APPLICATION FOR PRODUCT LICENCES

1 Name of Product: KONYNE®, Factor IX Complex (Human)

2 Full name and address of proposed licence holder:
Cutter Laboratories Ltd.
10 Quarry Street
Guildford, Surrey, GU1 3UZ, U.K.

3 Trading style to be shown on licence if different from above: Not applicable

4 Role of proposed licence holder:

(i) as person responsible for composition of product manufactured in U
*(ii) as person who imports or procures its importation.
(iii) as person who first sells or supplies it as a medicinal product.

5 Activities for which licence is required:

* (i) selling or supplying product in the UK.
(ii) procuring the manufacture or assembly of the product for sale or supply in the UK.
(iii) importing or procuring the importation of the product.
(iv)

6 Applicants own reference no: None

7 Details of earlier applications:
1. Koate PL 1605/0004
2. CPD Anticoagulant in plastic bags, 1605/0003
3. Plasbumin-5 and Plasbumin-25 submitted 6/16/80

8 To cover sale and supply of the product manufactured before the grant of the licence: ~~YES~~/NO

9 Scientific Evidence:

(i) Chemistry and Pharmacy Pages
(ii) Experimental and Biological Studies Pages
(iii) Clinical Trials Pages Abridged Submission

10 Number of pages of supplementary information:

11 I/We apply for the grant of a product licence to the proposed holder named above in respect of the produc to which the Product Particulars on Page 2 refer and in accordance with the other particulars annexed; th said licence to be for a period of five years and subject to the following provisions -

11.1. All the Standard Provisions applicable to product licences under regulations for the time being in force under Section 47 of The Medicines Act 1968.

11.2. The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars as Uses, and shall be sold or supplied in accordance with the said Product Particulars except in so far as may from time to time be approved by the licensing authority.

11.3. The specification of the constituents and of the finished product shall be in accordance with the information contained in or furnished in connection with the application.

11.4. The product is to be manufactured only in accordance with the methods set out in this application o furnished in connection with it.

11.5. No material information has been omitted (within the knowledge of the signatory).

Date July 3, 1980

Signature GRO-C

State capacity in which signed.

MLA 201 Page 1 - Addendum

Do you give your consent to the disclosure to the British Pharmacopoeia Commission of information given in or in connection with this application or to the pharmaceutical standards applicable to the product or its active ingredient on the understanding that such information will not be used in the compilation of a pharmacopoeia monograph without prior reference to you?

(YES)/NO

Signature GRO-C Date July 3, 1980

PRODUCT PARTICULARS

1 **Name of Product:** Konyne®
Factor IX Complex (Human)

2 **Pharmaceutical form:** Sterile lyophilized powder for reconstitution with sterile water for administration. Intravenous injectable.

3 **Active constituents** Partially purified factor IX fraction as well as concentrated factors II, VII and X.

4 **Uses:** Konyne is indicated whenever one or more of the specific coagulation factors must be elevated in order to correct or prevent a dangerous bleeding episode. See product direction insert for details.

5 **Recommended dose and dosage schedule:** See product direction insert.

6 **Contra-indications, Precautions and Warnings:** See product direction insert.

7 **Method of retail sale or supply:** By direct government contract and private sale.

8 **Manufacturer of dosage form:** Cutter Laboratories, Inc.
Berkeley, California 94710 U.S.A.

A. Konyne manufacturing locations:

Berkeley, California 94710
Clayton, North Carolina 27520

B. Sterile Water for Injection:

Chattanooga, Tennessee 37406

Applicants reference number (as on page 1) none

Applicants signature GRO-C

PART 1B - Supplementary Details

1. Product Literature

2. Background

3. Persons involved in the Manufacture of the Finished Product and their distribution in the U.K.

PART 1B - Supplementary Details

1. Product Literature

Package insert, carton and container label attached.

2. Background

2.1 Applications in other countries

a. U.S.A. licensed product, December 31, 1968 (copy attached)

b. Canadian licensed product, June 26, 1969

c. Internationally registered in Germany, Israel, Indonesia, Pakistan, Chile, Colombia, Dominican Republic, Ecuador, Guatemala, Norway, Taiwan.

2.2 a. Product monograph appears in U.S.P. XX

b. A generic review of the product by David L. Aronson M.D. appeared in Seminars in Thrombosis and Hemostasis, Vol. VI, No. 1, 1979.

3. Persons Involved in the Manufacture of the Finished Product and their Distribution in the U.K.

3.1 Manufacturer and Assembler

Cutter Laboratories, Inc.

