

Australia

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SPRUSON & FERGUSON

656200

**PATENT REQUEST: STANDARD PATENT**

We, the Applicant/Nominated Person specified below, request we be granted a patent for the invention disclosed in the accompanying standard complete specification.

**[70,71] Applicant/Nominated Person:**

American Cyanamid Company, of 1937 West Main Street, Stamford, Connecticut, 06904, UNITED STATES OF AMERICA

**[54] Invention Title:**

Implant Compositions Containing a Biologically Active Protein, Peptide or Polypeptide

**[72] Inventors:**

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**Basic Convention Application Details**

<b>[31] Application No</b>	<b>[33] Country</b>	<b>[32] Date of Application</b>
719,898	US	24 June 1991

**Basic Applicants:** William David Steber, Susan Mancini Cady, David Farley Johnson and Theresa Rice

DATED 13 April, 1994

American Cyanamid Company



Registered Patent Attorney

IRN: 209770

INSTR CODE: 50380

[N:VLBU]03876:LMM

## AUSTRALIA

Patents Act 1990

## NOTICE OF ENTITLEMENT

I Alphonse R. Noë,  
of 470 Haviland Road, Stamford, State of Connecticut, United States  
of America, being authorized by the Applicant/Nominated Person in  
respect of an application entitled:

IMPLANT COMPOSITIONS CONTAINING A BIOLOGICALLY ACTIVE  
PROTEIN, PEPTIDE OR POLYPEPTIDE

state the following:

The Applicant/Nominated Person has entitlement from the actual  
inventor(s) as follows:

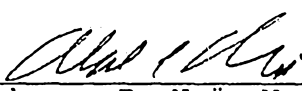
The Applicant/Nominated Person is the assignee of the actual  
inventor(s).

The Applicant/Nominated Person is entitled to rely on the basic  
application(s) listed on the Patent Request as follows:

The Applicant/Nominated Person is the assignee of the basic  
applicant(s).

The basic application(s) listed on the Patent Request is/are the  
application(s) first made in a Convention Country in respect of the  
invention.

Dated this 21 day of April 1992.

  
Alphonse R. Noë, Manager  
Patent Law Department

IRN: 185135  
MOC/7368D

INSTR CODE: 50380



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**(12) PATENT ABRIDGMENT**      **(11) Document No. AU-B-18470/92**  
**(19) AUSTRALIAN PATENT OFFICE**      **(10) Acceptance No. 656200**

- (54) Title  
**IMPLANT COMPOSITIONS CONTAINING A BIOLOGICALLY ACTIVE PROTEIN, PEPTIDE OR POLYPEPTIDE**
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**A61K 047/44**
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**AMERICAN CYANAMID COMPANY**
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- (56) Prior Art Documents  
**AU 86103/91 A61K 9/22**  
**US 4863736**
- (57) Claim

1. An implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterised by a semipermeable compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to about 80% of a biologically active protein, peptide or polypeptide, about 10% to about 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or mixture thereof and 0% to about 25% of a sugar, and wherein the coated composition does not bio-erode during the period of administration of the protein, peptide or polypeptide.

9. A process for the preparation of an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterized by:

- (a) mixing the biologically active protein, peptide or polypeptide with a molten fat, wax or mixture thereof

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(10) 656200

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and optionally with a buffer, salt or sugar to form a coarse powder;

(b) compacting one to three layers of the coarse powder to form a compacted mass;

(c) punching the compacted mass with a tapered projection to form a tapered indentation in the compacted mass; and

(d) coating the indented compacted mass with a semipermeable material such that the indentation remains essentially uncoated and becomes a passageway through the coating, and wherein the coated composition does not bio-erode during the period of administration of the protein, peptide or polypeptide.

7. A method for elevating and maintaining elevated blood levels of a biologically active protein, peptide or polypeptide, increasing growth rate, improving feed efficiency, improving lean meat to fat ratio and increasing milk production in lactating animals characterized by parenterally administering to the animal an implantable composition as characterized by claim 1.

