Statistics on Biotechnology Use. Year 2021

Methodology

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INE. National Statistics Institute

I Background

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 was 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 Community Innovation Survey in Enterprises and Statistics on R&D Activities. From 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 acquisition of R&D (external R&D) in biotechnology.

This operation is collected in coordination with the Statistics on R&D Activities in each of the sectors defined by the Frascati Manual (see section "Statistical Unit and Reporting Unit")

Due to this coordination and to the fact that on January 1, 2021, European Regulation 2019/2152 regarding European business statistics comes into force, which repeals, among others, 995/2012 (Regulation in which the Statistics on the Use of Biotechnology), in the 2021 edition, as an application of said regulation, the statistical unit of the S. of R&D in the Business sector is modified and therefore, that of the E. of the Use of Biotechnology in this same sector, passing to be the Statistical Company as defined in the European Union Regulation 696/93, relative to the statistical units of observation and analysis of the production system.

II New for the 2021 edition: new practical implementation of the "enterprise" statistical unit

The statistical definition of the "Enterprise" statistical unit is established by a regulation of the European Union (696/93) that defines it as the "smallest combination of legal units that is an organized unit producing goods or services and that enjoys a certain degree of decision-making autonomy, particularly when using the resources available to it." The company exercises one or more activities in one or more places. An enterprise can correspond to a single legal unit."

Until the 2020 reference year, the INE, like most European Union statistical offices, has identified the enterprise statistical unit with the Legal Unit (in the Spanish case, through the NIF) for operational purposes. Thus, **for statistical purposes each Legal Unit formed an enterprise**.

However, the progressive complexity of the way in which **enterprise groups** operate internally nowadays caused the European Statistical System (ESS) to search for an improvement as regards the way in which the activity of these groups is reflected in enterprises' official statistics. Legal Units that belong to enterprise groups sometimes sell their products or provide their services exclusively or mainly within the group, without being market-oriented or having decision-making power over the entire production process.

For all these reasons, and in accordance with the European Statistical System (SEE), **based on data with reference 2021, the Statistics on the use of Biotechnology in companies establishes a new practical application of the statistical concept of Enterprise**, by which an 'enterprise' can be:

- An independent Legal Unit that is not part of the enterprise group, meaning that it should have decision-making autonomy.

- An enterprise group formed for one or more Legal Units.

- A subset of one or more Legal Units of an enterprise group.

This change in the treatment of enterprises, which has also been implemented in the *Statistical Use of the Central Enterprise Register (SUCER), was announced by the INE in a Press Release dated December 17, 2019:*

https://www.ine.es/prensa/nueva_definicion_empresa.pdf

It should be noted that most of the Enterprises are independent Legal Units, so the Enterprise=Legal Unit identity remains valid. The change will only affect Legal Units (LU) that are part of Enterprise Groups (3.1% of the total). The latter are quite important in economic and employment terms, however, meaning that the S. of the use of Biotechnology in the business sector data series prepared under the new Statistical Enterprise approach is not strictly comparable to that of previous years, prepared under the traditional criteria based on separate Legal Units.

In order to elaborate the S. of the use of Biotechnology in Companies under this new 'Statistical Enterprise' approach, a method was developed based on the following steps, each of which will be described in greater detail in the corresponding sections of this methodological document.

1. Delineation of the Statistical Enterprises that operate in enterprise groups using the so-called *Profiling* methodology and typification of the Legal Units comprising them (see details in section 3.3 of this document)

2. Adjustment of the sample design and the information collection phase (see details in sections 5 and 6 of this document).

3. Aggregation of the Legal Units that make up each sample Statistical Enterprise and study of the combinations of typologies of said Legal Units (see details in section 7.2.1).

4. Consolidation of sample Statistical Enterprises that consist of more than one Legal Unit and that have relationships between them. For these enterprises, flows between their Legal Units are identified to proceed with the cancellation of intra-company transactions (see details in section 7.2.2).

5. Construction of complete statistics, based on Statistical Enterprises, whether they are independent Legal Units or enterprise group Enterprises (see details in section 7.2.3).

