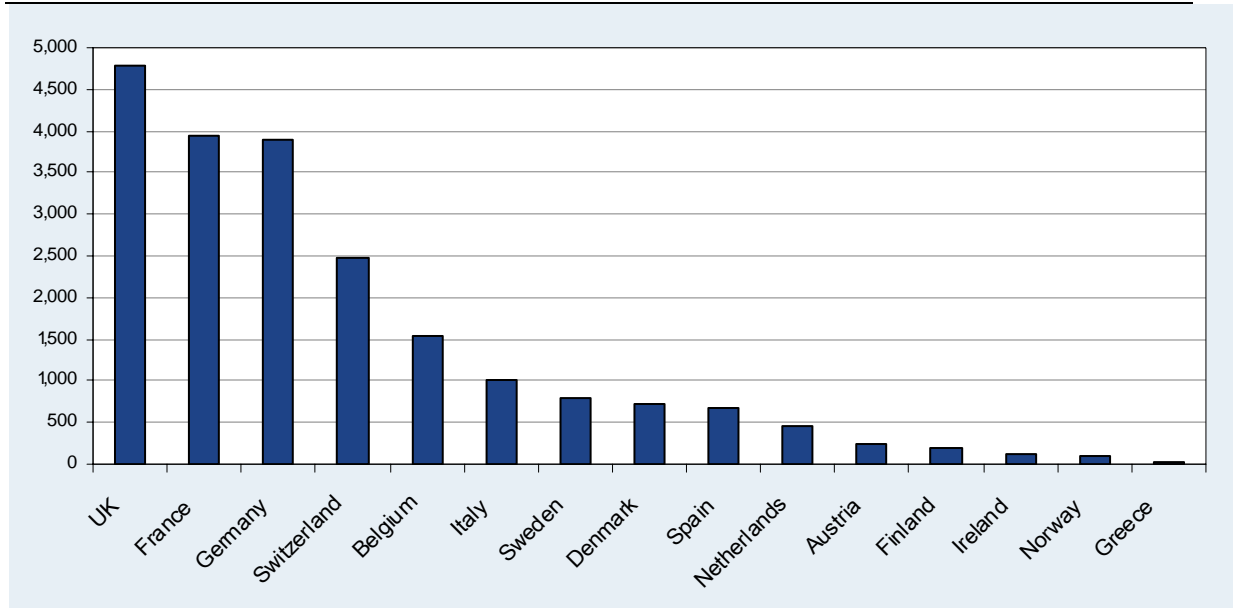
Source: EFPIA

CHART 2 R&D EXPENDITURE OF THE PHARMACEUTICAL SECTOR IN PERCENTAGES OF SALES ON THE NATIONAL MARKET



Source: EFPIA

CHART 3 R&D EXPENDITURE OF THE EUROPEAN PHARMACEUTICAL SECTOR IN 2004
(in €million)



