

INSTITUTO NACIONAL DE ESTADISTICA



Statistics on Biotechnology Use. Year 2014

Methodology

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1. Objectives

The objective of this study is the measurement of the national effort in biotechnology-related activities, so that it is capable of providing the necessary information for the taking of adequate scientific-technological policy decisions. In this regard, the objective is to ascertain the type of biotechnology-related activities that are carried out in each of the sectors in which the economy is divided; the final application areas of the products obtained via the development of biotechnologies; economic and human resources appointed to the biotechnology-related productive and investigation activity in Spain.

In order to determine financial resources, the aggregate Domestic Expenditure in Biotechnology R&D Activities is calculated, which is comprised by the set of biotechnology R&D expenditures in Spain for each sector into which the economy has been broken down, notwithstanding the source of the funds and the financial backer's nationality. Capital structure and composition will be studied within expenditures. To ascertain human potential, the Personnel (researchers and other personnel) dedicated to biotechnology R&D activities in full-time equivalence is calculated.

Another objective is to determine the number of units engaged in biotechnology-related activities in Spain, and the benefit generated by sales of biotechnology products. Thus, in addition to the aggregates above, the following are calculated: Expenditure on Biotechnology-related Activities conducted in Spain and Personnel dedicated to the same, on a full-time equivalent.

2. Background

This survey is in line with what's established in Regulation 995/2012 on science and technology statistics. Up to this moment, the number of countries in which this survey is conducted is very small. The first initiative to study biotechnology R&D took place between 2000 and 2004, within a group made up ad hoc by the OECD. The works undertaken by this group focused in determining main questionnaire features and defining concepts. Biotechnology use statistics are currently the aim of study of a group of OECD experts in science and technology matters (NESTI group).

Spain is one of the field's statistical research pioneering countries, a study was carried out during year 2003 and 2004 setting the background for the development of a formal survey on biotechnology R&D activities. It was developed through a module included in the Innovation and R&D questionnaire. Beginning this year, not only all known units performing biotechnology R&D activities, but also all those units carrying out any activity related to biotechnology, were studied comprehensively.

Beginning in 2006, the scope of the biotechnologies statistics was extended, considering those units with biotechnology-related activities (not only R&D in biotechnology) to be the target of study.

The 2008 data already yields the external acquisition of R&D in biotechnology.

3. Scopes

POPULATION SCOPE

Companies, public organisations, universities and non-profit private institutions engaged in biotechnology activities located in the national territory are studied by means of this statistics.

This scope will remain delimited by the definitions and regulations which feature below.

TERRITORIAL SCOPE

This extends to all of Spain.

TEMPORAL SCOPE

The main reference period of this statistic is the year immediately prior to the year the data is collected. For expenditure, the reference period will be the natural year. With regards to personnel, to determine the number of persons who work in biotechnology, the statistics use both the annual average and the full-time equivalence of the personnel carrying out biotechnology-related activities (persons/year).

The statistic is included the National Statistics Plan and is conducted on a yearly basis, regarding companies, a module is included within the Innovation Survey for companies. For the remaining economic sectors (Public Administrations, Higher Education and non-profit Private Institutions) this module is attached to the Statistics on R&D activities questionnaire. This survey coordination is carried out with the purpose of optimising the available resources without interrupting the basic information supply, and enabling information requests from national and international institutions and those derived from the National Statistical Plan to continue being served.

4. Statistical unit

COMPANY SECTOR

This sector includes, in the following groups:

a) Companies, bodies and institutions whose main activity is the production of goods and services destined to sale at a price that corresponds to economic reality. A company is defined as all juridical units which constitute an organisational unit producing goods and services, and which enjoy certain decision-making autonomy, mainly when it comes to employing the current resources that it has available. From a practical point of view, and in its broader case, the concept company concept corresponds to that of a legal unit, in other words, with that of every individual or legal entity (corporations, co-operatives,...) whose activity is recognized by Law, and who is identified by the corresponding Tax Identification Number (NIF).

Essentially, this group is formed by private companies (companies and quasi-companies), some of which have as their main activity R&D, but also included are public companies whose main activity consists in the production of goods and services destined to sale, although, due to social reasons, the price of these products and services may be below their production costs.

b) Private non-profit institutions (including research associations) that are mainly at the service of companies and which, to a large extent, are financed and controlled by same.

Within this sector, a subsectorisation is carried out in:

- public companies
- private companies without foreign participation
- private companies with a participation of less than 10% of foreign capital
- private companies with a participation greater than or equal to 10% and less than 50% of foreign capital

- private companies with a participation of at least 50% of foreign capital
- research associations and other research institutions

PUBLIC ADMINISTRATION SECTOR

This sector comprises:

a) Institutions that provide the community, free of charge or at conventional prices, public interest services that would not be economical or easy to provide in another manner, which administer public issues and carry out the economic and social policy of the group.

This group must include all public institutions (except public companies and higher education institutions) irrespective of the manner in which they are included within the national budget and their level of jurisdiction (central, autonomous,...) The activities of these centres are very diverse and numerous, and are usually related to the Public Administration, defence, public order, health, education, culture, economic promotion and development, well-being, scientific and technical development,...

b) Private non-profit institutions mainly controlled and financed by the Public Administration.

With in this sector a subsectorisation is carried out, as follows:

- State administration
- Autonomous administration
- Local administration
- Other centres

State administration institutions, comprised in this sector are the State, its dependant Autonomous Institutions of same, as well as state corporations, public institutions,...., which, given their main activity and resource origin, can be considered as part of the Public Administration Sector. Also considered a part of this sector are the entities that administer Social Security, as well as hospitals that depend on same, and which perform this function on behalf of the State.