Konyne Production Location:

1. Berkeley, California, 94710
2. Clayton, North Carolina 27520

Sterile Water for Injection Production Location:

Chattanooga, Tennessee 37406

3.2 Arrangements for Storage

3.3 Importer

Cutter Laboratories Ltd, the license holder.

3.4 Responsibility for Quality Control

a. Cutter Laboratories, Inc. U.S.A.

b. Cutter Laboratories, Inc. U.S.A.

CUTTER LABORATORIES, INC.

Product License

FACTOR IX COMPLEX (HUMAN)

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Washington

Product License

This is to certify that Cutter Laboratories, Inc.
Berkeley, California *through the establishment identified as* Cutter Laboratories, Inc.
located at Berkeley, California
is hereby authorized to propagate or manufacture and prepare for sale the following:

Factor IX Complex (Human)

this Department having been satisfied that the requirements of the Public Health Service Act, approved July 1, 1944 (58 Stat. 682), for the regulation of biological products and of the regulations thereunder have been met with respect to the product(s) specified above.
Establishment License No. 8

Date: 12 31-68

GRO-C

Assistant Secretary
for Health and Scientific Affairs

1. Product Literature

CUTTER LABORATORIES, INC.

KONYNE®

Pharmaceutical Data on Dosage Form

PART II

1. Finished Product

1.1 Description

Konyne, Factor IX Complex is a sterile, dried powder consisting of a purified plasma fraction containing Factor IX as well as concentrated Factors II, VII and X.

The concentrate is packaged with a vial of sterile water for reconstitution and a sterile filter needle.

1.2 Complete Formula:

1.2.1. Active Constituents — Purified protein fraction

1.2.2. Other Constituents — 0.09M Sodium Chloride
0.05M Sodium Citrate

Content of 500 unit package:

Lyophilized powder	920 mg
Protein content approx.	500 mg
Sodium Chloride	108 mg
Sodium citrate as dihydrate	309 mg
Sterile Water for Reconstitution	20 ml

1.2.3. Overage

Not applicable. Each container is filled to a specified volume and potency evaluation is made on the finished product.

1.3 Containers

Konyne Bottle: Type I or Type II clear glass
Stopper: Gray natural rubber
Seal: Plastic flip-off

Sterile Water for Injection, U.S.P.
Vial: Type I or Type II clear glass
Stopper: Dark gray natural rubber
Seal: Plastic flip-off

PART II

2. Manufacture of Dosage Form

2.1 Manufacturing Formula

Plasma is obtained from human donors, collected according to procedures that conform to the requirements of the Food and Drug Administration. Pooled human plasma is fractionated by the Cohn cold alcohol process to a protein fraction.

2.2. Manufacturing Process

The protein fraction is further purified by adsorption and elution techniques. The preparation is dissolved in a non-pyrogenic diluent of 0.9M sodium chloride and 0.05M sodium citrate. The bulk solution is clarified and sterile filtered through a 0.2 micron non-asbestos filter into a sterile vessel.

2.3 Assembling Process

The sterile solution is aseptically filled into sterile non-pyrogenic containers, freeze-dried, sealed and stored at 2-8°C.

PART II

3. Quality Control

3.1 Specifications of Constituents

All reagents and raw materials used in the preparation of Konyne are tested and meet requirements of the U.S.P. or NF standards. Reagent specifications are maintained by the Quality Assurance Department.

Human plasma is obtained from blood and plasma collection centers that are registered with the U.S. Food and Drug Administration. Collection procedures conform to the standards described in the U.S. Code of Federal Regulations Title 21, Part 640.

Each unit of plasma used for production is tested by an FDA approved procedure and found nonreactive for hepatitis B surface antigen using a test of at least third generation sensitivity.

3.2 In-Process Control

Cutter Laboratories maintains written Standard Operating Procedures for the production process and complies with good manufacturing practices.

Sterilizers, autoclaves and dryers go through special qualification and validation procedures before being used for production. In addition, dispensing equipment, such as filling machines, must go through a calibration run to be qualified. Regular calibration and certification of the equipment are maintained.

Each batch production record is a detailed account of raw materials and product components comprising the batch and all significant processing details relating to the batch. All weighings, countings and other significant measurements are checked by two competent individuals. The weight or volume of the final batch is recorded to serve as a quantitative base for material balance and calculation. The filling, drying and finishing records complete the documentation for the final container production.

All label copy is maintained under controlled procedures and is issued to the finishing department by a documented process. Label accountability is maintained.

The tally of final containers must equal the theoretical yield calculated from the known volume of the bulk prior to filling minus the test samples, discards, breakage or normal finishing line losses. Any unexplained discrepancy between theoretical and actual yield is investigated and explained.