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**COMPLETE SPECIFICATION**

**FOR A STANDARD PATENT**

**ORIGINAL**

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of Applicant:

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UNITED STATES OF AMERICA

Actual Inventor(s):

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Sydney, New South Wales, 2000, Australia

Invention Title:

Implant Compositions Containing a Biologically Active  
Protein, Peptide or Polypeptide

The following statement is a full description of this invention, including the  
best method of performing it known to me/us:-

## IMPLANT COMPOSITIONS CONTAINING A BIOLOGICALLY ACTIVE PROTEIN, PEPTIDE OR POLYPEPTIDE

The need for and the difficulties encountered in the development of methods and compositions which continuously release pharmaceutical preparations in a uniform manner over extended periods of time are well known.

The present invention relates to an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time which comprises a semipermeable, compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to about 80% of a biologically active protein, peptide or polypeptide, about 10% to about 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or mixture thereof and 0% to about 25% of a sugar.

Surprisingly, it has been found that increased blood levels of biologically active proteins, peptides and polypeptides may be obtained and maintained for extended periods of time by implanting animals with the semipermeable, compacted, indented and partially coated composition of the present invention.

According to a first embodiment of this invention there is provided an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterized by a semipermeable, compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to about 80% of a biologically active protein, peptide or polypeptide, about 10% to about 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or mixture thereof and 0% to about 25% of a sugar, and wherein the coated composition does not bio-erode during the period of administration of the protein, peptide or polypeptide.

According to a second embodiment of this invention there is provided a method for elevating and maintaining elevated blood levels of a biologically active protein, peptide or polypeptide, increasing growth rate, improving feed efficiency, improving lean meat to fat ratio and increasing milk production in lactating animals characterized by parenterally administering to the animal an implantable composition as characterized by the first embodiment.

According to a third embodiment of this invention there is provided a process for the preparation of an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterized by:



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(a) mixing the biologically active protein, peptide or polypeptide with a molten fat, wax or mixture thereof and optionally with a buffer, salt or sugar to form a coarse powder;

(b) compacting one to three layers of the coarse powder to form a compacted  
5 mass;

(c) punching the compacted mass with a tapered projection to form a tapered indentation in the compacted mass; and

(d) coating the indented compacted mass with a semipermeable material such that the indentation remains essentially uncoated and becomes a passageway through the  
10 coating, and wherein the coated composition does not bio-erode during the period of administration of the protein, peptide or polypeptide.

The implantable composition of the present invention is preferably a compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis

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from about 20% to 80% of a biologically active protein, peptide or polypeptide, about 10% to 75% of a fat or wax or mixture thereof, about 1% to 20% of a buffer or salt or mixture thereof and about 1% to 25% of a sugar.

5           A more preferred implantable composition of this invention is a compacted, indented and partially coated composition containing from one to three layers each of which contains on a weight basis from about 35% to 70% of a biologically active protein, peptide or  
10 polypeptide, about 15% to 50% of a fat or wax or mixture thereof, about 1% to 10% of a buffer or salt or mixture thereof and about 5% to 15% of a sugar.

          Biologically active proteins, peptides and polypeptides suitable for administration in the composition of the present invention include somatotropins, somatomedins, growth factor, and other biologically  
15 active fragments and derivatives thereof. Preferred proteins include porcine, ovine, equine, bovine, avian and human somatotropins; and is meant to encompass those which are of natural, synthetic, recombinant or  
20 biosynthetic origin. More preferred proteins are somatotropins with alterations in the  $\alpha$ -helix 3 region,  $\alpha$ -helix 2 region, combinations thereof and in combination with other mutations with E34 rpST, I122L +  
25 E34 rpST and A6TS11R + E34 rpST being most preferred.

          Waxes and fats which are suitable for use in the composition of the present invention in general have melting points higher than 40°C. The wax of the invention may be defined as a low-melting organic  
30 mixture or compound of high molecular weight, solid at room temperature and generally similar in composition to fats and oils except that it contains no glycerides. Some are hydrocarbons; others are esters of fatty acids and alcohols. These compounds include saturated or  
35 unsaturated long chain  $C_{10}$ - $C_{24}$  fatty acids, alcohols, esters, salts, ethers or mixtures thereof. They are



5 classed among the lipids. Waxes are thermoplastic, but since they are not high polymers, they are not considered in the family of plastics. Common properties are water repellency; smooth texture; nontoxicity; freedom from objectionable odor and color. They are combustible and have good dielectric properties. They are soluble in most organic solvents and are insoluble in water.