This similar happens with the institutions dependent on Autonomous and local administrations.

HIGHER EDUCATION SECTOR

This sector includes all the universities (faculties, technical schools and university schools), PNPI working for higher education institutions, technological institutions and other post-secondary institutions, irrespective of the source of their financial resources and their legal situation. It likewise includes all research institutions, test stations, astronomy observatories and private hospitals that fall under the control of higher education institutions, which are administered by same or are associated to the latter.

The following subsectorisation is made within this sector:

- Public Universities
- Private universities
- Other centres

PRIVATE NON-PROFIT INSTITUTIONS (PNPI) SECTOR

The field covered by this sector has been noticeably reduced in the revision of the Frascati Manual in 2002. It includes private non-profit institutions outside the market and at the service of households (that is, the public in general) and individuals. They provide individual or group services to households, either free of charge or at below market prices. They may be constituted by associations of

persons that provide goods or services destined mainly to its own members or with philanthropic ends. These institutions are financed with fees, contributions or donations from its members or sponsors, and with subsidies granted by companies and the Public Administration. Included within this sector are institutions such as professional associations or cultural societies, charity organisations, aid or assistance bodies, trade unions, consumer associations,...

By agreement, this sector covers all particular (household) residual R&D activities, including biotechnology R&D activities. R&D tasks of individuals must solely be carried out in their free time, within their own facilities and with their own resources or with the aid of a non-refundable subsidy.

Excluded from this sector are the following non-profit private institutions:

- Those in which the main activity is carried out to the service of companies.
- Those that mainly serve the public administrations.
- Those which are completely or mainly funded and controlled by Public Administrations.
- Those that offer higher education services or which are controlled by higher education institutes.

ABROAD

This sector comprises all the institutions and individuals located overseas, with the exception of vehicles, boats, airplanes and satellites used by Spanish institutions, and the experimental land acquired by same. Also included are international organisations (except companies), including their installations and activities, within our borders.

Other countries appear in the R&D survey solely as financing sources for the R&D carried out by national units.

This sector is subdivided into:

- European Union
- Foreign countries, with the exception of the European Union

5. Variables and their definition

There is a set of variables which appear in the main innovation questionnaire, which are used to classify biotechnology study results.

ECONOMIC ACTIVITY

This variable is only investigated in the company sector and is included in the main innovation questionnaire, and is therefore also useful for classifying biotechnological companies.

The economic activity carried out by a company is defined as the creation of added value via the production of goods and services.

R&D company activities (and therefore biotechnology R&D) are classified in accordance with the main economic activity which they develop, understanding the main economic activity to be that which generates the greatest added value. Faced with the difficulty implied in calculating added value for companies that carry out several activities, the main activity is considered to be that which generates the greatest turnover or, in its absence, that which occupies the largest number of employees.

The classification used is the National Classification of Economic Activities (CNAE-2009) , compiled according to the conditions established in the Regulation

passed of NACE Rev.2. This classification serves to determine who is to carry out the research.

DIMENSION OR SIZE OF COMPANY

This variable is the only one investigated in the company sector and is also included within the main innovation questionnaire.

The dimension of the companies is one of the most important variables when determining the behaviour of the companies. This dimension may be established either by ascertaining the magnitude of turnover, or by considering the number of persons that comprise the staff of the company.

EMPLOYED PERSONNEL

This variable is studied only in the company sector.

It corresponds to the number of persons who work in a company, as well as the persons who, though working outside of the company, belong to it and are paid by it (for example, sales representatives and delivery, repair and maintenance personnel who work on behalf of the company). This includes both paid and unpaid personnel.

A worker who works through a temporary agency is an employee of the agency and not of the unit (company) in which he/she works.

Paid personnel is comprised of those workers linked to the company by a work contract and who are paid in fixed or periodical sums in the form of a salary, wages, commission, piecework or payment in kind.

This may be fixed personnel (with a permanent labour contract or link) or temporary personnel (with a fixed duration contract).

Also considered to be paid personnel are the following: owners paid by their work; students with a formal commitment by which they contribute to company production in exchange for remuneration and/or education services; employees hired via a contract aimed specifically at encouraging the hiring of unemployed persons; home-based workers if there is an explicit agreement to pay them according to the work they do and if they are included in the payroll.

Also considered to be paid personnel are as follows: part-time workers, seasonal workers and persons who are on strike or are on short-term leave, excluding those who are on long-term leave.

Unpaid employed personnel is comprised of those persons who manage or participate actively in the workings of a company without receiving a fixed remuneration or wages. Included in this category are the following: the owners, autonomous partners who perform an activity in the company and family assistance. Not included are exclusively capitalist partners, nor relatives of the owner who do not participate actively in the company, nor the persons who are included in the payroll of another company in which they carry out their main activity.

TURNOVER

This variable is only investigated in the companies sector and is included within the innovation questionnaire.

It is comprised of the amounts invoiced by the company during the reference year for the provision of services and the sale of goods that are the object of traffic of the company. VAT is not included in the valuation of turnover.

This coincides with the total amount resulting from the sum of sales (accounted for in net terms, deducting sales returns, as well as discounts over volume sales. Neither cash discounts nor discounts over sales due to early payment are deducted) of goods manufactured by the company itself (or by third parties, via subcontracted production), be they finished, semi-finished sub-products, recyclable residues or material, plus the net sales of goods or merchandise acquired by the company for their subsequent sale without processing, plus the amount for services rendered to other companies (including revenues from subcontracting).

