COMMISSION DECISION

of 26 November 2003

on the aid which Italy is planning to implement for Industria Farmaceutica Cesare Serono SpA for the development of new chemical synthesis processes for oral pharmaceutical forms of polypeptides and conjugated substances

(notified under document number C(2003) 3519)

(Only the Italian text is authentic)

(Text with EEA relevance)

(2004/169/EC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community, and in particular the first subparagraph of Article 88(2) thereof,

Having regard to the Agreement on the European Economic Area, and in particular Article 62(1)(a) thereof,

Having regard to Council Regulation (EC) No 659/1999 ([1]),

Having called on interested parties to submit their comments ([2]),

Whereas:

1. PROCEDURE

(1) By letter registered as received by the Commission on 27 March 2002 (A/32355), the Italian authorities notified, pursuant to Article 88(3) of the EC Treaty, planned aid for the pharmaceutical company Cesare Serono SpA (IFS).

(2) By letters D/52251 of 7 May 2002, D/54639 and D/54654 of 12 August 2002 and D/56044 of 25 October 2002, the Commission requested additional information regarding the notified aid.

(3) On 8 August 2002 (letter A/36069), 23 August 2002 (letter A/36253), 7 October 2002 (letter A/37252), 21 October 2002 (letter A/37664) and 26 November 2002 (letter A/38716) the Italian authorities submitted the information requested.

(4) By letter SG(2003) D/228432 dated 7 February 2003, the Commission informed Italy that it had decided to initiate the procedure laid down in Article 88(2) of the EC Treaty (hereinafter 'the decision to initiate the procedure') in respect of the proposed measure.

(5) The decision to initiate the procedure was published in the *Official Journal of the European Union*. The Commission called on interested parties to submit their comments within the prescribed period (one month), pursuant to Article 6(1) of Regulation (EC) No 659/1999.

(6) The Commission received comments from IFS on 13 June 2003.

(7) By letter D/53893 of 17 June 2003, the Commission forwarded IFS' comments to the Italian Government.

(8) The Republic of Italy has not replied officially to the Commission letters of 7 February 2003 and 17 June 2003.

2. DETAILED DESCRIPTION OF THE AID MEASURE

2.1. Legal basis and object of the measure

(9) The legal basis for the aid is Legislative Decree No 297 of 27 July 1999 ([3]). This is an existing scheme approved by the Commission on 26 July 2000 (letter SG(2000) D/430165, State aid N 173/2000) ([4]).

(10) The object of the aid consists in developing new chemical synthesis processes for oral pharmaceutical forms of polypeptides and conjugated substances ('sviluppo di forme farmaceutiche orali ottenute da nuove molecole di natura sintetica, polipeptidica e sostanze coniugate').

([1]) OJ L 83, 27.3.1999, p. 1.
([2]) OJ C 110, 8.5.2003, p. 2.
([3]) And its implementing regulation: Ministerial Decree No 593 of 8 August 2000.
([4]) OJ C 310, 28.10.2000, p. 17.

(11) This project will enable IFS to strengthen its position in its traditional therapeutic sectors (neurology, fertility) while at the same time developing initiatives in therapeutic sectors which are new for the company (anti-inflammatory, anti-cancer, cardiology).

(12) The project is subdivided into a number of detailed stages or 'steps' each of which is characterised by a specific scientific content:

— step 1: definition — at laboratory level — of the processes of chemical synthesis of small molecules, polypeptides and conjugated substances for the preparation of active ingredients destined for preclinical testing,

— step 2: development of a production process for the fractions destined for clinical testing of Phase I,

— step 3: experimental verification and validation of the semi-quantitative method and preparation of the pharmaceutical forms for both the stability test and clinical testing,

— step 4: definition and development of analytical methods for the qualitative and quantitative definition of the reaction intermediaries, active ingredients, degradation products and contaminants, and of the oral pharmaceutical forms,

— step 5: preclinical tests on laboratory animals, such as rodents and dogs (toxicology and pharmacokinetics),

— step 6: clinical tests on healthy patients (Phase I): evaluation of the effectiveness, collateral effects and therapeutic properties.