The essential idea is that if the Legal Units of a Statistical Enterprise exclusively or primarily serve other Legal Units of the same Enterprise (for example, selling products under a vertical integration of the production process or providing services as an auxiliary relationship), these servile Legal Units must be combined with the others which they support to form the authentic "Enterprise" statistical unit. As such, the corresponding variables must be combined and consolidated. Legal Units that are not part of groups continue to be considered Enterprises in and of themselves.

The implementation strategy for the statistical unit 'enterprise' in the S. of Biotechnology in Companies terms of sample design and information collection is based on three points:

- **The basic information unit is still the Legal Unit.**

This point is based on the fact that it is at this level that it is easier for the informant to obtain the required information on the use of Biotechnology. While it does not provide all the information necessary to generate the S. on the use of Biotechnology, this information is the main basis for it.

Information at the Statistical Enterprise level will be derived from a process of grouping and consolidating information from the Legal Units that comprise it.

- **The statistical burden on informants must be neutral.**

That is, in no case should the statistical burden on enterprises be increased.

- **In view of the needs of the National Statistical Plan (PEN), it must be possible to provide information both from the perspective of the Legal Units and the Enterprises as a statistical unit.**

It must be considered that there are PEN operations, such as those related to National Accounts, which require information at a level other than that of the Statistical Enterprise. The procedure established should allow for these estimates to be obtained.

This new approach to Business Statistics has been implemented in the S. of the use of Biotechnology in the Business sector for the period 2021 and will continue for subsequent years. Since the statistical results of the S. of the use of Biotechnology and its distribution by activities and enterprise size is affected by the change, both data from the traditional approach (based on Legal Units) and the new approach (based on

Statistical Enterprises) **is disseminated for the 2021-2022 reference year,** so that users of these statistics are able to compare.

III Methodology of the Statistics on the use of Biotechnology

1 Objectives

The objective of this study is the measurement of national efforts in biotechnology-related activities, in order to provide the necessary information for adequate decision-making in scientific-technological policy. 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 know the financial resources, the aggregate Expenditure on Internal R&D Activities related to Biotechnology is calculated, which is formed by the set of expenditures executed in R&D in biotechnology in Spain by each of the sectors into which the economy has been divided, whatever the origin of the funds and the nationality of the financer. Within the expenses, the structure and formation of capital are studied. In order to know the human potential, the Personnel (researchers and other personnel) dedicated to internal R&D activities related to biotechnology in full-time equivalence are obtained.

Another of the objectives is to find out the number of units that have activities related to biotechnology in Spain and the profit generated by the sales of biotechnological products. Thus, in addition to the previous aggregates, the following are calculated: *Expenditure on Activities related to Biotechnology* carried out in Spain and *Personnel dedicated to them,* in full-time equivalence.

2 Scopes

2.1 POPULATION SCOPE

Enterprises public organisations, universities, other higher-education institutions 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.

2.2 TERRITORIAL SCOPE

This extends to all of Spain.

2.3 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 enterprises, a module is included within the Innovation Survey for enterprises. 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.

3 Statistical unit and reporting unit

3.1 STATISTICAL UNIT

The **statistical unit** of analysis may be defined as the element or component of the target population to which the tabulation of data and the aggregated statistics obtained as a result of the surveys refer.

For sectors other than the business sector, the statistical unit coincides with the reporting unit.

The basic statistical unit for these operations is **the enterprise**, which is understood as the *'smallest combination of legal units that forms an organizational unit producing goods or services and that enjoys certain decision-making autonomy, particularly when using the resources available to it. The enterprise can carry out one or more activities in one or several places.' A business can correspond to a single legal unit*." (definition of the Regulation of the European Union 696/93).

As explained in section II, from the S. of the use of Biotechnology for the business sector 2021 onwards, a new concept of "Company" is applied, which we will refer to hereinafter as "Statistical Company" and which differs from previous editions in that, from now on, the analogy Company=Legal Unit will no longer always be true. In other words, some Statistical Businesses may be made up of two or more Legal Units.