PART II

3.2.2. Sampling for Quality Control

1. Samples of finished bulk are taken for sterility testing.

2. Samples for evaluation are taken by Quality Assurance Inspectors during the filling and finishing of the production lot.

3. Final container samples are given to the Quality Assurance Department for chemical and biological testing.

4. Finished final containers and test protocol for each lot are sent to the Bureau of Biologics, FDA for evaluation and release action.

5. Retention samples of the finished product are kept in storage at least 6 months after the product's expiration date.

PART II

3.3 Finished Product Specifications

FACTOR IX COMPLEX (HUMAN)

KONYNE®

Limits of Assay - Test Methods

Assay	Limits	Test Methods
Factor IX	Not Less Than 400 units per vial	The assay is based on a Modified Partial Thromboplastin Time. Quantitation of the sample is made by comparing its clot time in the test with that achieved by dilutions of a Standard.
Factor II	300-600 units	Owren one-stage prothrombin assay method is used. Quantitation of the sample is made by comparing its clot time in the test with that achieved by dilutions of a Standard.
Non-Activated Partial Thromboplastin Time	Average clotting time of sample is greater than average clotting time of standard.	Clotting times are determined by a mixture of non-activated human plasma, non-activated partial thromboplastin, 1:10 and 1:100 buffered dilutions of prothrombin complex concentrate standard and/or test samples in the presence of $CaCl_2$.
Loss on Drying	Not more than 3%	Measure loss on drying at 60°C for 4 hours at less than 200u Hg.
Chloride	70-105 mEq/L	U.S.P. Procedure
Sodium	190-285 mEq/L	Determined by atomic absorption spectrophotometry.
pH	6.4 - 7.4	Measured at 24-26°C by glass electrode on the reconstituted product.
Sterility	Pass test	Performed according to the method filed with the Bureau of Biologics, Food and Drug Administration that meets the requirements prescribed in the Code of Federal Regulations, (21CFR) Section 610.12.
Pyrogen	Pass test	Follow the Bureau of Biologics method: 2 ml of reconstituted product per kg of rabbit body weight are injected. U.S. Code of Federal Regulations (21CFR) Section 610.13(b).

PART II

3.3 Finished Product Specifications
Cont'd

Factor IX Complex (Human)

KONYNE®

Limits of Assay - Test Methods

Assay	Limits	Test Methods
Safety	Pass test	Procedure described in the U.S. Code of Federal Regulations (21CFR), Section 610.11.
Identity	Pass test	By precipitin test: Anti-human rabbit serum - positive Anti-bovine rabbit serum - negative Anti-equine rabbit serum - negative

PART II

5. Stability - Konyne

5.1 Attached are data sheets for 3 lots of Konyne Lot Nos. NC 9006, M 5542, M 5754.

5.2 Two year stability data is presented for product stored at 5°C and 25°C.

5.3 The containers used for the studies were Type I glass stoppered with natural rubber.

5.4 See data sheets for results.

5.5 The stability data analyses were performed using the same test procedures as those used for the finished product, item 3.3. Coagulation tests are performed by a one-stage factor assay. Electrophoresis pattern obtained using cellulose acetate electrophoresis.

5.6 Stability data supports product shelf life for 2 years.

5.7 Current U.S. approved shelf life is 2 years at 2°-8°C.

5.8 Recommended storage is 2° to 8°C. Freezing should be avoided as breakage of the diluent bottle might occur.

Factor IX concentrate may be stored up to one month at temperatures not to exceed 37°C (99°F) during travel.

5.9 Cutter Laboratories has an ongoing stability program for the evaluation of the biological products being produced.

CUTTER LABORATORIES, INC.

STABILITY DATA

KONYNE®

QAF C073

STABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GR O-C

APPROVED BY GR O-C

PRODUCT TYPE: BFR1

Remarks: Date of Mfg based on last valid potency Assay
Lot shelf life - 2 years at 2-8°

Product Konyne® Factor IX Complex (Human)

Code No. 620 - 20

Size 500u (20ml) T1, 20mm Nat. Rubber
Procedure CC# 63408, QAF-401, 402, 403, 404; DC 200; QAB10-010
Storage Conditions 5°
USA, Product shelf life 2 years

Mfg. Lot No. NC 9006
Mfg. Date 7/12/77
Exp. Date 7/12/79
Mfg. Location Clayton
Date on 11/22/77
Reason on Stability 5°

JUN 18 1979

$ Tests marked with dollar sign are done at initial and final test points only.