The major types are as follows:

10 I. Natural

1. Animal (beeswax, lanolin, shellac wax, Chinese insect wax)
2. Vegetable (carnauba, candelilla, bayberry, sugarcane)

15 3. Mineral

- (a) Fossil or earth waxes (ozocerite, ceresin, montan)
- (b) Petroleum waxes (paraffin, microcrystalline slack or scale wax)

20 II. Synthetic

1. Ethylenic polymers and polyol ether-esters ("Carbowax")
2. Chlorinated naphthalenes ("Hallowax")
- 25 3. Hydrocarbon type via Fischer-Tropsch synthesis

30 The fat of the present invention may be defined as a glyceryl ester of higher fatty acids such as myristic, stearic and palmitic. Such esters and their mixtures are solids at room temperatures and exhibit crystalline structure. Lard and tallow are examples. There is no chemical difference between a fat and an oil, the only distinction being that fats are solid at room temperature and oils are liquid. The term "fat" usually refers to triglycerides specifically, whereas "lipid" is all-inclusive.

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The fat is preferably composed of mono-, di- or triglyceryl esters of long chain  $C_{10}-C_{24}$  fatty acids. The mono-, di-, or triglycerides are composed predominantly of myristates, stearates, palmitates, laurates, linoleates, linolenates, oleates, and residues or mixtures thereof, having melting points greater than  $50^{\circ}\text{C}$ , being most preferred. Glyceryl trimyristate is a most preferred fat.

Sugars suitable for use in the composition of the present invention include mono-, di- or trisaccharides such as glucose, mannose, sorbitol, mannitol, lactose, sucrose, maltose, cellobiose and raffinose. Preferred sugars are non-reducing mono-, di- or trisaccharides with sucrose, raffinose, sorbitol and mannitol being most preferred.

Buffers are added to the implant compositions of the present invention to adjust the pH of the composition to a value of from about 6.0 to 8.5 in order to effect the solubility of the somatotropin and consequently the release of the somatotropin from the implant composition. Buffers suitable for use in the compositions of the invention include sodium and potassium phosphates, borates, carbonates, glycinates and the like or mixtures thereof with a mixture of monobasic sodium phosphate and dibasic sodium phosphate being preferred to adjust the pH of the compositions to a preferred value of from about 6.5 to 8.0.

Salts suitable for use in the composition of this invention include salts such as sodium chloride, potassium chloride and the like.

Additives such as stabilizers, preservatives, surfactants or mixtures thereof may be included in the compositions of the invention. Preferred stabilizers include dehydroacetic acid, salicylanilide, sorbic acid, boric acid, benzoic acid, and salts thereof; hydroxypropyl cellulose, hydroxypropyl methylcellulose,

sodium nitrite and sodium nitrate. The amounts of said additives suitable for use in the invention range from about 0.1% to 20% on a weight basis.

5 Surprisingly, it has been found that increased blood levels of somatotropins may be obtained and maintained for extended periods of time by im-  
planting animals with the composition of the invention. Elevated blood levels of the biologically active  
10 proteins, peptides and polypeptides are generally observed and associated with beneficial and/or therapeutic effects. The effects include weight gain, increased growth rate, improved feed efficiency, decreased body fat, improved lean meat to fat ratio, improved muscle size and increased milk production in  
15 lactating animals. Maintaining the elevated blood levels is an indication of the slow release of the active ingredient. Properties such as increased growth rate, improved feed efficiency, increased lean meat and increased milk production are generally observed when  
20 elevated blood levels of the active ingredient is maintained. The invention includes the use of the compositions herein to increase growth rate, improve feed efficiency, increase lean meat in animals, improve milk production and increase and maintain levels of  
25 somatotropins in the blood stream of animals.

Implantable composition of the present invention useful for the administration of a biologically active protein, peptide or polypeptide may be prepared by incorporating the active ingredient, buffer  
30 or salt or mixture thereof and sugar with a molten fat, wax or mixture thereof to obtain a coarse powder. Compacted and indented compositions are then prepared with a tablet press set up with conventional implant sizes such as 5/32, 1/8 inches and the like using a  
35 special top punch. The top punch has a tapered projection on the center line of the punch which will form a

conical indentation in the composition when compressed. One to three layers of the coarse powder is then placed into the die and compressed with the special top punch to form compacted and indented compositions. In a preferred embodiment of the invention the amount of biologically active protein, peptide or polypeptide present in each layer increases away from the indentation. The compacted and indented compositions are then coated with one or two layers of a semipermeable material to form the implantable compositions of the invention. The indentation remains essentially uncoated and becomes a passageway for the active ingredient to exit the composition of the invention over an extended period of time.