Turnover does not include the sale of fixed assets or the subsidies received for producing. The amount of turnover is calculated as the sum of the net sales of merchandise and the rendering of services.

The rest of Variables that are detailed hereunder are specifically included in the biotechnology module, although the majority of them have analogue questions in the main questionnaire.

EXPENDITURE ON BIOTECHNOLOGY-RELATED ACTIVITIES

Biotechnology is the application of science and technology to living organisms, as well as to their parts, products and models, to alter living or inert material, for the purpose of producing knowledge, goods and/or services.

Biotechnology expenses are considered to be those amounts used for biotechnology-related activities, carried out within the unit, regardless of the origin of the funds.

PERSONNEL IN BIOTECHNOLOGY-RELATED ACTIVITIES

The measurement of the personnel employed in biotechnology-related activities is the other means of obtaining the input in biotechnology.

It includes, as personnel in biotechnology-related activities, all personnel employed directly in biotechnological activities, without distinction of the level of responsibility, as well as those who provide services that are directly linked to work using biotechnology, as managers, administrators and office personnel.

Personnel data may be measured in two ways, in the number of physical persons and in the full-time equivalence.

Number of physical persons

The data regarding the total number of persons who are full-or part-time employees in biotechnology-related activities, allow for establishing correspondences with other data series, such as, for example, those regarding education or employment or those of the population censuses. On the other hand, the data regarding physical persons are the most appropriate measurement for collecting complementary information on the characteristics of the personnel in biotechnology, such as sex, occupation or country of origin.

Full-time equivalence (FTE) during the year

For the purposes of the measurement of personnel, it is important to introduce the concept of a full-time equivalent working day, as the biotechnological activity of the personnel tends to be, in many cases, a partial or secondary activity. The following is considered:

- Full-time personnel in biotechnology-related activities are those persons who use at least 90 percent of their working day for activities that use biotechnology.

- Part-time personnel in biotechnology-related activities are those persons who dedicate approximately 10 to 90 percent of their working day to activities that use biotechnology, and the rest to other activities.

This also includes persons who have carried out biotechnology activities during a period of time that is less than a calendar year.

- Full-time equivalence of the part-time personnel to the sum of the fractions of time they have dedicated to activities that make use of biotechnology.
- Personnel employed in biotechnology-related activities on a full-time equivalence completes the sum of the personnel that works full-time plus the equivalence of said dedication of the personnel that works par-time.

In addition, the personnel employed in biotechnology-related activities is requested, broken down by gender.

The rest of the variables that follow may be found specifically in the module on biotechnology use.

CURRENT BIOTECHNOLOGY USE

Questions are made regarding the series of biotechnology activities in which the company is engaged. This section also includes research in any of the areas of biotechnology. Biotechnology can be related to human, animal, plant or environmental health.

1. The **genetic code. DNA** related technologies (genomics, pharmacogenetics, genic probe, sequencing/synthesis/amplification of DNA, genetic engineering).

The genetic code is the set of rules which each RNA codon (tri-nucleotide unit) maps into a determined amino acid in the proteins. This section includes DNA related technologies, such as genomics, which studies the set of genes in an organism, tissue or type of cells and its functions.

Pharmacogenetics studies the impact of genetic variations on drug efficacy and toxicity.

Also included is the work with genic probes, which consist in DNA and RNA molecules tagged by means of different methods in order to identify targets, genes or genic products. There are three types of genic probes: genomic, complementary DNA (cDNA) and RNA

DNA sequencing, synthesis and amplification and genetic engineering are also detailed. DNA sequencing consists in determining a DNA molecule's nucleotide or basis order, and synthesizing a DNA molecule with a predetermined sequence is carried out on the basis of its constituting nucleotides. DNA amplification consists in producing additional copies of a DNA molecule.

When speaking about genetic engineering we refer to the set of techniques to alter cell or organism genetic constitution by selectively eliminating, inserting or modifying genes or gene groups.

2. **Functional units.** Protein and other molecule related technologies (protein/peptide sequencing/synthesis, lipids/glucides/proteins, proteomics, hormones and growth factors, cell receptors/signalling/pheromones).

These activities are normally carried out with the purpose of finding drugs once the weak point of an illness has been found.

Peptide and protein sequencing consists in determining the order of the aminoacids comprising a peptide or protein. On the other hand, peptide and

protein synthesis consists in generating a peptide or a protein with a pre-determined sequence by means of mRNA (biochemical methods) or by constituting aminoacids (by means of a synthesizer).

When speaking about glycoengineering we are referring to the biological addition of sugars to lipids and proteins.

Proteomics is the science studying the proteome. By studying, we mean studying at least three things: identifying at once all proteins producing a cell, tissue or organism determining how said proteins interact, and finally, finding the precise three-dimensional structure for each of these proteins. We might define it as the complete set of proteins present in a cell, tissue or organ with the purpose of identifying the qualitative level, its structures and its interrelations.

This section also includes hormone and growth related factors, which are the mediating peptides affecting cell growth, division and/or differentiation.

A cell receptor is a protein which selectively adheres to a specific molecule originating a biological response.

Signal makes reference to molecules, which originate a certain cell response.

Pheromones are intercellular mediating compounds which are released by an organism and affect the metabolism or behaviour of another organism, generally belonging to the same species.