	Chemical Testing													Coagulation Testing						
		Electrophoretic Pattern																		
Time	Protein gms/vial 1	γ-globulins % 2	β2-globulins % 3	β1-globulins % 4	α-globulins % 5	Albumin % 6	PRE ALBUMIN % 7	pH Undiluted 6.40 - 7.40 8	Chloride 70-105 mEq/L 9	Sodium 130-285 mEq/L 10	Moisture 0.0 - 3.0% = 11	Clarity %T 580 nm 12	Solubility Time 0.0 - 3.0 min 13	Factor IX 400 - 625 units/vial 14	Specific Factor IX u/mg Protein 15	Factor II 300 - 600 units/vial 16	Factor X units/vial 17	Thrombin - Initial u 0.00-0.001 ml 18	Thrombin - 3 hours 0.00-0.002 ml 19
	011015	015018	019 018	023018	033018	037018	039018	045023	250050	256051	261052	269053	329054	411064	413065	415089	417066	419067	421068
7/12/77	0.484	—	—	—	—	—	—	7.0	88	258	0.4	—	0.75	550	1.1	370	470	—	—
1/24/78	0.489	0	0	7.8	81.2	3.4	7.6	7.0	—	—	0.62	96.2	0.50	556	1.1	398	489	—	—
7/15/78	0.507	0	0	7	81	2	10	7.02	—	—	1.40	95.1	1.0	559	1.10	418	464	—	—
1/5/79	0.490	0	0	9	79	4	8	7.04	—	—	1.12	94.8	1.9	644	1.30	481	387	—	—
6/15/79	0.501	0	0	9	80	2	10	7.00	—	—	—	95.7	2.2	650	1.35	362	560	—	—

PRODUCT TYPE: BFR1

STABILITY EVALUATION RECORD

CUTTER Laboratories, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GRO C

APPROVED BY GR C O

Code No. 620 - 20

MAY 18 1979 DATA ENTRY

Product Konyne® Factor IX Complex (Human)

Size

Procedure CC# 63408, QAK-901, 902, 903, 904; BC 240; QAC10-020

Storage Conditions 5°

Mfg. Lot No.
Mfg. Date
Exp. Date
Mfg. Location
Date on
Reason on

$ Tests marked with dollar sign are done at initial and final test points only.

Time	Bio-Tests: NAPTI 1:10 NLT 60 seconds (21)	NAPTI 1:100 NLT 90 seconds (21)	Pyrogen Pass - Fail ($)	Safety Pass - Fail ($)	Initials/ Date	COMMENTS
	4230L1	429090	528042	530012		
7/12/77	107	178	Pass	Pass	MJB 11-23-77	
1/24/78	133	242	—	—	MJB 4/13/78	
7/15/78	138	294	—	—	MJB 9/15/78	
1/5/79	144	278	—	—	MJB 3/26/79	
6/15/79	137	245	—	—	MJB 9/13/79	

STABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GRO-C

APPROVED BY GR O-C

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size 500U (20 ml), T1, 20mm Nat. Rubber
Procedure CCH 63409, QAK 701, 702, 703, 704, PC-190, 9/19/79 8 1979
Storage Conditions 25°C DATA ENTRY
USA, Product shelf life 2 years

Mfg. Lot No. NC 5006
Mfg. Date 1/12/77
Exp. Date 7/12/79
Mfg. Location Clayton
Date on 8/01/78
Reason on 1.L.L.G. at 25°

$ Tests marked with dollar sign are done at initial and final test points only.

Done

	Chemical Testing											Coagulation Testing							
		Electrophoretic Pattern																	
Time	Protein - gms/vial	γ-globulins % 2	β2-globulins % 3	β1-globulins % 4	α-globulins % 5	Albumin % 6	Pre Albumin % 7	pH Undiluted 6.40 - 7.40 $ 8	Chloride 70 - 105 mEq/L $ 9	Sodium 130-285 mEq/L $ 10	Moisture 0.0 - 3.0% 11	Clarity NTU 580 nm 12	Solubility Time 0.0 - 3.0 min 13	Factor IX 400-625 u/vial 14	Specific Activity Factor IX u/mg Protein 15	Factor II 300 - 600 units/vial 16	Factor X units/vial 17	Thrombin - 0.00-0.002 u Initial u/ml 18	Thrombin - 3 hours u 0.00-0.001 u/ml 19
	011015	015018	019018	023018	033018	037018	039018	045-023	250 050	256051	261052	269053	329054	411064	413065	415-069	417066	419067	421068
7/12/77	0.484	—	—	—	—	—	—	7.0	88	254	0.4	—	0.75	550	1.1	370	470	—	—
1/24/78	0.489	0	0	7.8	81.2	3.4	7.6	7.0	—	—	0.62	96.2	0.50	556	1.1	379	489	—	—
10/01/78	0.490	0	0	7	82	3	8.	7.02	—	—	—	96.2	1.9	724	1.5	385	601	—	—
12/01/78	0.489	0	0	8	81	4	7.	6.99	—	—	1.74	96.2	1.8	579	1.2	431	527	—	—
2/15/79	0.501	0	0	9	80	2	9.	7.02	—	—	1.40	96.3	1.0	565	1.13	386	570	—	—
4-05-79	.491	0	0	8	82	1	9.	6.98	—	—	1.64	96.4	1.5	601	1.22	366	615	—	—
6-05-79	.483	0	0	8	83	1	8	6.99	—	—	2.47	96.2	1	650	1.3	362	560	—	—
8-05-79	.504	0	0	8	80	2	9	6.96	—	—	2.01	95.9	2.5	564	1.1	378	507	—	—