Source: EFPIA

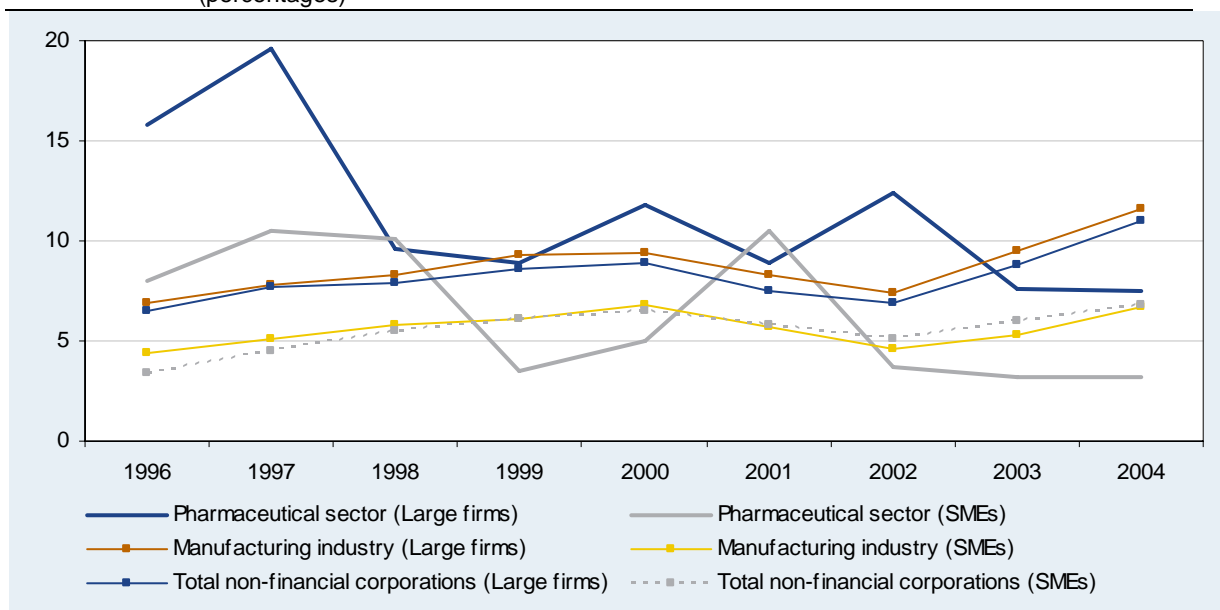
Annex 3

Profitability of companies in the pharmaceutical sector

The profitability of all firms registered for the survey was calculated on the basis of the annual accounts filed with the NBB's Central Balance Sheet Office⁶⁹.

The "(net) return on equity", or in other words the companies' ability to make a profit, is presented in the form of a median, as this yardstick refers to the situation of the central firm – i.e. 50 p.c. of companies, regardless of their size, have a ratio which is above this median value, while the other 50 p.c. have a ratio below it – and therefore reflects the picture for the population as a whole to a greater extent than the globalisation criterion⁷⁰, since the latter – particularly at the level of the business branches – is more influenced by (exceptional) movements within (large) individual companies. As is usual in the case of the ratio analysis, a distinction is made between large firms and small/medium-sized enterprises (SMEs), as the method of financing and the financial position of firms differ according to the size of the business.

CHART 4 RETURN ON EQUITY
(percentages)



Source: NBB

The calculations reveal that the median values for both types of firms tended to decline overall during the period 1996-2004. The large firms generally had a higher level of profitability than the SMEs: during the period 2002-2004, or in other words the period of the R&D survey, the difference between the two averaged over 5 percentage points.

⁶⁹ In this connection, see 1.3 "Sample" in the main text of this paper. The calculations concerning profitability and failure prediction naturally took account only of the data for firms which file annual accounts with the NBB.

⁷⁰ The globalisation is obtained more specifically as the ratio of the sum of the numerators to the sum of the denominators.

TABLE 4 **RETURN ON EQUITY**
(percentages)

	Large firms			SMEs		
	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>
Pharmaceutical sector	12.4	7.6	7.5	3.7	3.2	3.2
Manufacturing industry	7.4	9.5	11.6	4.6	5.3	6.7
Total non-financial corporations	6.9	8.8	11.0	5.1	6.0	6.8

Source: NBB

Comparison of the profitability of the pharmaceutical sector with other branches of industry reveals that the downward trend in the pharmaceutical sector was in contrast to the rather upward trend seen for manufacturing industry as a whole and for non-financial corporations during the past decade. As a result of that divergence, profitability in the pharmaceutical sector is now lower than in manufacturing industry or non-financial corporations as a whole – in contrast to the situation a few years ago. Although it is generally true that large firms have higher profitability than SMEs, the difference appears to be more marked in the pharmaceutical sector than elsewhere over the period considered (table 4).