3. Cell engineering and tissue cultures (cell/tissue cultures, tissue engineering, hybridisation, cell fusion, immune response stimulators or vaccines, embryo manipulation).

The third activity classified in the questionnaire is cell and tissue engineering cultures. Cultures include cell and tissular cultures. Cell cultures are techniques enabling "in vitro" cell growth and preservation, aiming to preserve its main physiological, biochemical and genetic properties.

Tissue cultures are the set of techniques enabling "in vitro" tissue culture, aiming to preserve its main physiological, biochemical and genetic properties.

When talking about hybridisation, we make reference to the molecule, cell or organism generating process, combined with genetic material from different organisms. In traditional techniques, hybrids were produced by crossing different animal and plant varieties by aligning or mating two single strand equivalent and complementary DNA molecules. Hybridisation can be defined as the process of combining two complementary single stranded nucleic acids to produce a double strand molecule. Cellular fusion technology and transgenic manipulation are the new hybridisation techniques introduced by genetic manipulation. DNA hybridisation shall also be included in this section.

Cell fusion is the process by which two cells are melded (fusion) generating a single cell with both cell's genetic material.

Also included in this section are immune response stimulants, whose investigation is aimed at studying any substance originating a determined response of the immune system.

Thermotherapythere section within cell and tissue engineering cultures is vaccine investigation. A vaccine is the preparation of weakened or dead pathogen microorganisms or molecules (generally proteins or DNA) or derived products thereof, which are inoculated into persons or animals to induce antibody generation, immunizing them against the illness caused by the pathogen.

Recent studies focusing on embryo manipulation are included in this section, understanding as embryo manipulation all techniques intended to modify an embryo's content, like cells or genetic material, for example.

4. **Bioprocesses.** (bio-reactors, fermentation, bioprocessing, biolixiviation, biopulping, biowhitening, biodesulphurization, bioremediation and biofiltering). Biotechnological processes or bioprocesses usually try to use micro-organisms and their products to produce and develop foods in combination with studies whose aim is to make better use of agricultural products for the same ends.

Some of the applications in which bioprocesses are frequently used could be: endoglucose production, enzymatic production of sorbitol, for non traditional cultures in fructose syrup production, as an alternative to ethanol production or for fructooligosaccharides and insulin. It can also be used in enzyme separation for the production of fructooligosaccharides from insulin, for probiotic organism propagation in animal foods and for the development of pre and probiotic foods. Other types of bioprocesses are those used in yeast fermentation for chrome and selenium production, drying, modulation, simulation and optimisation of fermentation for chromatic separation moderation.

Bioreactor is defined as the vessel used in the "in situ" measurement and control of all variables involved in fermentation or bioprocessing processes.

Fermentation is an aerobic or anaerobic process, mainly induced by microorganisms, which, based on a organic substrate, obtain the energy they require to grow and develop, and generate numerous metabolic waste products which have an industrial application.

Bioprocessing is the technique from which microorganisms, live cells or components thereof are used to produce the desired final product. Bioprocessing, which involves use of enzymes and microorganisms to transform food raw materials in a variety of products, offers a great opportunity to stimulate agro-industrial development in developing countries. Its processes are measurable, environmentally harmless, and can be applied in an economical way and linked to existing practices in these countries. However, many traditional bioprocessing techniques which are used in developing countries require considerable scientific and technological improvements.

On the other hand, biolixiviation is the use of microorganisms to have mixed compound separated. in last years for extraction of minerals financial allocation.

Biopulping is generally used in wood pulping processes in the cellulose industry. Biopulping is the production of cellulose pulp using procedures which include a biological treatment and biowhitening consists in pulp whitening using procedures which include a biological treatment.

Biological desulphurisation or bio-desulphurisation has the purpose of eliminating sulphur compounds contained in a material, by means of biological processes. It is currently being used to diminish sulphur in hydrocarbons, and therefore reduce environmental pollution. Biological decontamination or bioremediation consists in the use of microorganisms to transform and destroy environmental pollutants.

To finish with this section, bio-filtration is mentioned, which consists on a filtering method which uses bacteria to convert toxic compounds in other non toxic substances.

5. **Sub-cellular organisms** (genic therapy and viral vectors). Genic therapy is a therapeutical strategy consisting in the insertion of nucleic acids in an individual's tissue to palliate or cure illness caused by genetic errors existing in any of his/her genes. The rise of gene therapy has been possible thanks to the

confluence of knowledge advances in fields such as: Molecular biology, Genetics, Virology, Biochemistry and Biophysics, among others.

When talking about viral vectors we are also making reference to genic therapy in most of the cases, under ideal circumstances they are frequently used in genic therapy. Viral vectors are viruses which have had foreign DNA inserted into them so that they introduce it in the cells or microorganisms infected by them.

6. **Biocomputing.** Construction of software products and databases for the management, analysis and integrations of data from genomics, proteomics, modelling sequences and biological systems.

7. **Nanobiotechnology.** This includes the instruments, materials or apparatus obtained from the combination of nanoscale engineering and biology, for the study of biosystems and applications in the administration of pharmaceuticals, diagnoses, etc.

8. **Other.** The remaining activities which have not been included in any of the previous sections can be included here. They can be included in any biotechnology area.

PRODUCTS OBTAINED FROM BIOTECHNOLOGY. FINAL APPLICATION AREAS

The products obtained from the use of biotechnology are the ones resulting from any of the activities detailed in the previous section. This information allows the company to be classified into a branch of activity and to clarify some of the questions in case there are any doubts.