3.2. REPORTING UNIT

They are the units from which the desired base information is obtained. For the purpose of collecting information, the units of analysis are grouped by sectors, the content of which is based on the Frascati Manual. The sectors considered are defined below, as well as the reporting unit for each of them.

Business Sector

The reporting unit, or rather, the unit from which the basic information is obtained. Response is facilitated due to it being perfectly defined and located and having necessary accounting and employment data, and homogeneous information is obtained. Legal Units can be companies with legal personality (limited companies) or natural persons (individual entrepreneurs).

Obtaining the information from the Legal Units proceeds from direct collection by completing the questionnaire.

Thus:

- When using the Legal Unit as a statistical unit, information is obtained from the Legal Units, and statistics are compiled under said Legal Units.

- When using the Statistical Business as a statistical unit, information is obtained from each of the Legal Units that make up the Business, and statistics are compiled by grouping (and in the necessary cases, consolidating) variables for all Legal Units that form the Business.

The business sector includes:

- All resident companies, including not only legally constituted companies, regardless of the residence of their shareholders. This group also encompasses any type of quasi-corporation, for example: entities that are capable of generating profit or any other financial gain for their owners, that are recognized by law as independent legal entities from their owners and are established for the purpose of carrying out carry out market production activities at economically significant prices.

- Unincorporated subsidiaries of non-resident companies that are considered residents, since they participate in production within the economic territory in the long term.

Any resident Private Non-Profit Institution (IPSFL) that produces goods or market services or provides services to other companies.

Public Administration Sector

The Public Administration sector is made up of the following groups of resident institutional units:

• All central, regional or local administration units, including Social Security funds, except:

1. units providing higher education services

2. centers in which there is no training component, but whose R&D activities are controlled by a higher education institution

• All non-market non-profit institutions that are controlled by units of the Administration and that do not belong to the higher education sector.

This sector does not include public companies, not even when the entire capital of said company belongs to a unit of the Administration. Public companies are included in the business sector, the difference that characterizes them is that public companies are market producers, while units classified in the Public Administration sector are not.

Within this sector, a sub-sectorization is carried out in:

− State Administration:
− Autonomous administration
− Local administration
− Private non-profit institutions mainly financed by the administration.

The administration bodies that are part of this sector are the State, the Autonomous Bodies dependent on it, as well as state companies, public entities, etc., which, due to their main activity and the origin of their resources, can be considered to belong to the sector. public administration. Units that are members of this sector are also considered to be the Social Security management entities, as well as the hospital centers that depend on it, and that carry out this function on behalf of the State.

The same thing happens with the bodies dependent on the regional and local administrations.

Higher Education Sector

The higher education sector is made up of all universities, technical schools and other institutions that offer official university education programs, regardless of the source of financing or legal nature, and all research institutes, centers, experimental stations and research clinics. that carry out R&D activities under the direct control or administration of a higher education institution.

The following subsectorisation is made within this sector:
− Public Universities
− Private universities
− Other centres

Private Non-Profit Institutions (PNPI) Sector

This sector includes:

• All Non-Profit Institutions Serving Households (ISFLSH), according to the definition of the National Accounts System, except those classified in the higher education sector.

• For the purposes of completeness of the presentation, households and individuals that participate or do not participate in market activities.

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

− Those in which the main activity is carried out to the service of enterprises.

− 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.

Rest of the world

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 enterprises), including their installations and activities, within our borders.

Rest of the World appear in the R&D survey solely as financing sources for the R&D carried out by national units.

3.3 DELINEATION OF STATISTICAL ENTERPRISES USING THE PROFILING METHODOLOGY

This process -essential for S. of the use of Biotechnology in Companies preparation in Statistical Enterprise terms- was developed by the INE Board of Directors Unit. The rules agreed upon in the European Statistical System working groups were applied, based on which the Profiling methodology (delineation of companies) was established as the best procedure for identifying companies when analysing Legal Units operating in group settings.

The delineation of companies within groups is carried out using a series of criteria whose final result is not only the definition of the Enterprises that operate within a group, but also the links between the Legal Units that comprise them and their primary characteristics.