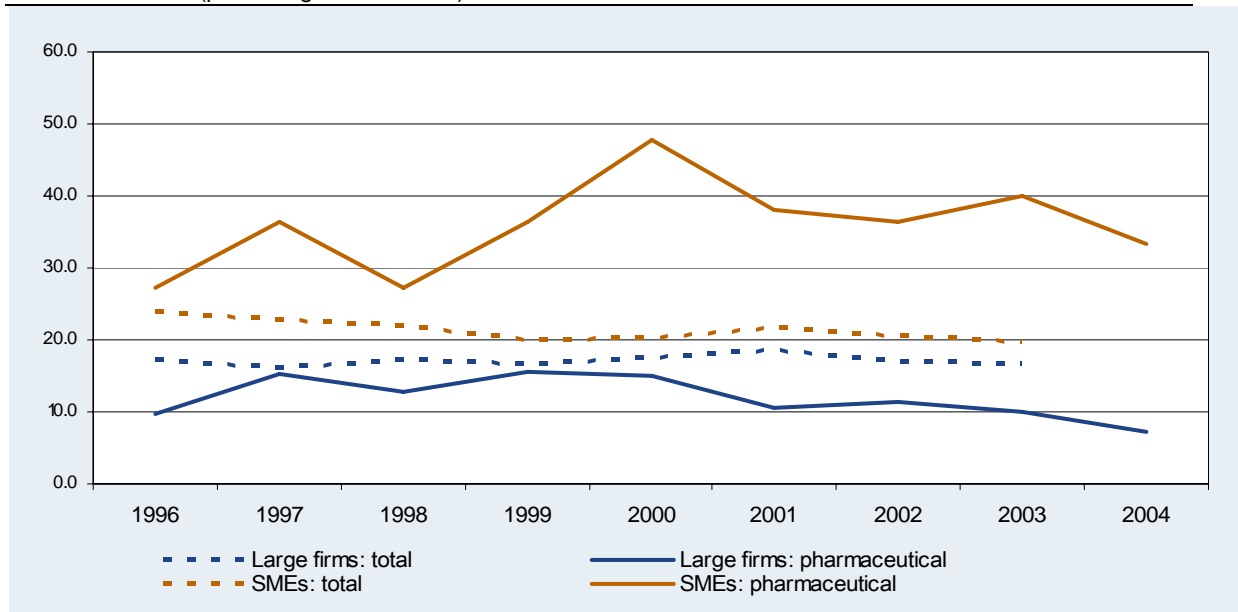
In order to assess the financial risks of the firms, the NBB has developed an internal failure prediction model⁷¹. This model classifies firms into four risk classes on the basis of eight variables concerning their financial situation. Classes 3 and 4 correspond to firms in difficulty and in serious difficulty respectively. A firm in either of those classes has a risk of failure (within 3 years) which is respectively 3-4 times or over 10 times greater than the average.

However, this classification of firms has to be interpreted with caution. Only a very small percentage of the firms will actually become bankrupt or be subject to judicial composition. The classification should really be viewed as an indication of financial health rather than a prediction of failure in the strict sense: firms in classes 3 and 4 are not necessarily doomed to failure, but they do face serious financial problems⁷².

⁷¹ The methodology of this model is explained in detail in Vivet (2004).

⁷² Apart from bankruptcy, these difficulties may lead to delays in the repayment of debts or the payment of suppliers, redundancies, restructuring or even the cessation of activity. However, Belgian firms which are part of large multinationals will often find that, if they are in difficulty, the parent company is prepared to offer them financial support, at least for a time.

**CHART 5 COMPANIES IN (SERIOUS) FINANCIAL DIFFICULTIES
(CLASSES 3 AND 4)
(percentages of the total)**



Source: NBB

Generally speaking, it can be said that the percentage of non-financial corporations in (serious) difficulties is slightly higher for SMEs than for large firms. In the pharmaceutical sector, this difference is much more marked since the sector contains relatively fewer large firms in financial difficulties, but the percentage of SMEs with financial problems is clearly higher than the general average for SMEs (chart 5).

Annex 4

Reference reimbursement for drugs and R&D

The Belgian government has taken various measures in recent years to control health care expenditure, and more particularly expenditure on the reimbursement of drugs. Some of those measures, such as price freezes and cuts, have a direct impact on drug prices. In contrast, the reference reimbursement system for eligible drugs, introduced on 1 June 2001 to encourage the prescription of cheap drugs, has an indirect effect on prices, as a general rule. Since the entry into force of this system, various additional measures have been passed, including the Health Act of 27 April 2005, which are in fact intended to reinforce and extend the reference reimbursement system.

However, reference reimbursement for drugs is controversial for a number of reasons, including the elimination of incentives for innovation. This would apply, in particular, under the rigid New Zealand prototype, advocated as a model for Belgium in recent years on account of its drug tender technique.

This annex therefore describes the system of reference reimbursement and the possible variants. On the basis of an analysis of the economic literature on this reimbursement system, it gives a brief account of the system's reported effects; of course, the impact on R&D receives particular attention.

Definition of reference reimbursement

General definition

Reference reimbursement for drugs is a system in which equivalent products are grouped together in classes, and the reimbursement for all products in the same class is based on the same reference price. Under such a reimbursement system, the producers are therefore free to set their prices – in contrast to a pure price control system; however, leaving aside the usual non-refundable element, any difference between the public price and the reference price is payable entirely by the patient.

Variants

A number of industrial countries are now applying a form of reference reimbursement. However, the existing systems vary considerably in two respects, namely the criterion used for grouping equivalent drugs and the determination of the reference price.