One asks which is the final application area of the products obtained through the use of biotechnology. The areas indicated are the following:

1. Human health. Application of red or health biotechnology, which is the biotechnology applied to medical processes, both in the field of therapy and in the diagnosis of illnesses.
2. Animal health and aquaculture. Use of biotechnology in medical procedures for animals. Biotechnology in aquaculture comprises a broad spectrum of technologies that offer opportunities to elevate the growth rate of cultured species and improved the management and preservation of wild populations.
3. Food. The biotechnology of food is a set of techniques or processes that use living organisms or substances that come from them to produce or modify a food, improve the plants or animals from which food is derived, or develop micro-organisms, such as bacteria, fungus or yeast, which intervene in the preparation processes of the same. The animals and plants from which food is derived have been modified by man in multiple aspects, to make them adequate for production needs, to improve their nutritional properties, or to change sensorial qualities (smell, flavour, shape, colour, texture).
4. Agriculture and forest production. Application of green or agricultural biotechnology, which includes the processes or techniques that modify or improve the physical or chemical characteristics of plants and animals. The products of agricultural biotechnology offer farmers greater income on producing more food in a smaller space, while simultaneously protecting the natural resources, such as land, water and forests. Agricultural biotechnology allows for obtaining plants that tolerate herbicides, are resistant to insects and diseases, and plants that can grow under unfavourable conditions.
5. Environment. Environmental biotechnology is the name granted to the use of biological processes to protect and restore environmental quality. Biotechnology helps to clean the environment, treating urban, agricultural and industrial waste, reducing air pollution or that of water or land

systems, such as the elimination of hydrocarbons (above all, from petroleum). The elimination or neutralisation of heavy metals, and even nuclear metals and the treatment of waste water.

6. Industry. Application of white or industrial biotechnology, which refers to the combination of biotechnological processes and biochemical processes. Industrial biotechnology is that which is applied to industrial processes, such as the design of micro-organisms to produce a chemical product, or the use of enzymes as industrial catalysts. It is also applied to biotechnology uses in the textile industry, in the creation of new materials, such as biodegradable plastics, and in the production of bio-fuels. Its main objective is the creation of products that are easily degradable, that consume less energy and generate less refuse during their production.

INTERNATIONALISATION OF BIOTECHNOLOGY-RELATED ACTIVITIES

One may ask whether they have income with international origin, related to biotechnological activities, in this case, collecting the amount. This income is broken down into a percentage, depending on whether it comes from the EU or the rest of the countries.

EXPENDITURE IN INTERNAL BIOTECHNOLOGY R&D ACTIVITIES

Any study, test, experiment, investigation, etc. performed in the previous fields or in any branch of biotechnology is considered as biotechnology R&D.

The measurement of R&D expenditure is one of the procedures for obtaining the input of the research activity. Specifically, biotechnology R&D expenditure enables to develop studies in this fields, which has been growing lately both in importance and level of repercussion.

Any amount destined to biotechnology R&D activities, carried out within the research department or unit (internal expenditure) or outside same (external expenditure), irrespective of the source of the funds is considered as an expense in biotechnology R&D activity. Expenses carried out outside the centre, but supporting internal biotechnology R&D tasks (biotechnology R&D supply purchases, for example) will also be included as internal expenditures in biotechnology R&D. The data relative to internal R&D expenditure must be collected from the information on internal biotechnology related R&D expenditure.

Nature of R&D expenditure

Internal expenditure include both current and capital costs.

Current expenditure

Within current expenditure a distinction is made between personnel expenses and other current expenses.

Personnel costs include the total remuneration of staff, including social security (wages and extraordinary payments, other salary supplements or diverse payments, such as bonuses, holiday pay, remunerations in kind, contributions to pension funds, corporate insurance paid by the company,...), that is, what is denominated as corporate personnel costs.

Wage costs of persons who provide indirect services and which are not taken into account in the data pertaining to biotechnology R&D personnel (principally, security and maintenance personnel, canteen service personnel, information technology, central library services and office management personnel) must be excluded and recorded as other current costs.

Only the *wages/study grants* and similar costs corresponding to postgraduate students must be included. Travel allowances of R&D personnel should also be included in other current costs.

Distinction will be made between remunerations to Investigators and the remaining personnel.

The remaining current costs include the costs of the acquisition of non inventory material and diverse supplies not considered capital goods; consumption of energy (gas, electricity,...) and water; books, magazines, reference material and subscriptions to libraries, participation in scientific companies, laboratory material (chemical products, animals,...); and the real and allocated cost of small prototypes or models manufactured externally. Administration and other general costs (such as office expenses, postal expenses, telecommunications, insurance and bank interest) should also be included, in the proportion that they affect biotechnology R&D activities.

Expenses in the form of indirect services (safety, storage; use, repair and maintenance works on buildings and equipment; computer and library services; cafeteria,...) should be included, either if they are services rendered by the own company or rented or purchased outside, in the proportion that they affect biotechnology R&D activities.

By agreement, supplies, either real or allocated in concept of real estate, facility and equipment amortisation, shall be excluded from internal expenditure measurements.

Capital expenditure

It is the gross investment in fixed capital used by units in biotechnology R&D programs.

It must be integrally declared within the period in which it has taken place, and cannot be considered an element of amortisation. It is necessary to record genuine costs, in such a manner that if other activities are carried out in the company, besides biotechnology R&D, a proportion of total expenditure must be allocated to the latter, calculated according to the use of these capital goods. This expenditure may be in land and buildings and in equipment and instruments.