F 0073

PRODUCT TYPE: BFR1

STABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GR O-C

APPROVED BY GR O-C

JAN 18 1979

DATA ENTRY

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size

Procedure CC# 63408; QAS-401, 902, 903, 904; BR 240; QAB 18-040

Storage Conditions 25°C

Mfg. Lot No. NC 9006
Mfg. Date 7/12/77
Exp. Date 7/12/79
Mfg. Location Clayton
Date on 5-1-78
Reason on Stability 21-0

1.

$ Tests marked with dollar sign are done at initial and final test points only.

Time	NAPTT 1:10 NLT 60 Seconds	NAPTT 1:100 NLT 90 Seconds	Bio-Tests: Pyrosen Pass - Fail	Bio-Tests: Safety Pass - Fail	Initials/ Date	Comments
	20	21	225	#3		
	423061	429090	528042	530042		
7/12/77	107	178	Pass	Pass	MJB 11-23-77	
1/24/78	133	242	—	—	MJB 4/13/78	
10/01/78	144	249	—	—	MJB 12/5/78	
12/01/78	141	285	—	—	MJB 1/3/79	
2-05-79	130	250	—	—	MJB 3/20/79	
4-05-79	128	224	—	—	MJB 6/5/79	
6-05-79	137	215	—	—	MJB 7/05/79	
8-05-79	140	277	Pass	Pass		

QAF 0073

BILITY EVALU ION RECO ARED BY GR O-C

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

APPROVED BY GRO -C

Code No. 620 - 20

PRODUCT TYPE: BFR1

REMARKS: Date of Mfg based on Last Valid Potency Assay
Lot Shelf Life 2 years at 2-8°

Product Konyne® Factor IX Complex (Human)

Size 50cc (20ml), T1, 20mm Nat. Rubber
Procedure CC# 63408, QAF-901, 902, 903, 904; BC200; QAB10-010
Storage Conditions 5°

Mfg. Lot No. M5542
Mfg. Date 6-24-76
Exp. Date 7-19-78
Mfg. Location Berkeley
Date on 1-05-77
Reason on Stability

$ Tests marked with dollar sign are done at initial and final test points only.

	Chemical Testing													Coagulation Testing						
		Electrophoretic Pattern																		
Time	Protein gms/vial	γ-globulins %	β2-globulins %	β1-globulins %	α-globulins %	Albumin %	PREALBUMIN c/o	pH Undiluted 6.40 - 7.40	Chloride 70-105 mEq/L $	Sodium 130-285 mEq/L $	Moisture 0.0 - 3.0%	Clarity ≠1580 nm	Solubility 0.0 - 3.0 min Time	Factor IX units/vial 400 - 625	Factor IX units/mg Protein Specific IX Activity	Factor II units/vial 400 - 625	Factor X units/vial	Thrombin - Initial 0.00-0.001 u/ml	Thrombin - 3 hours 0.00-0.002 u/ml	
	011015	015018	019018	023018	033018	037018	039018	045023	250050	256051	261052	269053	329054	411064	413065	415064	417066	419067	421068	
6-24-76	0.584	-	-	-	-	-	-	6.40	96	268	0.94	-	Pass	590	1.01	-	-	Pass	Pass	
3/01/77	0.577	0	0	9	79	5	7	6.92	-	-	1.39	95.5	0.98	-	-	-	-	-	-	
7/11/77	0.614	0	0	7	81	4	8	6.95	-	-	1.21	96.5	2.0	597	0.97	519	686	<0.001	<0.001	
10-25-77	0.593	0	0	9	78	5	8	6.88	-	-	1.52	96.2	0.9	635	1.07	437	671	-	-	
1-23-78	0.595	0	0	8.7	77.7	5.2	8.3	6.98	-	-	1.11	95.9	1.75	638	1.07	493	690	-	-	
6-15-78	0.613	0	0	6	77	7	10	6.98	-	-	1.73	95.3	1.70	606	0.99	426	599	-	-	
1-25-79	0.598	0	0	10	76	6	8	7.00	-	-	-	95.3	1.70	635	1.06	449	610	-	-	
7-10-79	0.614	0	0	10	76	6	8	6.94	-	-	-	95.7	1.0	691	1.12	470	635	-	-	