As a rule, distinction is made between three different types of reference reimbursement according to what is meant by the term "equivalence".⁷³

The first type uses the narrowest definition, namely chemical equivalence: only drugs with the same chemically active component are grouped together. This type is often also referred to as "generic equivalence".

The second type of reference reimbursement is based on pharmacological equivalence, and therefore groups drugs on the basis of chemically related ingredients which have the same effect. Finally, the third type uses the broadest criterion for grouping drugs, namely therapeutic

⁷³ The literature also refers to these types as "phases", although there need not be any chronological link between them.

equivalence. Here, drugs for the same disorder are put together in one class, but need not be chemically or pharmacologically equivalent.

When defining equivalence, there is an essential point of difference between the reference reimbursement variants applied in the different countries, in whether or not drugs under patent are included in the classes of drugs listed. As a result of the nature of the definition itself, generic substitutes only apply to non-patent drugs, namely products on which the patent has expired and their generic equivalents,⁷⁴ and this option applies only to the second and third types.

The reference price is the fixed basis for reimbursement applicable to all drugs in the same class or sub-class. That price is generally based on a particular point in the range of producer prices (e.g. the minimum, the median, the average...). If the reference price is determined by comparing prices within one country, it is called an internal reference; in the case of external reference, prices for the same or similar drugs in other countries are considered⁷⁵.

In 1989, Germany became the first country to introduce a reference reimbursement system. Since then, various other industrial countries have introduced one variant or another, including the Netherlands (1991), Sweden (1993), Denmark (1993), New Zealand (1993), the province of British Columbia in Canada (1995), Australia (1998), Italy (1996), Spain (2000) and Belgium (2001). As a result of these examples and on the recommendation of the World Bank, this model was also introduced in a number of Central and East European economies. Norway, which introduced the system in 1993, abandoned it after assessing the results in 2001, while Finland, which rejected the system in the last decade, is now reconsidering its introduction. In the past few years, a number of countries which apply a reference reimbursement system have made changes to the system or plan to do so in the near future. Subject to certain reservations⁷⁶, the table below shows the current situation regarding the characteristics of the various systems.

⁷⁴ A generic is a drug which contains the same active substance, in the same dose and form as the original branded drug, and has the same bio-availability, i.e. is absorbed in the same way by the human body. Generics cannot be placed on the market until the patent on the original branded drug has expired.

⁷⁵ In the case of therapeutic reference systems which group together drugs of differing composition, it is of course necessary to determine substitute dosages – i.e. dosages for different drugs having the same effect for patients – before determining the reference price.

⁷⁶ The information in the table is provided subject to certain reservations because the characteristics of the reference reimbursement system used in one particular country often differ according to the source, and inquiries to the various foreign institutions did not always produce an answer. However, it is worth mentioning that the European Commission is currently running a project (Pharmaceutical Pricing and Reimbursement Information) which aims to ascertain the characteristics of the drug pricing and reimbursement policy applied in the various European Union Member States. However, the results of this project will not be available until spring 2007.

TABLE 5 OVERVIEW OF REFERENCE REIMBURSEMENT SYSTEMS

Country	Year of introduction (+ termination)	Equivalence criterion for grouping drugs	Inclusion of patent medicines	Determination of reference price	Comments
Australia	1998	pharmacological equivalence	yes	lowest price in the group	
Belgium	2001	chemical equivalence	no	30 p.c. below the price of the original, branded drug	-possibility of extending groups (other dosages and forms of administration for the same active substance/other active substances for the same/similar indications) - introduction of differential reimbursement ("kiwi light")
Canada (British Columbia)	1995	pharmacological equivalence	yes	lowest price in the group	
Denmark	1993	chemical equivalence	no	lowest price in the group	- before 2005: average of lowest 2 prices in the group
Germany	1989	therapeutic equivalence	yes	median price (on the basis of a regression model)	-initially chemical equivalence; since 1992 and 1993 respectively, pharmacological and therapeutic equivalence -(new) patent medicines excluded in the period 1996-2003 -exceptions based on the innovation protection clause
France	2003	chemical equivalence	no	(1)	
Italy	2001-2004	chemical equivalence	no	weighted average of generic prices	
Netherlands	1991	therapeutic equivalence	yes	average price in the group	
New Zealand	1993	therapeutic equivalence (2)	yes	lowest price in the group/sub-group	- also sole supply tenders and cross-therapeutic deals
Norway	1993-2001	chemical equivalence	no	lowest price in the group + 5p.c.	-1998: extended to parallel imports -1999: extended to other forms of administration
Portugal	2002	chemical equivalence	no	highest generic price	
Spain	2000	chemical equivalence	no	highest price in the group -10 to 50 p.c.	
Sweden	1993-2002	chemical equivalence	no	lowest price in the group +10 pct	