Expenditure on land and buildings arise as a result of the purchase of land for biotechnology R&D purposes (for example, trial land, land for the construction of laboratories and pilot plants), as well as the construction costs of the buildings or the acquisition of same, including the costs for important renovation, modification, extension or repair work.

Expenditure on instruments and equipment includes the cost corresponding to the acquisition of inventoried equipment and material used in R&D tasks.

Expenditure on the acquisition of specific software for biotechnology R&D comprises the acquisition of software that is individually identifiable for its use in the development of R&D in biotechnology, including descriptions of the programs and documentation accompanying the systems software and applications. It also includes the quotas for licenses to use the acquired software.

Approximation to company accounting

i) Intangible assets

Investment (or disinvestment) in intangible assets is defined as increases (or reductions) in the real value of these types of resources (computer applications, R&D costs, goodwill, industrial property, administrative concessions,...) carried out by the institution during the reference year.

To statistical effects, only biotechnology R&D self-production shall be considered as internal expenditure in biotechnology R&D, making a distinction between current expenditure (biotechnology R&D personnel wages) and capital expenses.

On the other hand, this statistic does not only include costs arisen in successful R&D projects with solid grounds for technical project completion success, which is the accounting concept of R&D, but also the costs of unsuccessful R&D.

ii) Tangible fixed assets

With regards to investments in tangible assets, the General Accounting Plan covers the following accounts:

1. Natural land and assets
2. Constructions
3. Technical installations
4. Machinery
5. Tools
6. Other installations
7. Furniture
8. Information processing equipment
9. Transport elements
10. Other tangible fixed assets

Allocations for the amortisation of tangible or intangible fixed assets must not be included as an R&D cost., and therefore, in biotechnology R&D.

Source of biotechnology R&D funds

The intention with this question is to determine who finances the research.

Biotechnology R&D and R&D in general are activities which imply significant resource transfers between units, bodies and sectors. These transfers are measured with the information provided by those carrying out biotechnology R&D activities based on the amounts that said unit, organisation or sector has received from another unit, organisation or sector for the realisation of internal biotechnology R&D activities.

In order for this financial flow to be properly identified, two conditions must be met:

- a direct transfer of resources must exist
- this transfer should also be budgeted and genuinely used for R&D activities.

The transaction may be in the form of a contract, financial assistance or a donation, and may consist in a monetary contribution or the contribution of other resources (for example personnel or material). In the case of important non-monetary transfers, it is necessary to evaluate the market value of the transaction, because all transfers must be expressed in financial terms.

The units should include the brute amount of their expenditure, even is they are reduced by the concession of exemptions, deductions or aid paid subsequently.

The basic classification by source of funds is the following:

- Own funds
- From companies
- From the Public Administration

- From tertiary education centres
- From non-profit private institutions
- From abroad

Depending on each sector, it is possible to consider a further breakdown of this classification.

PERSONNEL IN INTERNAL BIOTECHNOLOGY R&D ACTIVITIES

The measure of personnel employed in R&D activities is the other manner in which R&D input may be obtained.

All personnel directly employed in biotechnology R&D activities, notwithstanding responsibility levels, as well as those rendering services directly linked with biotechnology R&D works, as managers, administrators and office workers will be considered as biotechnology R&D personnel. Persons rendering indirect services, such as canteen, security, maintenance,..., are excluded, even although their wages have to be accounted for as Other current expenditure in biotechnology R&D.

Personnel data in biotechnology R&D may be measured in two ways, in number of physical persons and in full-time equivalence.

Additionally, personnel employed in biotechnology R&D activities figures are provided broken down by gender.

Occupation of biotechnology R&D personnel

Biotechnology R&D personnel is classified according to the following categories:

• Researchers

These are scientists and engineers involved in the concept or creation of new knowledge, products, processes, methods and systems, and in the management of the corresponding projects.

Also included are managers and administrators dedicated to the planning and management of the scientific and technical aspects of the work of the researchers and which, normally, has a category equal or superior to that of persons employed directly as researchers, often dealing with former researchers or part time researchers.

Also included are postgraduate students with a "study salary/grant" who carry out R&D activities.

As a general rule, they possess advanced university education but, for the purposes of this study, also considered researchers are those persons that, being devoid of the aforesaid qualification, they occupy positions of this nature.

Evidently, investigators shall only be taken into account whenever they carry out biotechnology related R&D activities.

• Technicians and assistants

Technicians and similar personnel are persons whose main tasks require knowledge and technical experience in one or various fields: engineering, biological and physical sciences, or social sciences and humanities. They participate in R&D projects carrying out scientific and technical tasks applying operational principles and methods, generally under the supervision of researchers. Similar personnel carry out tasks corresponding to social sciences and humanities under the supervision of researchers.

Their tasks are mainly the following:

- search for bibliographic material and discover appropriate information sources in archives and libraries
- developing computer programs
- prepare material and the necessary equipment for the realisation of experiments, trials and analysis
- carry out experiments, trials and analysis
- carry out measurements and calculations and prepare tables and graphs
- carry out surveys and interviews
- guarantee logistical support to researchers.

Normally they possess intermediate-level university education (technical engineers and university diploma), but others do not, although they occupy positions of an comparable level. It can also include top level personnel entrusted with the use of very sophisticated apparatus, but they are distinguished from researchers in that the latter are in charge of directing or orienting research tasks.