UF 0073

PRODUCT TYPE: BFR1

STABILITY EVALUATION RECORD

CUTTER Laboratories, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GRO-C

APPROVED BY GRO-C

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size

Procedure CC# 63408, QAK-401, 902, 903, 904; BC240; QAG10-030

Storage Conditions 5°

Mfg. Lot No. M5542
Mfg. Date 6-24-76
Exp. Date 7-14-78
Mfg. Location Berkeley
Date on 1-05-77
Reason on Stability 50

$ Tests marked with dollar sign are done at initial and final test points only.

Time	NAPTT 1:10 NLT 60 Seconds	NAPTT 1:100 NLT 90 Seconds	Bio-Tests: Pyrogen Pass - Fail $	Bio-Tests: Safety Pass - Fail $	Initials/ Date											Comments
	123093	420090	528042	530012												
6-24-76	—	—	Pass	Pass	MJB 6-15-77											
3-02-77	—	—	—	—	MJB 6-15-77											
7-11-77	130	211	—	—	MJB 7-25-77											
10-25-77	115	214	—	—	MJB 11-3-77											
1-23-78	121	216	—	—	MJB 4/14/78											
6-15-78	129	243	Pass	Pass	MJB 9/15/78											
1-25-79	122	233	—	—	MJB 3/26/79											JAN 18 1979
7-10-79	127	246	Pass	Pass	MJB 9/24/79											DATA ENTRY

STABILITY EVALUATION RECORD

PREPARED BY GRO-C

APPROVED BY GRO-C

CUTTER *Laboratories, Inc.*
BIOLOGICAL PRODUCTS

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size 500 U (20ml); T1; 20mm Abt. Rubber
Procedure CC# 63408, QAK 901, 902, 903, 904, BC-140, QAB18-020
Storage Conditions 25°C

Mfg. Lot No. M5542
Mfg. Date 6-24-76
Exp. Date 7-14-78
Mfg. Location Berkeley
Date on 10-22-77
Reason on Stabil. 1 yr 25°

$ Tests marked with dollar sign are done at initial and final test points only.

Time	Chemical Testing: Protein gms/vial	Electrophoretic Pattern: γ-globulins %	B_2-globulins %	B_1-globulins %	α-globulins %	Albumin %	PRE Albumin %	pH Undiluted 6.40 - 7.40	Chloride 70 - 105 mEq/L $	Sodium 190-285 mEq/L $	Moisture 0.0 - 3.0%	Coagulation Testing: Clarity %T580 nm	Solubility Time 0.0 - 3.0 min	Factor IX 400-625 u/vial	Specific Activity Factor IX u/mg Protein	Factor II 300 - 600 units/vial	Factor X units/vial	Thrombin - Initial 0.00-0.001 u/ml	Thrombin - 3 hours 0.00-0.002 u/ml
	011015	015018	019018	023 018	033 018	037 018	039 018	045 023	250 050	256051	261052	269053	329054	411064	413065	415087	417066	419067	421068
6-24-76	0.594	-	-	-	-	-	-	6.90	96	268	0.94	-	Pass	590	1.01	-	-	Pass	Pass
12-21-77	0.605	<1	-	11	75.7	4.7	8.8	6.97	-	-	0.34	96	1.8	600	0.99	442	701	-	-
3-15-78	0.595	<1	0	11.2	74.7	5.6	8.4	6.95	-	-	1.51	96.2	1.1	603	1.01	484	601	-	-
4-20-78	0.593	0	0	9	77	6	7	6.95	-	-	-	96.4	1.0	582	0.98	428	585	-	-
																		-	-
8-20-78	0.593	0	0	10	77	5	8	6.92	-	-	2.25	95.9	1.1	629	1.06	396	742	-	-
10-20-78	0.599	0	0	9	79	4	8	6.89	-	-	2.16	96.4	1.2	526	1.38	455	652	-	-
12-15-78	0.546	0	0	10	76	6	8	6.91	-	-	2.40	95.7	1.8	721	1.2	440	659	-	-

JAN 18 1979

QAF 0073

STABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GR O-C

APPROVED BY GR O-C

PRODUCT TYPE: BFR1

Code No. 620 -20

Product Konyne® Factor IX Complex (Human)

Size

Procedure CC# 63408; QAF-901, 902, 903, 904; BC240; QAB10-000

Storage Conditions 25°C

Mfg. Lot No. M5542
Mfg. Date 6-24-76
Exp. Date
Mfg. Location
Date on
Reason on

$ Tests marked with dollar sign are done at initial and final test points only.