Details can be found in the Methodology available on the INE website, at the following link:

https://www.ine.es/metodologia/t37/t3730200_profiling.pdf

Some of the principles and criteria used for enterprise delineation are highlighted below, especially those that affect the subsequent preparation of the *S. of the use of Biotechnology in Companies.*

To start with, *Profiling* takes into account the following questions :

- **Market / non-market criteria.** All Legal Units that make up market-producing statistical enterprises must also be market-based. The Institutional Sector Code is, therefore, a critical variable in the enterprise creation processes. A unit is defined as market if it is classified as S11, S12 or S14 in terms of its Institutional Sector (non-financial corporations, financial institutions and Households as individual entrepreneurs, respectively). If it is classified as S13, S15 or S2 it will be considered non-market.

- **Holdings and Headquarters**. These are units with very specific functions within enterrpise groups (codes CNAE-2009 6420 and 7010). Given the needs of various users, these activities are considered *productive.*

Through the *Profiling* methodology, each of the Legal Units of an enterprise group is perfectly assigned to the company of which it is part. The following relationships occur:

- An enterprise group can have a single enterprise or be made up of several enterprises.

- Each enterprise can contain a single Legal Unit or several Legal Units.

When a market-producing enterprise (institutional sectors S11, S12 or S14) is made up of several Legal Units, *Profiling* also identifies certain relationships between these Units, such as:

- **Progressive vertical integration**. This type of integration occurs when different Legal Units carry out different stages of the same production process. The outputs of the early stages are the inputs for the later ones, with the particularity that only the final stage output is sold to the market. For example, Activity 29.3 (Manufacture of components, parts and accessories for motor vehicles) is considered an *upstream* activity of Activity 29.1 (Manufacture of motor vehicles) which is the *downstream* activity.

  The following types of Legal Units arise from this relationship:
  - U for the *Upstream* at the beginning of the chain (in the previous example, the Legal Unit with Activity 29.3)
  - D (or X if also integrated in an industry-commerce chain, which will be described in the subsequent point) for the *Downstream at* the end of the chain (in the previous example, the Legal Unit with Activity 29.1)

  To identify these Legal Units, we start from a predefined list of activity combinations and verify certain non-relevant conditions in the affected Legal Units.

- **Backward Integration Industry-Wholesale Trade** This type of integration occurs when several Legal Units in the same Statistical Enterprise are in charge of different phases of a chained industrial-commercial process; that is, when a trade unit is in charge of selling products from the industrial unit with which it is connected within the Enterprise to the market. For example, activity 45.1 (motor vehicle trade) and activity 29.1 (Manufacture of motor vehicles)

The following types of Legal Units arise from this relationship:

- C for the Legal Unit that markets the product (in the example, the Legal Unit whose activity is 45.1)
- I (or X, if it also forms part of a progressive Industrial chain, already explained in the previous point) for the Legal Unit that manufactures the product (in the example, the Legal Unit whose activity is 29.1)

To identify these Legal Units, we start from a predefined list of activity combinations and verify certain non-relevant conditions in the affected Legal Units

- **Auxiliary units (A)** : Auxiliary Legal Units that provide services to other Legal Units in the Statistical Enterprise.

- **Productive units**. Legal Units that have not been identified with the aforementioned characteristics (U, D, I, X, C, A) are classified as productive

In summary, the Legal Units that make up a Statistical Enterprise will always be classified into one of the following types:

- U: Legal Units with *Upstream* activity in vertical integration (can be considered the industrial auxiliary unit).
- D: Legal Units with *Downstream* activity in vertical integration (can be considered the industrial productive unit).
- I: Industrial Legal Units that make up the Industry-Trade chain.
- C: Trade Legal Units that make up the Industry-Trade chain.
- X: Industrial Legal Units that are part of both a vertical integration and an industry-trade chain.
- A: Auxiliary Legal Units that provide services to other Legal Units in the Statistical Enterprise.
- P: Productive Legal Units that are not part of *Upstream-Downstream* or Industry-Trade chains

These typologies of market enterprise Legal Units, defined in the enterprise delineation process according to the *Profiling* methodology, will facilitate the subsequent task of consolidating the Statistical Enterprise variables.