Auxiliary staff includes workers, qualified or unqualified, and secretarial and office personnel who participate in the realisation of R&D projects, or whom are directly related to said projects.

Included in this category are all managers and administrators mainly occupied in financial matters, personnel management and administration in general, provided their activities are directly related to R&D tasks.

As in the case of researchers, researches shall only be taken into account if they are involved in biotechnology related R&D activities.

EXPENDITURE ON EXTERNAL BIOTECHNOLOGY R&D ACTIVITIES

This shall only consider to be external expenditure those amounts paid for the work in biotechnology R&D that is specifically commissioned by the unit of other units. It shall not include institutional quotas for financing other companies, research associations, etc., that do not imply a direct purchase of R&D in biotechnology.

The basic classification of external biotechnology R&D expenses is the following:

- Biotechnology R&D purchases in Spain (without VAT)
- Biotechnology R&D purchases abroad (without taxes)

INTELLECTUAL PROPERTY PROTECTION

The information required regarding intellectual property is the number of patent applications on the year of the survey. It has to be considered that each patent will only be accounted for one time, despite having been applied for in several offices.

6. Sample design

Directories

Due to the coordination of the R&D Statistic and the Innovation in Companies Survey (IS), and that the section on biotechnology is an additional module included in this questionnaire, the population framework is the Central Business Register (CBR). This is an organised information register with identification, localisation and territorial distribution data, and classification by size and economic activity of companies, obtained from administrative sources and complemented by other information that stems from current INE statistical operations.

Likewise, the survey includes within the population object of the study a directory of units (companies, public research organisations,...) that are considered as possible research units, either because they were considered as such in prior years, or because they have received public financing for the realisation of R&D during the reference year of the survey, or because they enjoy fiscal deductions. Starting from this **directory** of allegedly research companies, there is another directory, more restricted, comprised by **potential biotechnology research** companies. This directory is developed in a very similar way as the R&D Innovation survey, biotechnology R&D subsidies both for the Central Administration and for Autonomous Communities listings are requested. In addition, this includes a listing provided by ASEBIO (Spanish Association of Biocompanies) and this is added to available data from previous years. The directory made available on a yearly basis, is exhaustively investigated.

Considering that the Statistics on Biotechnology Use comprise an additional module of the Innovation Survey (IS), it must be indicated that the population of target companies of the IS is stratified through the crossing of the following variables:

- a) Company size: The following intervals are considered:
- Fewer than 10 employees
 - 10 to 49 employees
 - 50 to 199 employees
 - 200 or more employees

The strata constituted by companies with 200 or more employees must be analysed exhaustively.

- b) Autonomous Community in which the company is headquartered.
- c) Branch of main activity according to CNAE-2009: 56 divisions or activity groups are considered, their listing set out in detail in Chart 1.

Chart 1. Divisions or activity groups for stratification and correspondence with the National Classification of Economic Activities (CNAE-2009)

Divisions or activity groups	CNAE-2009
1. Agriculture, livestock breeding, forestry and fishing	01, 02, 03
2. Extraction of anthracite, coal and lignite	05
3. Extraction of crude petroleum and natural gas	06
4. Extraction of metallic ores	07
5. Other mining and quarrying	08
6. Extraction industry support activities	09
7. Food Industry	10
8. Manufacture of beverages	11
9. Tobacco industry	12
10. Textile industry	13
11. Manufacture of garments	14
12. Leather and footwear industry	15
13. Manufacture of wood and of products of wood and cork, except furniture; basketmaking and wickerwork.	16
14. Paper industry	17
15. Graphic arts and reproduction of recorded media	18
16. Manufacture of coke and refined petroleum products	19
17. Chemical industry	20
18. Manufacture of pharmaceutical products	21
19. Rubber and plastic material transformation industry	22
20. Manufacture of other non-metallic ore products	23

21. Metallurgy; manufacture of iron, steel and ferro-alloy products	24
22. Manufacture of metal products, except machinery and equipment	25
23. Manufacture of computer, electronic and optical products	26
24. Manufacture of electrical material and equipment	27
25. Manufacture of electrical material and equipment	28
26. Manufacture of motor vehicles, trailers and semi-trailers	29
27. Manufacture of other transport material	30
28. Manufacture of furniture	31
29. Other manufacturing industries	32
30. Repair and installation of machinery and equipment	33
31. Supply of electrical energy, gas, steam and air conditioning	35
32. Water supply, waste management and decontamination activities	36
33. Collection and treatment of wastewater	37
34. Collection, treatment and disposal of waste; evaluation	38
35. Decontamination activities and other waste management services	39
36. Construction, civil engineering, specialised construction activities	41, 42, 43
37. Sale and repair of motor vehicles and motorcycles	45
38. Wholesale commerce and commerce intermediaries, except of motor vehicles and motorcycles	46
39. Retail trade, except motor vehicles and motorcycles	47
40. Land transport and transport via pipelines	49
41. Sea and transport by domestic navigable routes	50
42. Air transport	51
43. storage and activities connected to transport	52
44. Postal and courier activities	53
45. Accommodation services, food and beverage services	55, 56
46. Publishing	58
47. Motion picture, video and television programme activities, sound recording and music publishing. Radio and television programming and broadcasting activities	59, 60
48. Telecommunications	61
49. Programming, consultancy and other activities related to IT	62
50. Information services	63
51. Financial service activities, except insurance and pension funding	64
52. Insurance, reinsurance and pension funding, except compulsory social security	65
53. Activities auxiliary to financial services and insurance activities	66
54. Real estate activities	68
55. Professional, scientific and technical activities: Administrative and support service activities	69, 70, 74, 75, 77, 78, 79, 80, 81, 82
56. Architectural and engineering activities; technical testing and analysis	71
57. Scientific research and development	72
58. Advertising and market research	73
59. Human health and social work activities; creative, arts and entertainment activities; repair of computers and personal and household goods; other personal service activities	86, 87, 88, 90, 91, 92, 93, 95, 96

Said sampling stratification is used in order to randomly obtain companies that potentially use biotechnology and that were not initially included in the comprehensively researched directory.