Sources: among others Danzon (2003), Lopez-Casasnovas & Puig-Junoy (2001), Mestré-Ferrandiz (2003) and EU (Pharmaceutical Pricing and Reimbursement Information project)

(1) Information on the exact determination of the reference price was not supplied, but would be linked to the prices for generics.

(2) Catalogued by Mestré-Ferrandiz (2003) as pharmacological equivalence.

Reference reimbursement in New Zealand

In 1993, reforms in the New Zealand health sector led to the establishment of Pharmac (Pharmaceutical Management Agency Limited), an independent public body with the specific objective of improving control over government expenditure on drugs. In that context, Pharmac manages the list of subsidised drugs (Pharmaceutical Schedule), and takes decisions on the inclusion of products in the list, the levels of subsidy and the guidelines and conditions for prescribing the products.

Pharmac uses a system of reference prices for drug reimbursement. The detailed reference classes and the strategies applied by Pharmac to keep costs under control appear to make the New Zealand model a rigid variant of the system: the drugs eligible for reimbursement in New Zealand are subdivided into therapeutic groups and subgroups⁷⁷, without a distinction between non-patent and patented products. The reference prices correspond to the lowest price in each sub-group⁷⁸. New (innovative) drugs are only reimbursed if they are included in the existing sub-group and the price is set below the current reference price for that sub-group⁷⁹.

In addition to the reference price mechanism, Pharmac uses a range of other strategies to keep expenditure under control. Those strategies are aimed both at the demand side (e.g. national guidelines on the prescribing of certain drugs; only specialists may prescribe certain drugs, etc.) and the supply side of the market. On the supply side the main instruments are "cross product deals" and "tenders". "Cross-product deals" are agreements with pharmaceutical firms whereby new drugs are included in a particular sub-group and reimbursed in exchange for reductions in the prices of existing products in other sub-groups (leading to a lower new reference price in the latter groups)⁸⁰. The tender technique⁸¹ is used for non-patent drugs⁸²: in exchange for a low price, producers then gain a larger market share, generally for 3 years (preferred supplier contract), or the whole market (sole supply contract), in which case all competitors are removed from the reimbursement list. It is particularly this last aspect of the New Zealand drugs policy, namely the tender technique, that is known in Belgium as the "kiwi model".

Reference reimbursement in Belgium

On the basis of such factors as therapeutic effectiveness and social importance, drugs eligible for reimbursement in Belgium (branded drugs, generics and copies) are divided into five categories linked to a particular level of reimbursement. Since 2001, that reimbursement has been based on the principle of reference reimbursement, whereby the government aims to encourage the prescribing of cheap drugs: the basis for reimbursement of an original drug for which a cheaper version is available (often a generic or copy) is cut by 30 p.c.⁸³. There are now generics available

⁷⁷ This concerns respectively drugs used for the same or a similar disorder, and drugs which produce the same or similar effects for the treatment of the same or similar disorders.

⁷⁸ Although the manufacturers can, in principle, charge more than the reference price, Pharmac could in some cases decide to refuse reimbursement of the product.

⁷⁹ New drugs can also be reimbursed if they are the subject of a special deal (cross-product, price/volume deal...) with Pharmac; see below.

⁸⁰ In the specific case of new drugs, Pharmac also uses price/volume contracts for limited launches (e.g. for a specified target group).

⁸¹ Roughly one-third of the drugs listed in the Pharmaceutical Schedule form the subject of such tenders.

⁸² According to PhRMA, however, some tenders have also concerned patented drugs.

⁸³ At the time of acceptance for reimbursement, a generic must be cheaper than the original drug; that lower price is due mainly to the absence of R&D costs. At the time of introduction of the reference reimbursement system, the reduction was only 16 p.c., but was later increased to 20 p.c., then 26 p.c., and 30 p.c. since 1 July 2005.

for around 300 original drugs. In the case of drugs for which there are no generic variants, the non-refundable element is still calculated, as it always was, as a percentage of the actual cost (consumer price).