4   Variables and their definition

ECONOMIC ACTIVITY

This variable is only investigated in the enterprise sector.

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

R&D enterprise activities of the units (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 the units 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 ENTERPRISE

This variable is the only one investigated in the enterprise sector.

The dimension of the legal units is one of the most important variables when determining the behaviour of the units. 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 legal unit.

EMPLOYED PERSONNEL

This variable is studied only in the enterprise sector.

It corresponds to the number of persons who work in a legal unit, as well as the persons who, though working outside of the legal unit, belong to it and are paid by it (for example, sales representatives and delivery, repair and maintenance personnel who work on behalf of the enterprise). 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 legal unit in which he/she works.

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

TURNOVER

This variable is only investigated in the enterprise sector.

It is comprised of the amounts invoiced by the enterprise during the reference year for the provision of services and the sale of goods that are the object of traffic of the enterprise. 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 manufactures by the enterprise 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 enterprise for their subsequent sale without processing, plus the amount for services rendered to other enterprises (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.

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 ro 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.

– **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.

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 enterprise/local unit 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.

1. 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.

Proetomics 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.

2. 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.

3. 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.

4. 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 enterprise to be classified into a branch of activity and to clarify some of the questions in case there are any doubts.

It is asked 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

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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 ON INTERNAL R&D BIOTECHNOLOGY 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 R&D biotechnology tasks (biotechnology R&D supply purchases, for example) will also be included as internal R&D expenditure in biotechnology.

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 labour cost 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 enterprise,...), 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 labour cost of investigators and the rest of personnel labour cost.

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 enterprises, 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 enterprise/local unit 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 form 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 enterprise/local unit, 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, in equipment and instruments, in the acquisition of specific R&D software and other intellectual property products specific to the performance of R&D activities.

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 acenterpriseing the systems software and applications. It also includes the quotas for licenses to use the acquired software.

Expenditure on other specific intellectual property products for carrying out R&D activities includes the costs of acquiring patents, long-term licenses and other intangible assets employed in R&D and which are used for more than one year. Other intangible assets that can be disclosed in the unit's internal financial accounts, such as marketing assets and goodwill, should not be included.

Approximation to enterprise 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 R&D expenditure in biotechnology, 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:

Internal source of funds

   Own funds

External source of funds

   Funds from the enterprise sector

   Funds from the Public Administration

   Funds from the higher education sector

   Funds from sector PNPI

   Funds from sector Rest of the world

PERSONNEL ON 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 R&D BIOTECHNOLOGY 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 enterprises, research associations, etc., that do not imply a direct purchase of R&D in biotechnology.

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

- Biotechnology R&D (external R&D) purchases in Spain (without VAT)
- Biotechnology R&D (external R&D) purchases in the rest of the world (without taxes)

5   Sample design

5.1   DIRECTORIES

Due to the coordination of the R&D Statistic and the Innovation in Enterprises 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 enterprises, 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 (enterprises, 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 enterprises, there is another directory, more restricted, comprised by **potential biotechnology research** enterprises. 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 Bioenterprises) 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) in even reference years and of the Statistics on R&D activities in odd reference years, it must be indicated that the population of target enterprises is stratified through the crossing of the following variables:

a) Enterprise 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 enterprises with 200 or more employees must be analysed exhaustively.

b) Autonomous Community in which the enterprise 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

Divisions or activity groups	CNAE-2009
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 sample stratification is used to randomly obtain companies that are potential users of biotechnology and that were not initially included in the exhaustively investigated directory.

5.2 SIZE OF THE SAMPLE. ALLOCATION

The sample size of the Biotechnology use statistics is around 3,500 units, of which more than 2,500 are legal units, around 500 are public research organisations (including public hospitals), around 200 are universities and other higher education centres, and more than 100 are private non-profit institutions. The legal units (ULE), public organisations, higher education centers and private non-profit institutions that conform the directory of possible research units have been exhaustively analysed.