(13) More specifically, the products that will be studied throughout the above mentioned 'steps' fall within three groups of molecules:

A. *Small molecules*

From the screening of about 1 million molecules obtained in its foreign subsidiaries, IFS expects to obtain some 40 000 'hits'. These in turn will lead to the identification of three to five 'lead' compounds (proteins), or active ingredients for drug applications. A new laboratory in Guidonia Montecelio will, by following both GLP (good laboratory practice) and GMP (good management practice), develop new methods for the chemical synthesis of small molecules in order to obtain active ingredients and finished pharmaceutical forms in sufficient quantity ('kiloscale') for the subsequent preclinical and Phase I clinical testing, i.e. clinical tests on healthy patients. The target is to obtain around 12 such molecules per year by the end of the project's lifetime. Unlike large molecules, small molecules are capable of interfering with intracellular events inside the cell, like a protein, and thus blocking the pathology. They are more adapted for the oral pharmaceutical form and are better resistant in the gastrointestinal ambient.

B. *Polypeptides*

Polypeptides are the 'active' part of the protein which liaises with the cell receptor. They replace the protein in this link. The project is designed to develop their chemical synthesis as an alternative to genetic manipulation.

C. *Conjugated forms*

By exploiting its excellence in the biotech field, IFS will be able to create synergies with the more 'classic' organic chemistry (mix of simple molecules with complex macromolecules). Conjugated forms combine active ingredients and inert chemical compounds so to minimise the production of antibodies. In this connection, the Italian authorities have presented a detailed training project for specific activities (R & D, analytical techniques, quality and security standards, and links with universities).

In order to carry out the R & D projects, the company needs to expand the Guidonia Montecelio site (Rome). The new building (4 500 m^3) will house a staff of 40 (17 researchers, 13 technicians and 10 administrative personnel). This new laboratory will have the task of devising procedures for the chemical synthesis of new molecules, producing active ingredients in kiloscale quantities and defining their pharmaceutical forms.

2.2. **Form of the aid**

(14) The proposed aid is provided in the form of an outright grant.

2.3. **Aid intensity, recipient and eligible costs**

(15) The aid recipient (IFS) is part of the multinational group Serono SA, which has its headquarters in Geneva. Serono SA is the third-largest biotech company in the world, with a turnover of USD 1,38 billion (2001).

(16) Eligible costs include personnel, overheads, equipment, consultancy, materials and buildings.

(17) All costs related to preclinical and Phase I clinical testing are entered as consultancy costs, as they will be subcontracted to IFS sites other than Guidonia Montecelio (Colleretto Giacosa, Turin, and Bourne Hall, Cambridge).

(18) The following table gives a breakdown of the proposed aid intensities per category of eligible costs. All amounts are expressed in EUR million.

Categories of eligible costs	Proposed amount	Proposed aid intensity (excluding regional bonuses)	Maximum grant in view of these intensities
1. Personnel	10 585	50 %	5 292
2. Buildings, equipment and instruments	26 905	50 %	13 452,5
3. Consultancy (A) Preclinical tests	12 000	50 %	6 000
3. Consultancy (B) Clinical tests (Phase I)	8 000	25 %	2 000
4. Other operating expenses	6 351	50 %	3 175,5
5. Overheads	7 500	50 %	3 750
6. Training	1 455	50 %	727
Total	72 766		34 397

(19) The Italian authorities have proposed the maximum intensities allowed for industrial development and precompetitive R & D activities.

(20) Training is considered to be general training within the meaning of Article 2 of Commission Regulation (EC) No 68/2001 of 12 January 2001 on the application of Articles 87 and 88 of the EC Treaty to training aid ([5]), as the qualifications and skills acquired in the new laboratory are transferable to other R & D fields. The allowed intensity is 50 % in line with Article 4(3) of the Regulation.