Semipermeable materials suitable for coating the compressed and indented compositions of the present invention include semipermeable polymers such as methacrylate ester copolymers, ethyl cellulose polymers and the like. Additives such as plasticizers and fillers may be added to the semipermeable polymers in amounts of from 1% to 20% on a weight basis with triethyl citrate and talc being a preferred plasticizer and filler respectively. The thickness of each coating surrounding the compacted and indented compositions is from about 0.5 mils to 25 mils.

In order to facilitate a further understanding of the invention, the following examples are presented to illustrate more specific details thereof. The invention is not to be limited thereby except as defined in the claims.

EXAMPLE 1

Preparation of implant compositions for the parenteral administration of somatotropins

5           1. Preparation of somatotropin, sugar, buffer and additives in a size range suitable for incorporation in the fat, wax or mixture thereof by spray drying may be accomplished by dissolving the somatotropin and sugar in water and then adding the desired buffer solution such as a 1:2 mixture of  
10           monobasic and dibasic sodium phosphate. Additives such as hydroxypropyl cellulose may be added and allowed to dissolve. The solution is then spray-dried in a Buchi mini spray drier, model #190.

15           2. Preparation of granular powder. A homogeneous mixture of the spray dried powder in the molten fat, wax or mixture thereof is prepared and the resulting mixture is cooled to give a powder. The powder is tableted using a Stokes model #512 tablet  
20           press set up with 5/8 inch punches and dies. These tablets are milled using a benchtop Glen Mills Micro-hammerMill to form a coarse granular powder.

25           3. Preparation of compacted and indented compositions. Layered, compacted and indented compositions are made with a Stokes model #521 single tablet press set up with a 5/32 inch die and special top punch. The top punch has a 3mm tapered projection on the center line of the punch. The base of the projec-  
30           tion is about 1mm. To make layered, compacted and indented compositions, the inner end granular powder is placed into the die first and lightly tamped, then the indent end granular powder is placed into the die. The press is operated by hand, so that each implant is made  
35           one at a time. To make uniform implants, a 1/8 inch die and special top punch is used. The top punch has a

3 mm tapered projection on the center line of the punch and the base of the projection is about 1 mm. The desired amount of granular powder is placed into the die and the uniform, compacted and indented compositions are prepared by operating the press by hand.

4. Preparation of partially coated implant compositions. The compacted and indented compositions are coated with one or two layers of a semipermeable polymeric material using a MINI HI-COATER® (trademark of Vector Laboratories). The surface within the indentation remains essentially uncoated and becomes a passageway for the active ingredient to exit the composition of the invention over an extended period of time.

Utilizing the above procedure with the materials listed in Table I below yields the implant compositions listed in Table II below.

TABLE I

- 20 Somatotropin
- a. I122L + E34 rpST
  - b. E34 rpST
  - c. A6TS11R + E34 rpST
  - d. CAM - rpST
  - 25 e. bovine somatotropin
- Fat or Wax
- f. glyceryl trimyristate
  - g. glyceryl tristearate

TABLE I (continued)

**Sugar**

- h. sucrose
- i. lactose

**Buffer**

- 5 j. (1:2) mixture of monobasic and dibasic sodium phosphate
- k. monobasic sodium phosphate
- l. sodium borate

10 **Additive**

- m. hydroxypropyl cellulose

**Coating**

- 15 n. poly(ethylacrylate, methylmethacrylate)  
(EUDRAGIT® NE30D) containing 8% by weight talc
- o. poly(ethylacrylate, methylmethacrylate)  
(EUDRAGIT® NE30D) containing 15% by weight talc
- 20 p. poly(ethylacrylate, methylmethacrylate)  
trimethylammonioethylmethacrylate chloride  
(EUDRAGIT® RL30D) containing 15% by weight triethyl citrate
- 25 q. poly(ethylacrylate, methylmethacrylate)  
trimethylammonioethylmethacrylate chloride  
(EUDRAGIT® RS30D) containing 15% by weight triethyl citrate

EUDRAGIT® is a trademark of Rohm Pharma GmbH.