5,3 ESTIMATORS

Only in the business sector is it necessary to calculate estimators as it is coordinated with R&D in the business sector or with Innovation, since both have a census part and a sample part. The calculation of estimators is carried out at the legal unit level (ULE) in the first place and then at the statistical company level (UEE).

In the other sectors, the operation is census.

Estimator of the total at the Legal Unit (LU) level:

The estimators are those of expansion, adjusted for the lack of response, changes in stratum and excess coverage.

The estimator of the total of a characteristic X in a domain d (any subgroup of the population, which does not have to coincide with the strata) is given by:

$$\hat{X}_d = \sum_{\substack{j=1 \\ j \in d}}^{n_{dr}} x_j \, F_j$$

Where:

- n_{dr}: number of sample LUs of the domain that respond to the survey.

- x_j: is the value of characteristic X of the LU j belonging to domain d.

- F_j: is the elevation factor of the LU j and for its calculation proceed as follows:

  a) If the LU j was selected in a stratum h and according to the questionnaire data it is found in a different stratum k, then the elevation factor F_j is the one initially associated with the LU j, that is:

  $$F_j = \frac{N_h}{n_h}$$

  Where N_h is the number of LUs in the initial population (DIRCE) of stratum h and n_h is the theoretical sample size in h.

  b) If LU j continues to belong to the same stratum h where it was selected, then the elevation factor F_j is estimated taking into account over-coverage, non-response and stratum changes as follows:

$$F_j = \frac{\widehat{N}_h^*}{n_h^*}$$

Where:

- n_h^*: Number of LUs in the sample from stratum h that respond and have not changed stratum.
- $\widehat{N}_h^* = N_h \left(1 - \frac{n_h{}''}{n_h}\right) - \sum_{\substack{j=1 \\ h \neq k}}^{n_h^k} F_j$

Being:

$n_h{}''$: Number of LU samples from stratum h with a duplicate or out-of-scope incidence of the type.

n_h^k: Number of LUs selected in stratum h, and which are in a different stratum k, according to the questionnaire.

c) In general, for exhaustive or outlier LUs,

$$F_j = 1$$

Estimator of the total at the level of the Enterprise Statistical Unit (UEE):

The estimator of the total for characteristic Y in a domain d is given by the following expression:

$$\widehat{Y}_d = \sum_{\substack{i=1 \\ i \in d}}^{n_{dr}^B} y_i w_i$$

Where:

- n_{dr}^B: number of SEU belonging to domain d that respond through some of their sample LU to the survey.
- y_i: is the value of characteristic Y of SEU i belonging to domain d.
- w_i: is the elevation factor of the SEU i and is calculated, first applying indirect sampling as follows:

$$w_i' = \frac{m_i}{\sum_{j \in i}^{M_i} (F_j)^{-1}}$$

Being:

M_i: Number of LU j of the SEU i contained in the Profiling

m_i : Number of LUs in the sample of SEU i

F_j: LU j elevation factor in stratum h

And second, applying a calibration, so that the estimator of the total R&D expenditure at the LU level coincides with the estimator at the SEU level.

6   Collection of the information

The Innovation and R&D questionnaire is submitted to all enterprises 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 enterprise is found to be conducting biotechnology R&D but without appearing in the directory, the module would be later sent to said enterprise.

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 enterprises will have a period of 15 days to return the completed survey.

The collection unit establishes an initial telephone contact with the enterprise 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, enterprises 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 enterprises, by email.

7   Processing of the information

7.1   INFORMATION PROCESSING FOR THE REPORTING UNIT

The phases for the treatment of the information for the Legal Unit in the Business sector and the units of the rest of the sectors are the following

- Control and manual debugging of company questionnaires in the collection unit, in order to recover possible missing data or correct errors in the questionnaires

- Recording, filtering and interactive correction of inconsistencies of the information validated in the collection unit, taking into account the variability of the data between the main questionnaire and the biotechnology module

- Control of the information received from the collection unit in the promoter service

- Control of coverage and treatment of errors in the promoter service

- Imputation of partial non-response.

- Preparation of a first phase of tables analysing the results.