2.4. **Budget and duration**

(21) The R & D project will cost EUR 72 991 000. It is expected to last seven years (two years for the expansion of the laboratory and then five years for the R & D activities).

3. **GROUNDS FOR INITIATING THE PROCEDURE**

(22) In its decision to initiate the procedure, the Commission approved the aid measure as notified by the Italian Government, except for one aspect.

(23) Its doubts originated with the preclinical testing 'step' (see point 12, fifth indent, and the above table at 3(A)) since its classification as industrial research and, indirectly, the granting of an aid intensity of 50 % gge were not sufficiently justified. The classification of such tests as research, the eligible costs and the incentive effect of the aid were not questioned in the decision initiating the procedure.

(24) Preclinical tests precede the Phase I clinical tests. They consist in testing active principles on various animal species increasingly closely related to man.

(25) On the one hand, the preclinical test protocols are based on a series of experiments on a number of different animal species the results of which are collected and critically analysed to check whether Phase I tests can be launched. This could be viewed as planned research and critical investigation, which would then qualify as industrial research.

(26) On the other hand, preclinical tests, like Phase I clinical tests, are based on 'prototype' versions of the product, albeit very crude ones. In this respect, they could, like Phase I clinical tests, be regarded as precompetitive

([5]) OJ L 10, 13.1.2001, p. 20.

development activities (since they precede Phase I tests and are conducted with less mature products, they are clearly not closer to the market than Phase I tests are).

(27) Accordingly, the Commission was unable to rule out the possibility that at least some of the preclinical test activities could be classified as closer-to-market precompetitive development. Therefore, it could not authorise prima facie the 50 % aid intensity (in gge) proposed by the Italian authorities, rather than the 25 % intensity (in gge) provided for by the R & D framework for precompetitive development.

4. COMMENTS FROM INTERESTED PARTIES

(28) On 13 June 2003 IFS submitted comments pursuant to Article 6(1) of Regulation (EC) No 659/1999. It argues that preclinical testing is industrial research within the meaning of the R & D framework. The central argument is that activities carried out under this 'step' do not necessarily reach the subsequent 'step', since the chemical synthesis of an active principle is hardly ever optimised and its expected toxicological effects are not yet known, as is evidenced by the following:

— Around 60 to 70 % of the molecules are eliminated as they do not survive one or more stages of the toxicological preclinical tests,

— Around 20 to 30 % of the total are sent to the medicinal chemistry (discovery) laboratory to be subjected to a 'lead optimistion' process during which the chemical structure of the protein is modified in order to minimize the undesirable toxic effects of the product,

— A mere 10 % of the molecules reach the subsequent 'step', namely Phase I clinical testing.

(29) Furthermore, tests conducted on laboratory animals have very little in common with applications on healthy human patients in Phase I.

(30) Therefore, IFS considers that preclinical studies indeed constitute 'critical investigation aimed at the acquisition of new knowledge, the objective being that such knowledge may be useful in developing new products, processes or services'.

(31) On top of this, IFS proposes a more precise quantification of consultancy costs (preclinical and Phase I clinical testing). The total investment costs should be amended accordingly. On the other hand, IFS proposes to add a new cost item 'University' amounting to EUR 775 million, without stating whether it ranks as industrial research or precompetitive development.

5. ASSESSMENT

5.1. Legality of the aid

(32) The Italian authorities have fulfilled their obligation pursuant to Article 88(3) of the Treaty by notifying the scheme to the Commission before it came to effect.

5.2. Existence of aid within the meaning of Article 87(1) of the Treaty

(33) Article 87(1) states that 'any aid granted by a Member State or through State resources in any form whatsoever which distorts or threatens to distort competition by favouring certain undertakings or the production of certain goods shall, insofar as it affects trade between Member States, be incompatible with the common market.'