As part of further economy measures, the government made provision, in the Health Act of 27 April 2005, for the possibility of extending reference reimbursement to all dosages and all forms of administration for the active substance included in the system, and extension – via a procedure for each class – to drugs containing other active ingredients for which the indications are the same or similar. It also introduced the "kiwi-light" model, based on the New Zealand tender technique, but this model will first be tested on cholesterol-reducing drugs – at almost 10 p.c. of expenditure, these are the largest category in the pharmaceutical budget – before being applied to other categories of drugs. However, the Belgian version of the model varies from the New Zealand original in several respects. Indeed it uses market inquiries instead of a tender; in contrast to what happens in New Zealand, the reimbursement here will not be restricted to the cheapest drug, and that drug does not acquire a monopoly, although it will receive more by way of reimbursement than the more expensive competitors. There are two variants of this "differential" reimbursement. The first variant consists in maintaining the status quo for the cheapest drug and demoting the other drugs by one reimbursement category (with the same price and basis of comparison). In the second variant, the basis of reimbursement of all drugs is reduced to the cheapest. The first variant was chosen for the cholesterol-reducing drugs: more particularly, this means that from 1 January 2007 the rate of reimbursement for the cheapest medicinal product found in the survey will be 75 p.c., while for the other drugs only 50 p.c. (of the reimbursement basis) will be reimbursed by the health insurers. However, in contrast to the original draft law, the Belgian system is confined to non-patent drugs⁸⁴. Nevertheless, the length of time for which the reimbursement advantage will apply is currently still unclear.

In line with the reference reimbursement, the Belgian drugs policy also has measures aimed specifically at the demand side. For example, since 1 October 2005 it has been possible to prescribe by substance name (VOS), and the prescribing practice of doctors is monitored: they have to prescribe generics in 27 p.c. of cases⁸⁵.

⁸⁴ In the case of cholesterol-reducing drugs, the system applies to only a minority of the available medication, since around 70 p.c. of the drugs are patented.

⁸⁵ Despite the various government measures in recent years to encourage the sale of cheap drugs, the penetration of generics has remained remarkably low in Belgium: according to data from the umbrella organisation, EFPIA, generics accounted for only 6 p.c. of total sales (in terms of value) on the Belgian market in 2004, one of the lowest percentages in Europe. However, according to figures announced by the government, generics recorded a significant increase in their market share in mid 2006, and this was attributed to measures taken in 2005.

Results of reference reimbursement

Theoretical aim

The obvious aim of reference reimbursement is to maintain control of expenditure on prescription drugs, via reimbursement by the third party bearing the cost.

The underlying reasoning here is that the pharmaceutical market is less price-sensitive on the demand side⁸⁶ and there is a degree of market power on the supply side⁸⁷, so that it is necessary to encourage competition in order to reduce prices. It is assumed that the patients subject to the reference reimbursement system become more price-sensitive since they themselves have to pay the excess on top of the reference price, while firms will cut their prices in order to safeguard their market share. This results in cheaper drugs and hence lower expenditure, with greater predictability for the budget⁸⁸.

Empirical findings⁸⁹

Although the basic idea behind reference reimbursement is attractively simple, the literature draws attention to the potential weaknesses of such a system, particularly if it involves more than just generic equivalence.

However, experience of this system in other countries cannot be simply assumed to be generally applicable. Not only do the exact details of the system vary from one country to another, the effects of such a system cannot be precisely ascertained, since there are generally various other drugs policy measures in force on both the demand and the supply side in the countries concerned⁹⁰. In considering the findings in the literature, it is therefore necessary to focus on the general direction rather than the exact extent of the effects found.

Expenditure

One general finding which emerges from the empirical literature is that the system of reference reimbursement is not in itself an effective means of maintaining control over the drugs budget. In the short term, this system may reduce expenditure on drugs, but in the medium to long term additional measures are needed to achieve that.

There are various reasons why a reference reimbursement system does not succeed (permanently) in achieving its objective. Not only are the effects on price competition less significant than hoped, the system also targets only one component of expenditure, while volume and changes to the prescription mix are not addressed, or are even encouraged in the wrong direction (cf. *infra*).

⁸⁶ This lower price sensitivity is due to problems of asymmetric information among both physicians and patients, and to the existence of systems of reimbursement by a third payer.

⁸⁷ Since not all firms are active in all therapeutic fields, there is likely to be oligopolistic competition on the drugs market, with comparable but not totally identical products.