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TABLE II

Implant Compositions

		Somato-	Fat or				Layer	First	Second
		tropin	Wax/	Sugar/	Buffer/	Additive/	weight	Coating/	Coating/
	Composition	% w/w	% w/w	% w/w	% w/w	% w/w	(mg)	mils	mils
5	1 RE <sup>1</sup>	a/35.0	f/50.0	h/12.5	j/2.5	-	30	p/2	n/5
	IE <sup>2</sup>	a/70.0	f/17.6	h/8.2	j/4.1	-	90		
	2 RE	a/35.0	f/50.0	h/12.5	j/2.5	-	50	p/2	n/5
10	IE	a/70.0	f/17.6	h/8.2	j/4.1	-	80		
	3 RE	a/35.0	f/50.0	h/12.5	j/2.5	-	30	p/2	n/5
	IE	a/65.0	f/23.5	h/7.6	j/3.8	-	90		
15	4 RE	a/35.0	f/50.0	h/22.5	j/2.5	-	20	p/2	n/5
	IE	a/65.0	f/23.5	h/7.6	j/3.8	-	90		
	5 RE	a/40.0	f/50.0	h/7.5	j/2.5	-	50	p/2	n/5
20	IE	a/70.0	f/17.6	h/8.2	j/4.1	-	80		



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**TABLE II (Continued)**

<u>Composition</u>		<u>Somato-</u> <u>tropin</u> <u>% w/w</u>	<u>Fat or</u> <u>Wax/</u> <u>% w/w</u>	<u>Sugar/</u> <u>% w/w</u>	<u>Buffer/</u> <u>% w/w</u>	<u>Additive/</u> <u>% w/w</u>	<u>Layer</u> <u>weight</u> <u>(mg)</u>	<u>First</u> <u>Coating/</u> <u>mils</u>	<u>Second</u> <u>Coating/</u> <u>mils</u>
6	RE	a/40.0	f/50.0	h/7.5	j/2.5	-	50	p/2	n/5
	IE	a/65.0	f/23.5	h/7.6	j/3.8	-	80		
7	RE	a/40.0	f/20.0	h/20.0	j/4.0	m/16.0	10	p/2	n/5
	IE	a/55.0	f/31.0	h/10.3	j/3.4	-	110		
8	RE	a/40.0	f/20.0	h/20.0	j/4.0	m/16.0	20	p/2	n/5
	IE	a/55.0	f/31.3	h/10.3	j/3.4	-	100		
9	RE	a/35.0	f/30.0	h/17.5	j/3.5	m/14.0	20	p/2	n/5
	IE	a/55.0	f/31.3	h/10.3	j/3.4	-	100		
10	RE	b/40.0	f/50.0	h/7.5	j/2.5	-	50	n/5	-
	IE	b/65.0	f/18.7	h/12.2	j/4.1	-	70		

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TABLE II (Continued)

<u>Composition</u>		<u>Somato-</u> <u>tropin</u> <u>% w/w</u>	<u>Fat or</u> <u>Wax/</u> <u>% w/w</u>	<u>Sugar/</u> <u>% w/w</u>	<u>Buffer/</u> <u>% w/w</u>	<u>Additive/</u> <u>% w/w</u>	<u>Layer</u> <u>weight</u> <u>(mg)</u>	<u>First</u> <u>Coating/</u> <u>mils</u>	<u>Second</u> <u>Coating/</u> <u>mils</u>
11	RE	b/50.0	f/37.5	h/9.4	j/3.1	-	40	q/2.5	o/6
	IE	b/60.0	f/25.0	h/11.3	j/3.8	-	80		
12	RE	c/45.0	f/43.8	h/8.4	j/2.8	-	40	p/1	n/7
	IE	c/60.0	f/25.0	h/11.3	j/3.8	-	80		
13	RE	c/50.0	f/37.5	h/9.4	j/3.1	-	40	q/2	o/6
	IE	c/60.0	f/25.0	h/11.3	j/3.8	-	80		
14	Uniform	a/53.8	g/31.2	i/13.5	k/1.5	-	80	n/5	
15	Uniform	d/55.0	f/31.3	h/10.3	j/3.4	-	120	q/1	o/6.5

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TABLE II (Continued)