(34) The measure favours through State resources (outright grant) an undertaking which is a large multinational (IFS, head of the multinational group Serono SA). The measure is therefore *selective* in scope. Having regard to the economic activity carried out by the recipient enterprise, the aid potentially has a distortionary effect on the conditions of competition that may affect trade between Member States within the meaning of Article 87(1).

5.3. Assessment of the aid in the light of Article 87(2) and (3) of the Treaty

(35) Article 87(3)(c) of the Treaty states that '[…] may be considered to be compatible with the common market […] aid to facilitate the development of certain economic activities […], where such aid does not adversely affect trading conditions to an extent contrary to the common interest'.

(36) The doubts expressed by the Commission concern R & D aid and the assessment must therefore be made in the light of the Community framework for State aid for research and development [6].

(37) The second indent in Annex I to the framework defines industrial research as 'planned research of critical

[6] OJ C 45, 17.2.1996, p. 6.

investigation aimed at the acquisition of new knowledge, the objective being that such knowledge may be useful in developing new products, processes or services or in bringing about a significant improvement in existing products, processes or services.'

(38) The third indent in Annex I to the framework defines precompetitive development activity as 'the shaping of the results of industrial research into a plan, arrangement of design for new, altered or improved products, processes or services, whether they are intended to be sold or used, including the creation of an initial prototype which could not be used commercially. This may also include the conceptual formulation and design of other products, processes or services and initial demonstration projects or pilot projects, provided that such projects cannot be converted or used for industrial applications or commercial exploitation. It does not include the routine or periodic changes made to products, production lines, manufacturing processes, existing services and other operations in progress, even if such changes may represent improvements.'

(39) On the basis of the evidence provided by IFS and in view of the very high rate of unsuccessful tests (60 to 70 %) during the development phase of preclinical testing, the Commission is of the opinion that such an activity cannot be considered as technical certification or prototype validation, i.e. the conceptual formulation of other products or processes or initial demonstration projects or pilot projects within the meaning of the third indent in Annex I to the framework.

(40) By contrast, the Commission considers that the preclinical testing carried out by the company is aimed more at acquiring new knowledge which might prove essential only at a later stage of development. The success rate of 10 % appears to be in line with the average in the sector and proves that the results obtained in this drug development phase are still a very long way from both the production of a particular drug and its marketing. The Commission has also taken into account the high costs of these tests.

(41) In the present case, preclinical testing may, therefore, be considered as industrial research within the meaning of the R & D framework.

(42) With regard to the recalculation of eligible costs (new quantification of consultancy costs and addition of a new cost item), the Commission cannot take these factors into consideration in the present decision. It notes that the Italian authorities have not notified any change to the measures and that they are the only ones allowed to do so pursuant to Article 88(3) of the Treaty.

6. **CONCLUSION**

(43) In the light of the foregoing observations, the Commission takes the view that the preclinical testing 'step' of the measures notified as N 213/2002, complies with the provisions laid down in the Community framework for State aid for research and development, and in particular the second indent (industrial research), and may consequently benefit from a derogation under Article 87(3)(c) of the Treaty to the extent of 50 % gge according to point 5.3 of the Framework,

HAS ADOPTED THIS DECISION:

Article 1

The preclinical testing 'step' of the project notified by the Republic of Italy for the development of new chemical synthesis processes for oral pharmaceutical forms of polypeptides and conjugated substances constitutes industrial research within the meaning of the Community framework for State aid for research and development and may, therefore, be funded to the extent of 50 % gross grant equivalent.

The aid not exceeding this intensity is, therefore, compatible with the common market pursuant to Article 87(3)(c) of the EC Treaty.

Article 2

This Decision is addressed to the Republic of Italy.

Done at Brussels, 26 November 2003.

For the Commission

Mario MONTI

Member of the Commission