⁸⁸ Lopez-Casasnovas and Puig-Junoy (2001).

⁸⁹ Danzon (2001); Lopez-Casasnovas and Puig-Junoy (2001); Dijkgraaf (2004).

⁹⁰ Danzon and Ketcham (2003).

The countries where this system was introduced found that prices initially tended to fall to the reference level for the class in question⁹¹. However, various authors remark that setting a reference level does not automatically engender competition below that level⁹². A number of studies⁹³ also state that the relevant competition on the drugs market tends to take place between the branded drug and the generic version of the same active substance, rather than between products which are therapeutic alternatives⁹⁴. Studies⁹⁵ relating to Sweden have also shown that the savings achieved in the short term may be at the expense of competition in the long term: owing to lower profitability following introduction of reference reimbursement, there was a 50 p.c. decline in the number of generics entering the market. The Norwegian report evaluating the reference reimbursement system explicitly states that the competition effects are minor, because demand is not price-sensitive⁹⁶. A reduction in the reimbursement price does not in fact always guarantee the substitution of a cheaper drug. The price-sensitivity of demand depends mainly on the price-sensitivity of each of the parties involved in the decision-making process: apart from consumers/patients, it is therefore also necessary to encourage the physicians and pharmacists to bring about a change in demand. But in practice, it is found that the producers compete not only on price but also in other ways, such as by influencing the prescribing behaviour of doctors, in order to maintain/increase their market share⁹⁷.

Depending on the range of products covered by the system, the reference prices often apply to only a small proportion of the drugs eligible for reimbursement. Moreover, producers can try to minimise the effect of the reference prices on their total income by increasing the prices of their drugs not covered by the reference system; what is more, new and more expensive drugs are constantly coming onto the market. The effect of reference reimbursement on the general drug price level is therefore not all that clear. Indeed, it was repeatedly found that not only did the price increase, so did the market share of the products not covered by the reference system; in particular, there were noticeable shifts towards new/improved drugs – which were therefore more expensive because they were protected by a patent. This phenomenon was also seen in Belgium after the introduction of the reference reimbursement system⁹⁸. Finally, a reference reimbursement system offers no intrinsic incentives for addressing the volume of medication.

Side effects: distribution effects, health effects and substitution within health expenditure

Reference reimbursement is expected to produce significant side effects as a result of the assumed homogeneity of drugs in the same class. However, these products can generate a varying therapeutic response in patients (e.g. effectiveness, interactions or side effects) so that they are not considered equivalent. Naturally, the likelihood of such variations is greater the broader the class definition, as in the case of therapeutic substitution. As a result, reference reimbursement can lead to unfair discrimination against vulnerable groups (the elderly, the chronically sick,...) in two ways: first, in the financial sense, if they decide not to substitute cheaper products and are therefore liable in full for the extra cost associated with the higher priced drugs (distribution effects); second, in

⁹¹ The importance of the specific context and implementation of the concept in the assessment of reference reimbursement is evident in this connection from the example of Germany. Here it was found that some generic producers raised their prices to the reference level, as that level was determined as the statistical median.

⁹² Brouwer and Rutten (2001); Danzon (2001). Lopez-Casasnovas and Puig-Junoy (2001) actually state: "Even so, it has to be said that RP in New Zealand had failed by international standards to deliver low prices for generics" (p. 28).

⁹³ Pavcnik(2002); Danzon and Ketcham (2003).

⁹⁴ Conversely, a number of studies point to the existence of a "generic paradox", whereby the average prices of the branded products tended to increase following the introduction of the generics, without any loss of market share.

⁹⁵ Jönsson (1994); Ekelund (2000)

⁹⁶ ECON (2000).

⁹⁷ Dijkgraaf (2004).

⁹⁸ RIZIV (2004); Simoens (2005).

regard to the health risk if – on cost grounds – they do decide to substitute cheaper drugs which may be less effective for them (health effects). The additional health problems which might result could ultimately give rise to an increase in expenditure on other aspects of health care (GP consultations, hospital admissions, etc.) or even additional consumption of medication (substitute health expenditure).

Side effects on R&D

However, reference reimbursement is also controversial on account of the potential impact on R&D. Yet it is noticeable that, in contrast to the price responses by producers, the implications for R&D are rarely examined in depth by the economic literature, and there is hardly any theoretical or empirical backing for the points of view. Although the various authors appear to agree that effects do exist, there is not always a consensus on the direction of the effects.