<u>Composition</u>		<u>Somato-</u> <u>tropin</u> <u>% w/w</u>	<u>Fat or</u> <u>Wax/</u> <u>% w/w</u>	<u>Sugar/</u> <u>% w/w</u>	<u>Buffer/</u> <u>% w/w</u>	<u>Additive/</u> <u>% w/w</u>	<u>Layer</u> <u>weight</u> <u>(mg)</u>	<u>First</u> <u>Coating/</u> <u>mils</u>	<u>Second</u> <u>Coating/</u> <u>mils</u>
16	RE	c/50.0	f/44.4	-	j/4.4 1/1.1	-	40	q/1	o/6.5
	IE	c/60.0	f/33.3	-	j/5.3 1/1.3	-	90		
17	RE	e/50.0	f/37.5	h/8.8	j/2.9	-	40	q/1	o/6.5
	IE	e/60.0	f/25.0	h/11.3	j/3.8	-	80		

<sup>1</sup>RE = Release end

<sup>2</sup>IE = Inner end

**EXAMPLE 2**

**Sustained release of compositions of the invention in pigs**

Pigs are divided into groups of four animals. Throughout the test, all pigs are fed the same ration containing 20% crude protein. The pigs are not treated for three days and daily porcine somatotropin blood levels are obtained for each group of animals. Then two implants, listed in Table II, are implanted in the ear of each pig. Somatotropin levels in the blood of the animals is determined by standard RIA techniques daily. The results of this experiment, summarized in Table III below, demonstrate the effectiveness of the compositions of the invention for increasing and maintaining elevated somatotropin levels in the blood for extended periods of time.

**TABLE III**  
Average Plasma rpST Concentration (ng/mL by  
Radioimmunoassay) for Pig Experiments

Time (Days)	Composition from Table II					
	2	7	10	11	12	13
-3	1.9	1.4	1.5	2.1	3.8	2.5
-2	0.9	2.2	2.6	4.9	2.4	3.8
-1	1.2	2.3	1.7	2.4	3.3	4.2
1	6.6	5.5	4.9	1.7	3.0	1.4
2	8.2	3.5	35.2	1.5	3.5	1.6
3	9.8	13.9	97.1	2.6	3.8	3.2
4	6.3	11.3	60.9	1.9	3.2	2.4
5	3.4	17.6	56.4	1.5	18.9	8.6
6	20.1	16.2	474.8	11.2	61.2	17.6
7	26.4	20.6	242.6	3.3	40.3	22.9
8	26.1	20.0	110.6	118.1	35.4	41.3
9	50.0	19.4	70.7	87.0	19.7	43.0
10	42.9	25.9	45.4	56.6	30.0	55.0
11	26.1	35.7	82.4	44.3	15.7	32.5
12	16.0	34.2	47.1	34.8	22.7	35.3
13	26.2	29.8	52.1	40.1	6.7	25.0
14	19.9	31.4	28.8	54.4	8.0	39.8
15	10.2	25.3	21.3	25.9	4.8	20.0
16	8.8	20.7	19.7	31.3	4.7	12.5
17	13.4	10.5	6.8	29.2	4.9	10.2
18	8.0	15.4	7.8	18.5	4.0	10.0
19	32.1	34.4	10.0	16.1	3.8	5.3
20	5.8	9.4	8.2	14.9	2.8	6.8
21	9.6	13.6	9.9	8.7	2.7	3.1
22	15.1	11.2	5.7	7.4	35.6	7.1
23	60.8	7.1	6.0	15.9	12.8	4.3
24	4.9	7.6	12.6	11.2	4.0	4.4
25	8.4	7.0	5.4	5.4	2.3	3.4
26	8.9	6.6	4.0	5.3	2.7	6.8
27	6.7	7.3	4.8	8.6	5.0	6.5

EXAMPLE 3

In Vitro dissolution evaluation of implants

Two implants are placed in a plastic tube containing 10 mL of a phosphate buffer solution (pH 7.4, 100 mM NaCl, 50mM  $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ , 0.2% Na azide) and the tube is placed in a water bath where the temperature of the water in the unit is maintained at 39°C. The tube is kept in the water bath for two days, then the solution is removed from the tube and analyzed for the appropriate somatotropin by HPLC and the solution is discarded. New phosphate buffer solution is added to the tube and the tube is placed into the water bath for three additional days and analyzed as described above. This procedure is repeated several times at various time intervals until the experiment is terminated. Table IV below summarizes the release rates of the appropriate somatotropin for several compositions listed in Table II.

