CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020807

CHEMISTRY REVIEW(S)

Linear

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
DIVISION OF GASTROENTEROLOGY AND COAGULATION PRODUCTS-HFD-180

Review of Chemistry, Manufacturing and Controls

DEC 23 1997

NDA #: 20-807
CHEMISTRY REVIEW: # 2

DATE REVIEWED: 12-22-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Dec 31, 1996	Jan 02, 1997	Jan 07, 1997
AMENDMENT	Oct 02, 1997	Oct 03, 1997	Oct 14,1997
AMENDMENT	Nov 21, 1997	Nov 24, 1997	Dec 01, 1997
AMENDMENT	Dec 08, 1997	Dec 09, 1997	Dec 01,1997

NAME & ADDRESS OF APPLICANT: Behringwerke AG, Marburg, FRG

U.S. Agent: ClinTrials Research Inc.
P.O. Box 13991
Research triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:	Refludan®
Nonproprietary/Established/USAN:	Lepirudin
Code Name/#:	HBW 023, r-hirudin
Chem.Type/Ther.Class:	Type 1 Anticoagulant

ANDA Suitability Petition / DESI / Patent Status:
US Patent Number 5,180,668 covers the drug substance lepirudin and its therapeutic use as an anticoagulant. Expiration date: Jan 19,2010. Type of patent: Drug. Patent owner: Hoeschst AG, Frankfurt/ Main, Germany. US representative of the patent owner: Hoechst Marion Russel Inc., 10236 Marion park Drive. Kansas city, MO 64137-1405.

PHARMACOLOGICAL CATEGORY/INDICATION:
Anticoagulation in adult patients with heparin-associated thrombocytopenia (HAT) Type II and thromboembolic disease

DOSAGE FORM:	Sterile powder for injection or infusion
STRENGTHS:	50 mg vial)
ROUTE OF ADMINISTRATION:	Intravenous injection or infusion
DISPENSED:	_X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[Leu^1, Thr^2]-63-desulfohirudin
$C_{287}H_{440}N_{80}O_{111}S_6$
Average Molecular mass: 6,979.53 g/mol
See structural formula attached.

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

Comments:

This constitutes a full response to the AI letter. The company partially responded in Amendments dated October 2,1997 and Nov 21, 1997, both are reviewed here.

The Microbiology questions addressed by the company were sent to the Microbiology Division for consult and the microbiologists review recommends the approval from the standpoint of product quality microbiology. For specific comments refer to the attached review by Dr. Hughes dated Nov 25,1997.

In July 14, 1997 the company submitted an information amendment providing for a change in ownership of NDA 20-807, Refludan from Behringwerke AG, Marburg Germany to Hoechst Marion Roussel Deutschland GmbH (HMR, Germany, Frankfurt, Germany and to identify ClinTrials Research, Inc. , research Triangle Park, NC as HMR Germany's US agent for this NDA. This change in ownership is a result of a global restructuring by Hoechst AG and agreement to merge between Hoechst AG and Behringwerke AG. The effective date is August 15, 1997.

HMR, Germany stipulates that only changes following from this change of ownership are in the area of organization and that it will continue to manufacture Refludan (lepirudin) for injection using the same equipment, manufacturing procedures and methods, specifications and facilities as described in the original application.

An information amendment was submitted Aug 13, 1997 requesting categorical exclusion from Environmental Assessment and withdrawl of pending Environmental Assessment. They attest that the estimated concentration of lepirudin at the point of entry into the aquatic environment will be below 1 part per billion. They wave their claim for exclusion if a Fonsi was signed on or before August 28, 1997.

CONCLUSIONS & RECOMMENDATIONS:

The CMC additional information provided by the company in this response to the approvable letter are adequate. From the standpoint of chemistry, this application can now be approved. Response from the Microbiology section sent for consultation indicates that the NDA is recommended for approval from the standpoint of product quality microbiology. The company should provide the updated validation methods and the list of samples needed for validation of each of the analytical methods as was indicated to them previously.

/S/

William K. Berlin, Ph.D.
Review Chemist, HFD-510

/S/ 12/23/97

Maria Elena Ysern, MSc
Review Chemist, HFD-180

/S/ 12-23-97

Stephen Moore, Ph.D
Chemistry Team Leader, HFD-510

cc:
Org. NDA 20-807
HFD-180/Division File
HFD-180/MYsern
HFD-510/WBerlin
HFD-180/JDubeau
HFD-510/S.Moore

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
DIVISION OF GASTROENTEROLOGY AND COAGULATION DRUG PRODUCTS - HFD-180

Review of Chemistry, Manufacturing and Controls

NDA : 20-807
CHEMISTRY REVIEW : #1 DATE REVIEWED: 04-23-97 APR 30 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	Dec 31, 1996	Jan 02, 1997	Jan 07, 1997

NAME & ADDRESS OF APPLICANT: Behringwerke AG, Marburg, FRG

U.S. Agent: ClinTrials Research Inc.
P.O. Box 13991
Research Triangle Park, NC 27709

APPEARS THIS WAY
ON ORIGINAL

DRUG PRODUCT NAME

Proprietary:	Refludan®
Nonproprietary/Established/USAN:	Lepirudin
Code Name/#:	HBW 023, r-hirudin
Chem.Type/Ther.Class:	Type 1 Anticoagulant

ANDA Suitability Petition / DESI / Patent Status:
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APPEARS THIS WAY
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CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[Leu^1, Thr^2]-63-desulfohirudin

$C_{287}H_{440}N_{80}O_{111}S_6$

Average Molecular mass: 6,979.53 g/mol

See structural formula attached

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

CONSULTS:
This NDA was consulted to the Division of Metabolic and Endocrine Drug Products, HFD- 510, for the CMC review to be done jointly with Division of Gastrointestinal and Coagulation Drug Products. HFD-180.