It appears to be generally accepted that the effects of reference reimbursement on R&D in the case of generic substitution are minimal, since patent protection applies and there are therefore still incentives for R&D. However, if patented drugs are also included in the reimbursement system, there appears to be a greater threat to future R&D⁹⁹. The reference price used in such a system is often the price of a generic product, and – in view of the limited R&D expenses for generics – that is often close to the production cost. But for the research-intensive pharmaceutical industry, such a price means erosion of the economic value of the patent, since such pricing does not allow for any compensation of the R&D costs incurred¹⁰⁰, destroying the incentive for R&D and innovation. In that case, reference reimbursement would influence not only the volume of R&D investments, but also the type of research carried out and access to new drugs.

Since the innovative pharmaceutical industry obtains most of its investment resources from its own (predicted) income, a lower profit margin under reference prices means a smaller budget available for research activities¹⁰¹. However, according to some studies, the level of R&D investment is significant for the rate at which new drugs are invented, so that a sub-optimum investment level would mean fewer new products in the longer term¹⁰². A study commissioned by the US Department of Commerce¹⁰³ calculated, for example, that price deregulation in 11 OECD countries¹⁰⁴, including Belgium, would lead to an increased R&D budget which, taking account of the current allocation of the research budgets by type of research, would yield 3 to 4 additional new molecules each year. In the specific case of Belgium, it may be that, owing to the small size of the drugs market, the incomes received here have little impact on the overall, worldwide R&D budgets of the research-intensive multinational pharmaceutical industry.

In a global market, however, the impact of a national pricing policy is not confined to national territory: by means of parallel imports and external reference, the lower prices – and hence also their effects on the research budget – can be transferred to other countries. There is then a real danger that the research-intensive pharmaceutical industry may respond by winding down its research activities in the countries concerned and/or postponing market launches in countries which adopt a "free rider" attitude towards pharmaceutical R&D. A number of studies have already

⁹⁹ In some cases, the exclusion of patented drugs from the reference reimbursement system is only partial (e.g. only patents relating to active substances, not processes, use or formulas).

¹⁰⁰ According to Danzon (1998), those costs account for 30-50 p.c. of the drug price.

¹⁰¹ Some authors qualify this argument to a substantial degree, as pharmaceutical firms are multi-product companies and their total income/profits need not decline if some of their sales fall outside the reference reimbursement system.

¹⁰² Kessler (sd); Lopez-Casasnovas and Puig-Juoy (2001).

¹⁰³ US Department of Commerce (2004).

¹⁰⁴ Apart from Belgium, this concerns Australia, Canada, France, Germany Japan, Italy, the Netherlands, Spain, Sweden and the UK.

indicated that, under systems with the strictest reference prices, fewer new drugs come onto the market than under less strict systems, with the inevitable potential implications¹⁰⁵. In the same connection, it was found that the drugs coming onto the market are fewer in number and slower to arrive where prices are lower, where the countries concerned are smaller, where parallel exports are greater and where the pharmaceutical company does not have a branch¹⁰⁶.

The effects of reference prices on R&D are nevertheless not confined to the level of the research efforts, but also concern the nature of the research carried out. However, the literature contains totally conflicting views on this.

One view states that under reference prices there will be less investment in gradual innovation – small but potentially significant improvements, compared to existing drugs for a particular disorder – because those drugs will have to compete with the existing branded products and generics, which ultimately creates a risk of concentration on obsolete products within a group of drugs. However, a break-through innovation creates a new market, and can therefore escape the reference price. But since a breakthrough is associated with a lower chance of success and higher development costs, the risk of higher prices for new drugs would increase in this scenario.

The other view states that, since the expected revenues under reference reimbursement decline, there will actually be a shift towards imitative rather than innovative drugs, since these imply smaller R&D budgets.

As we know, this problem of choice was in only one recent paper addressed in a formal way, based on a simplified setting – specifically for the Spanish (generic) variant of reference reimbursement¹⁰⁷. The author concluded that, although the switch to a reference price system may have a significant influence on the investment decision, the outcome is unclear: the (size of the) difference in R&D costs for developing the two types of new drugs is not the only factor; the market power of the company also plays a role (the greater its market power, the greater the likelihood of incremental innovation).

¹⁰⁵ Danzon and Ketcham (2003); the Belgian Senate (2005).

¹⁰⁶ Danzon, Wang and Wang (2003).

¹⁰⁷ Mestré-Ferrandiz (2001).

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