TABLE IV  
Release Rate (mg/day)

		<u>Composition</u>		
<u>Days</u>		<u>2</u>	<u>7</u>	<u>10</u>
0 - 2		0.6	0.6	1.0
2 - 5		3.8	7.6	11.4
5 - 9		7.2	7.0	6.9
9 - 12		5.3	3.4	4.2
12 - 16		2.7	1.7	2.1
16 - 19		1.6	1.3	1.8
19 - 23		1.3	0.9	1.4
23 - 28		0.9	0.6	1.0

Following the above procedure but analyzing the solutions for the appropriate somatotropin at different time intervals than described above gives the release rates summarized below in Tables V, VI and VII.

**TABLE V**  
**Release Rate (mg/day)**

<u>Days</u>	<u>Composition</u>	
	<u>11</u>	<u>13</u>
0 - 1	0.1	0.0
1 - 2	2.5	1.4
2 - 5	7.0	3.9
5 - 9	5.9	6.4
9 - 12	3.9	4.3
12 - 16	2.5	2.5
16 - 19	1.7	1.3
19 - 22	1.4	1.1
22 - 26	1.0	1.1
26 - 28	0.8	0.6

**TABLE VI**  
**Release Rate (mg/day)**

<u>Days</u>	<u>Composition</u>
	<u>12</u>
0 - 1	0.5
1 - 3	2.0
3 - 7	5.1
7 - 10	7.1
10 - 14	3.9
14 - 17	1.9
17 - 21	1.3
21 - 24	0.9
24 - 28	0.7

**TABLE VII**  
**Release Rate (mg/day)**

<u>Days</u>	<u>Composition</u>		
	<u>15</u>	<u>16</u>	<u>17</u>
0 - 1	0.0	0.0	0.0
1 - 2	2.2	0.7	0.7
2 - 5	1.5	3.0	3.3
5 - 9	3.9	4.4	4.5
9 - 12	4.6	4.1	2.6
12 - 16	2.4	2.3	1.1
16 - 20	1.5	1.6	0.7
20 - 23	0.9	1.2	0.4
23 - 26	0.9	1.1	0.3

Additionally, following the above procedure but using three implants gives the release rates summarized below in Table VIII.

**TABLE VIII**  
**Release Rate (mg/day)**

<u>Days</u>	<u>Composition</u>
	<u>14</u>
0 - 1	0.0
1 - 4	1.4
4 - 7	3.9
7 - 11	4.7
11 - 14	3.3
14 - 18	1.9
18 - 21	1.5
21 - 34	0.8



**The claims defining the invention are as follows:**

1. An implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterised by a semipermeable compacted, indented  
5 and partially coated composition containing from one to three layers each of which contains on a weight basis from about 20% to about 80% of a biologically active protein, peptide or polypeptide, about 10% to about 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or mixture thereof and 0% to about 25% of a sugar, and wherein the coated composition does not bio-erode during the period of administration of  
10 the protein, peptide or polypeptide.

2. The composition according to claim 1 wherein the biologically active protein, peptide or polypeptide is selected from the group consisting of somatotropins, somatomedins, and growth factors, including porcine, ovine, equine, bovine, avian and human somatotropins; the fat is selected from the group consisting of glyceryl  
15 trimyristate, glyceryl tripalmitate and glyceryl tristearate, the buffer is selected from the group consisting of sodium borate, sodium carbonate, monobasic sodium phosphate, dibasic sodium phosphate and mixtures thereof, the sugar is selected from the group consisting of glucose, mannose, sucrose, raffinose, sorbitol, mannitol and lactose; the coating comprises one or two layers of a semipermeable material and wherein said  
20 composition optionally is characterized by a stabilizer, a surfactant or mixtures thereof.

3. The composition according to claim 2 wherein the porcine somatotropin is selected from the group consisting of E34 rpST, I122L + E34 rpST and A6TS11R + E34 rpST.



4. The composition according to claim 2 wherein the buffer is a mixture of monobasic sodium phosphate and dibasic sodium phosphate.