Size of the sample. Allocation.

The sample size of the Biotechnology use statistics is 2,940 units, 2,020 of which are companies, approximately 599 are public research organisations (including public hospitals), 81 are universities and 115 are higher education centres, and 125 are private non-profit institutions. Companies, public organisations, universities and private non-profit institutions that conform the directory of possible research units have been exhaustively analysed.

ESTIMATORS

The estimator of the total of a characteristic X in domain m is given by:

$$\hat{X}_m = \sum_{j \in m} X_j \cdot F_j,$$

where X_j is the value of characteristic X from questionnaire j belonging to domain m.

F_j is the elevation factor from questionnaire j which is calculated as follows:

a) If company j was selected from a stratum h and according to the questionnaire data, it is found in another stratum k, then: $F_j = \frac{N_h}{n_h}$

b) If the company j continues to belong to the same stratum h, where it was selected, then: $F_j = \frac{\hat{N}_h^*}{n_h^*}$ ()

c) In specific cases that are appropriately specified $F_j = 1$

Variables used

N_h , number of companies in stratum h.

n_h , number of companies selected in stratum h.

$n_{h,r}^*$, number of companies that have replied, selected in stratum h and that have not changed stratum.

$$\hat{N}_h^* = N_h \left(1 - \frac{n_h^*}{n_h} \right) - \sum_{k \neq h} \sum_{j=1}^{n_h^k} F_j$$

where n_h^* is the number of companies selected in the stratum h and where duplicate - temporary closure or inactive incidents are applicable.

$n_{h,r}^k$, number of companies selected in stratum h, and which according to the questionnaire are in the different stratum k.

Sample errors are also calculated by expressing the variation of the estimator of the total stratified sample.

7. Collection of the information

The Innovation and R&D questionnaire is submitted to all companies in the sample, including in the biotechnology module only those organizations appearing in the specific biotechnology directory, although if at any point in time, during the gathering process, a company is found to be conducting biotechnology R&D but without appearing in the directory, the module would be later sent to said company.

The personnel involved in the survey tasks is obliged by law to preserve statistical secrecy.

The survey inspectors are responsible for the theoretical and practical training of the personnel involved and for the control of the information collection work. To this end, the corresponding manuals and documents for training and consultation are prepared.

The biotechnology module will be mailed by post to the informant units, together with a letter of presentation, the rules for its completion, and an informational pamphlet with the latest results of the R&D Statistics. The companies will have a period of 15 days to return the completed survey.

The collection unit establishes an initial telephone contact with the company to verify receipt of the questionnaire. Once the established period expires without the completed questionnaire having been received, the necessary telephone and written claims are carried out.

Biotechnology use statistics is considered in the National Statistical Plans as mandatory, just as the general R&D Statistics.

The collection unit puts into practice an integrated information collection procedure, which consists in the filtering and recording of the data as soon as the information is received. If necessary, companies are requested to provide the necessary clarification in relation with the data furnished.

R&D related information, and therefore on biotechnology R&D developed by the public administration, higher education and non-profit private institutions sectors, is directly gathered from the Service promoting the Statistics and is received the same way as that related to companies, by postal mail.

8. Processing of the information

The information processing phases are the following:

- Manual control and filtering of company questionnaires within the collection unit, in order to recover possible missing data or to correct questionnaires errors.
- Interactive recording, filtering and correction of inconsistencies in the information validated in the gathering unit, taking into account data variability between the main questionnaire and the biotechnology module.
- Control of the information received from the collection unit by the INE department promoting the survey
- Control of the scope and processing of errors by the INE department promoting the survey
- Imputation of partial non responses
- Elaboration of a first phase of tables analysing the results
- Use of macro edition techniques at the INE department promoting the survey to eliminate errors and inconsistencies in the aggregates, which have not been detected in the previous micro filtering phase
- Analysis of the data
- Creation of definitive data files
- Attainment of final result tables elaborated by the promoting service from the final data files corresponding to companies

9. Presentation of results

The tabulation of results presented in this publication has been structured as follows:

- Main indicators: this presents the evolution over time of expenditure and personnel intended for internal biotechnology-related R&D activities.

- National summary: this presents the following data:

 - Expenditure on biotechnology R&D activities, broken down according to type of expenditure and origin of funds.

 - Personnel dedicated to biotechnology R&D activities, by occupation and sex.

- Results by sector of execution: the tabulation of the results is presented for each one of the sectors (Business, Public Administrations, PNPI and Higher Education) containing the main variables and their breakdown.

- Results by Autonomous Community

This data is also available by Autonomous Community. Moreover, result tables meeting the information requirements of national and international institutions, as well as individual users interested in the subject may be obtained. In all cases statistical secrecy is maintained, with the limits delimited by sample errors.

Publication is available on the INE website.