- Use of macroediting techniques in the promoter service to eliminate errors and inconsistencies in the aggregates, which have not been detected in the previous phase of microdebugging

- Analysis of data

- Creation of a final data file.

- Obtaining definitive results tables by responsible departments, prepared using the definitive data file.

7.2 INFORMATION PROCESSING FOR THE STATISTICAL ENTERPRISE IN THE BUSINESS SECTOR

7.2.1 Aggregation of the Legal Units that make up the sample Statistical Enterprises and study of the Legal Unit typology combinations

For this sub-process, we work with the sample Statistical Companies, that is, those for which at least one of their Legal Units has entered the sample of the E. of R&D or Innovation, depending on whether the reference year is odd. or pair, and has marked that it performs Biotechnology tasks

For the sample Statistical Enterprises, complete information must be available on each and every one of the component legal units. This information comes either from the direct collection of questionnaires or in the case of Legal Units from administrative information (which, due to their smaller size, has not been included in the direct collection). In the cases and variables required, assignment techniques are used to complete the required information.

Once all the information is available for all the Legal Units of the Statistical Company, the consolidation is carried out according to the rules of section 7.2.2.

In addition, each Statistical Enterprise is typified according its combination of the different **types of Legal Units that comprise it** (see section 3.3 of this document). Statistical Enterprises may present any of the following combinations:

a) P only. Formed only by productive units.

b) P+A only. Formed by production and auxiliary units.

c) P or P+A, and also with U+D chains and/or with I+C chains

If the Statistical Enterprise is formed only by productive Legal Units (case a) it is not necessary to discount internal flows in the economic variables, it is only necessary to add said type of variables of all the productive Legal Units that form it.

In the remaining situations (cases b and c), the statistical enterprises contain Legal Units with linking relationships. It is thus necessary to identify the flows between them in order to cancel the Statistical Enterprise's internal transactions.

7.2.2 Consolidación

For this subprocess, we work with the sample Statistical Enterprises formed by more than one Legal Unit.

The objective of the consolidation is that, once it has been determined that there are Legal Units in the Statistical Enterprise with intra-company relations (that is, relations of vertical process integration, and/or industry-trade relations and/or relations of auxiliary) the servile Legal Units must be combined with the others which they support to identify and subtract these intra-company transactions. The corresponding variables must therefore be combined and consolidated.

7.2.2.1 Additive and non-additive variables

Quantitative variables are classified **as additive and non-additive.**

By way of example, the number of employees are considered additive; while variables such as turnover is non-additive.

Qualitative variables are not additive.

7.2.2.2 Consolidation of variables by type of variable

Dichotomous variables (YES/NO): The variable of the Statistical Company will have a value of "SI" if any legal unit had a value of "SI" in that variable.

Non-dichotomous qualitative variables: Question A2, if there are only Legal Units within the Statistical Company that consider biotechnology as a necessary tool, the Statistical Company will have the value "Necessary Tool for the production process", in any other case, the percentage of dedication to biotechnology will be obtained. and if the percentage is greater than or equal to 75%, the Statistical Company will have the value "Main and/or exclusive" and if it is less than 75%, the Statistical Company will have the value "A secondary business line". Question A4, the Statistical Company will have the highest value of all the Legal Units.

Income of international origin, expenditure on R&D, Personnel (in individuals or in EJC): they are considered additive variables.

Variables with percentages: The percentages weighted by the variable to which the percentage refers in each Legal Unit are added and divided by the variable to which the consolidated percentage in the Statistical Company refers.

7.2.3 Construction of statistics based on Statistical Enterprises

Once processing of the sample Statistical Enterprises formed by various Legal Units is completed, the files of the consolidated enterprises are integrated with those of Statistical Enterprises that are independent Legal Units to give the complete statistic, that is:

- Sampling set of independent Legal Units
- Sample set of Statistical Enterprises whose records condense information from one or more Legal Units of enterprise groups

After that, we proceed to calculate the elevation factors for Statistical Enterprises. This will generate high statistical results which, after appropriate analysis, will form the S. of the use of Biotechnology in the business sector based on the Statistical Enterprise.

8   Presentation of results

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

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