5. The composition according to claim 2 wherein the semipermeable material is a methacrylate ester copolymer containing on a weight basis from about 1% to 20% ethyl citrate or talc and the thickness of each coating is from about 0.5 mils to 25 mils.

6. The composition according to claim 1 wherein the amount of biologically active protein, peptide or polypeptide present in each layer increases away from the indentation.

7. A method for elevating and maintaining elevated blood levels of a biologically active protein, peptide or polypeptide, increasing growth rate, improving feed efficiency, improving lean meat to fat ratio and increasing milk production in lactating animals characterized by parenterally administering to the animal an implantable composition as characterized by claim 1.

8. The method according to claim 7 wherein the implantable composition is as characterized by claim 2.

9. A process for the preparation of an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time characterized by:

- (a) mixing the biologically active protein, peptide or polypeptide with a molten fat, wax or mixture thereof

and optionally with a buffer, salt or sugar to form a coarse powder;

(b) compacting one to three layers of the coarse powder to form a compacted mass;

(c) punching the compacted mass with a tapered projection to form a tapered  
5 indentation in the compacted mass; and

(d) coating the indented compacted mass with a semipermeable material such that the indentation remains essentially uncoated and becomes a passageway through the coating, and wherein the coated composition does not bio-erode during the period of administration of the protein, peptide or polypeptide.

10 10. The process according to claim 9 wherein step (b) and step (c) occur simultaneously.

11. The process according to claim 9 wherein the compacted mass is characterized by the composition of claim 1.

12. The process according to claim 9 wherein step (a) is further characterized by:

15 (a) dissolving the biologically active protein, peptide or polypeptide, and buffer or salt or mixture thereof, in water to form a solution;

(b) spray drying the solution to form a spray dried powder;

(c) dissolving the spray dried powder in the molten fat, wax or mixture thereof to form a homogeneous mixture;

20 (d) cooling the homogeneous mixture to form a powder;

(e) compressing the powder to form a compressed mass; and

(f) milling the compressed mass to form a coarse granular powder.

13. A process for the preparation of an implantable composition for the parenteral administration of an essentially uniform and continuous amount of a biologically active  
25 protein, peptide or polypeptide over an extended period of time, substantially as herein described with reference to Example 1.

14. An implantable composition whenever prepared by the process of any one of claims 9 to 13.

15. An implantable composition for the parenteral administration of an essentially  
30 uniform and continuous amount of a biologically active protein, peptide or polypeptide over an extended period of time, substantially as herein described with reference to any one of the Examples.

16. A method for elevating and maintaining elevated blood level of a biologically active protein, peptide or polypeptide in an animal, comprising parenterally administering  
35 to said animal an effective amount for elevating and maintaining elevated blood level of an implantable composition as defined in claim 14 or 15.

17. A method for increasing growth rate of an animal, comprising parenterally administering to said animal an effective amount for increasing growth rate of an implantable composition as defined in claim 14 or 15.



18. A method for improving feed efficiency in an animal, comprising parenterally administering to said animal an effective amount for improving feed efficiency of an implantable composition as defined in claim 14 or 15.

19. A method for improving lean meat to fat ratio in an animal, comprising  
5 parenterally administering to said animal an effective amount for improving lean meat to fat ratio of an implantable composition as defined in claim 14 or 15.

20. A method for increasing milk production in a lactating animal, comprising parenterally administering to said animal an effective amount for increasing milk production of an implantable composition as defined in claim 14 or 15.

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**Dated 13 April, 1994**  
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## **IMPLANT COMPOSITIONS CONTAINING A BIOLOGICALLY ACTIVE PROTEIN, PEPTIDE OR POLYPEPTIDE**

### *Abstract*

The invention relates to implant compositions for the parenteral administration of  
5 an essentially uniform and continuous amount of a biologically active protein, peptide or  
polypeptide over an extended period of time. The invention also relates to methods for  
increasing and maintaining elevated blood levels of biologically active proteins, peptides  
and polypeptides in animals.

The compositions are characterized by a compacted, indented and partially coated  
10 composition containing from one to three layers each of which contains on a weight basis  
from about 20% to 80% of a biologically active protein, peptide or polypeptide, about  
10% to 75% of a fat or wax or mixture thereof, 0% to about 20% of a buffer or salt or  
mixture thereof and 0% to about 25% of a sugar.