Time	Bio-Tests: NAOTT 1:10 NLT 60 Seconds	NAOTT 1:100 NLT 90 Seconds	Tyrosen Pass - Fail	Safety Pass - Fail	Initials/ Date	Comments
	4/23093	429090	528042	530042		
6-24-76	-	-	Pass	Pass	MJB 9/14/78	
12-21-77	123	231	—	—	MJB 9/14/78	
3-08-78	124	216	—	—	MJB 9/14/78	
4/20/78	128	210	—	—	LMB 9/28/78	
			—	—		
8-20-78	129	250	—	—	MJB 9/11/78	
10-20-78	126	222	Pass	Pass	MJB 11/17/78	
12/19/78	126	233	—	—	MJB 1/3/79	

JAN 1 8 1979

DATA ENTRY

CxF 0073

PRODUCT TYPE: BFR1

Remarks: Date of Mfg. based on last valid potency ASSAY. Lot shelf life -2 years, 2-8°C

ABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GR O-C

APPROVED BY GR O-C

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size 500 u (20ml), TT, 20 mm Nat. Rubber
Procedure CC# 63408, QAR-901, 902, 903, 904; BC 200; QA810-010
Storage Conditions 5°
USA, Product shelf life 2 YRS.

Mfg. Lot No. H5754
Mfg. Date 9-09-76
Exp. Date 10-04-78
Mfg. Location Berkeley
Date on 1-05-77
Reason on Stability 5°

$ Tests marked with dollar sign are done at initial and final test points only.

	Chemical Testing													Coagulation Testing						
		Electrophotetic Pattern																		
Time	Protein gms/vial	γ-globulins %	β_2-globulins %	β_1-globulins %	α-globulins %	Albumin %	PREALBUMIN %	pH Undiluted 6.40 - 7.40	Chloride 70-105 mEq/L $	Sodium 130-285 mEq/L $	Moisture 0.0 - 3.0%	Clarity FTS80 nm	0.0 - 3.0 min Time	Solubility units/vial	Factor IX 400 - 625 u/mg Protein	Specific IX units/vial	Factor II 300 - 600 units/vial	Factor X units/vial	Thrombin - Initial u 0.00-0.001 ml	Thrombin - 3 hours u 0.00-0.002 ml
Initial	011015	015018	019018	023018	033018	037018	039018	045013	250050	256051	261052	269053	329054	411064	413065	415089	417066	419067	421068
9-09-76	0.545	-	-	-	-	-	-	6.95	92	261	0.92	-	Pass	550	1.01	-	-	Pass	Pass
3/02/77	0.521	0	0	11	81.	3	6	6.98	-	-	1.36	94.2	0.89	-	-	-	-	-	-
9/12/77	0.570	0	0	11	79.	4	6	6.86	-	-	1.70	96	2.9	526	0.92	461	652	<0.001	<0.002
10/25/77	0.564	0	0	10	80.	3	7	7.00	-	-	1.36	96.5	1.40	640	1.13	443	624	-	-
3/15/78	0.580	0	0	10	80.	3	7	7.01	-	-	1.40	97.1	1.1	650	1.12	447	629	-	-
9/01/78	0.566	0	0	12	77.	4	7	6.99	-	-	1.41	96.2	1.0	653	1.05	440	614	-	-
3/01/79	0.567	0	0	10.5	78.6	3.7	7	6.97	-	-	1.61	96.	1.7	658	1.16	491	706	-	-
9/01/79	0.585	0	0	11.3	78.5	1	9.2	6.96	94	263	1.71	97.3	1.0	611	1.04	447	656	-	-

AF 0073

STABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY GRO-C

APPROVED BY GRO-C

Code No. 620 - 20

PRODUCT TYPE: BFR1

Product Konyne® Factor IX Complex (Human)

Size 500 u (30ml)
Procedure CCI 63408, QAK-901, 902, 903, 904; BC 240; QA 610-036
Storage Conditions 5°

Mfg. Lot No. M5754
Mfg. Date 9-01-76
Exp. Date 10-04-78
Mfg. Location Berkeley
Date on 1-03-77
Reason on Stability 5°

$ Tests marked with dollar sign are done at initial and final test points only.

Time	Bio-Tests: NAPTT 1:10 Clt 60 Seconds	Bio-Tests: NAPTT 1:100 Clt 90 Seconds	Bio-Tests: Pyrogen Pass - Fail $	Bio-Tests: Safety Pass - Fail $	Initials/ Date												COMMENTS
	423093	429070	528042	530012													
9-01-76	—	—	Pass	Pass	MJB 4/14/78												
3-02-77	—	—	—	—	MJB 4/14/78												
8-12-77	97	164	—	—	MJB 4/14/78												
10-25-77	91	154	—	—	MJB 4/14/78												
3-15-78	104	171	—	—	MJB 4/14/78												
9/01/78	113	194	Pass	Pass	MJB 10/9/78												
3/01/79	106	182	—	—	MJB 4/15/79												
9-18-79	89	149	Pass	Pass	MJB 11/5/79												

JAN 18 1979
DATA ENTRY

STABILITY EVALUATION RECORD

PREPARED BY GR O-C

CUTTER *Laboratories, Inc.*
BIOLOGICAL PRODUCTS

APPROVED BY GR O-C

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size 500U (20ml); T1; 20 mm Alat. Rubber

Procedure CC# 63408, QAK 901, 902, 903, 901; DC-240, QAQ10-040

Storage Conditions 25°C

Mfg. Lot No. MS 731
Mfg. Date 9-09-76
Exp. Date 10-11-78
Mfg. Location Berkeley
Date on 10-12-77
Reason on Stability 25°

$ Tests marked with dollar sign are done at initial and final test points only.

Done

Time	Protein gms/vial	Electrophoretic Pattern: γ-globulins %	B_2-globulins %	B_1-globulins %	α-globulins %	Albumin %	PRE Albumin %	pH Undiluted 6.40 - 7.40	Chloride 70 - 105 mEq/L $	Sodium 190-285 mEq/L $	Moisture 0.0 - 3.0%	Clarity %T580 nm	Solubility Time 0.0 - 3.0 min	Factor IX 400-625 u/vial	Specific Activity Factor IX u/mg Protein	Factor II 300 - 600 units/vial	Factor X units/vial	Thrombin - Initial 0.00-0.001 u/ml	Thrombin - 3 hours 0.00-0.002 u/ml
	011015	015018	019018	023 018	033 018	037 018	039 018	045 023	250 050	256051	261052	269053	329054	411 064	413065	415 089	417066	419067	421 068
9-09-76	0.545	-	-	-	-	-	-	6.95	92	261	0.92	-	Pass	550	1.01	-	-	Pass	Pass
2 mo 12-22-77	0.563	<1	-	11.2	77.6	2.8	7.5	6.97	—	—	1.27	96.5	1.25	607	1.08	472	655	-	-
4 mo 3-07-78	0.567	<1	-	11.9	77	4.2	6.9	6.95	—	—	1.41	96.6	1.5	623	1.10	480	618	-	-
6 mo 4/20/78	0.563	-	-	11	79	4	6	6.98	—	—	1.65	97.1	1.0	608	1.08	452	635	—	—
12 mo 9/20/78	0.563	0	0	10	78	5	7	6.91	—	—	2.32	97	0.75	647	1.05	484	625	—	—
10/20/78	0.565	0	0	15	77	2	6	6.92	—	—	2.41	97.1	0.88	655	1.16	491	557	—	—
12/15/78	0.566	0	0	9	80	4	7	6.91	—	—	2.36	96.8	1.7	664	1.17	440	648	—	—

CAF 0073

PRODUCT TYPE: BFR1

STABILITY EVALUATION RECORD

CUTTER *Laboratories*, Inc.
BIOLOGICAL PRODUCTS

PREPARED BY: GR O.C.

APPROVED BY: GR O.C.

Code No. 620 - 20

Product Konyne® Factor IX Complex (Human)

Size

Procedure CC# 63408; QAR-901, 902, 903, 904; BC240; QAB 18-020

Storage Conditions 25°C

Mfg. Lot No. M57541

Mfg. Date 7-01-76

Exp. Date 10-01-78

Mfg. Location Berkeley

Date on 10-22-76

Reason on

$ Tests marked with dollar sign are done at initial and final test points only.

Time	Bio-Tests: NLT 60 Sec. NIOTT 1:10	11LT 90 Seconds NAPTT 1:100	Pyrogen Pass - Fail $	Safety Pass - Fail $	Initials/ Date	Comments
	423083	429070	528042	530042		
9-01-76	–	–	Pass	Pass	M30 9/9/76 MJB	
12-22-77	97	161	–	–	4/4/78 MJB	
3-07-78	98	163	–	–	4/4/78 MJB	
4-20-78	101	161	–	–	5/04/78 MJB	
8-20-78	108	184	–	–	9/5/78 MJB	
10-20-78	102	170	Pass	Pass	11/14/78	
12-15-78	95	172	–	–		

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