The Environmental Assessment was sent for review to the Environmental Assessment division, on 2/10/1997, since Lepirudin is a New Molecular Entity. The deficiencies will be incorporated to in the letter to the company.

The Microbiology section was sent for review to the Microbiology Division on 02//97.

Stability data was consulted to the Division of Biometrics, HFD-720, for verification of the Expiry date.

A request for Trademark Review was submitted to the Labeling an Nomenclature Committee, on 2/7/97. The Labeling and Nomenclature Committee noted five look-alike/sound alike conflicts: Relafen, Rifadin, Rifampicin, Diflucan and Fludara, but the Committee feels there is a low potential for confusion. The word sterile is no longer used by USP in monograph titles. The appropriate established name for this product should be "lepirudin for injection" to be in conformance with USP parenteral nomenclature.

REMARKS/COMMENTS:
This application is submitted for the approval of lepirudin for anticoagulation in adult patients with heparin associated thrombocytopenia (HAT) type II and thromboembolic disease. HAT type II is a rare disease, occurring in approximately 54,000-180,000 patients in the US annually.

Naturally occurring hirudin (and the recombinant Lepirudin) inactivates thrombin by blocking the substrate (fibrinogen) binding following the formation of a 1:1 stoichiometric non-covalent complex. Lepirudin activity has been standardized as a function of thrombin activity, expressed in international WHO units according to the following: one anti-thrombin unit (ATU) of lepirudin is the amount required to neutralize 1U (WHO preparation 89/588) of thrombin at 37°C. Lepirudin is a recombinant protein, whose structure is based on the naturally occurring thrombin inhibitor hirudin. Lepirudin is produced in yeast cells which are transfected with an expression vector containing the hirudin gene. Lepirudin is composed of 65 amino acids and has a molecular weight of approximately 7000 Daltons. The biosynthetic molecule is identical to hirudin except for the substitution of leucine for isoleucine at the N-terminal end of the molecules and the absence of a sulfate group on the tyrosine at position 63.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint, this application can be approved, pending satisfactory response to minor chemistry deficiencies and satisfactory EER, which is pending.

Chemistry comments are detailed in the draft letter. Issue an information request letter.

/S/ 4/30/97

William K. Berlin, Ph.D.

/S/ 4/30/97

Maria E. Ysern, Msc
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 4/30/97

Stephen Moore, Ph.D.
Chemistry Team Leader, HFD-510

cc:
Org. NDA 20-807
HFD-180/Division File
HFD-180/MYsern
HFD-510/WBerlin
HFD-180/JDubeau/MFolkendt
HFD-510/S. Moore
HFD-820/JGibbs
HFD-180/EDuffy

APPEARS THIS WAY
ON ORIGINAL

R/D Init by: SMoore

Filename: Original.001

MY/dob **F/T 4/30/97/WP**: c:\wpfiles\chem\N\20807001.1my

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

Date: MAY 28 1997

NDA#	20-807
Applicant:	ClinTrials Research, Inc.
Name of Drug:	Refludan (lepirudin) Sterile Powder for Injection or Infusion
Statistical Reviewer:	Moh-Jee Ng (HFD-715)
Chemist:	Maria Ysern (HFD-180)
Date received by reviewer:	April 1, 1997
Data received by reviewer:	May 5, 1997
Volumes Reviewed:	13.176; 1 SAS data set diskette; May 12, 1997

Summary

. The sponsor proposed a 24-month expiry date based on 24-month data for Refludan stored at temperatures +10°C and +25°C.

. The proposed 24-month expiration date is supported by these data using both the sponsor's analysis and verified by this review.

I. Introduction

The sponsor submitted the results of the stability report on Refludan finished product. In this stability study, the storage temperatures were +10°C and +25°C. Three variable tests were performed 1) content , (2) related proteins and 3) potency. The three batches were 616 114 011, 616 116 011 and 616 120 011, and the test intervals were 0, 1, 3, 6, 9, 12, 18 and 24 months.

The data were provided by the sponsor on a 3.5 floppy diskette. The statistical method used by the sponsor is in accordance with the FDA's 'Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics" (February 1987). The sponsor used the FDA program.

II Sponsor's Results and Reviewer's Comments

Sponsor's analysis of covariance results are presented separately for the storage temperatures of +10°C and +25°C .

Table 1 and 2 below summarized the sponsor's results for storage temperature of +10°C and +25°C, respectively. The results support the sponsor proposal for an expiration period of 24 months. The sponsor's results have been verified by this reviewer.

Table 1
The stability of finished product at +10°C

Parameter	Label Claim	Specification Limits	Confidence Limit Approach	Batch	Regression Lines	Model Selection	Expiration Date
Content	50 mg		Lower 95% CL	114	Y=102.3690-0.076X	S*	84
				116	Y=101.0191-0.076X		84
				120	Y= 97.8940-0.076X		64
Potency	800,000 ATU		2-sided 95% CL	All			82
Related Proteins	-		Upper 95% CL	114	Y=2.9205+0.04063X	S*	65
				116	Y=2.3393+0.04063X		77
				120	Y=2.8856+0.04063X		66

S*: Separate intercepts and common slope
LS*: common intercept and common slope

Table 2
The stability of finished product at +25°C

Parameter	Label Claim	Specification Limits	Confidence Limit Approach	Batch	Regression Lines	Model Selection	Expiration Date
Content	50 mg		Lower 95% CL	114	Y=100.6713-0.0928X	S*	74
				116	Y= 99.5713-0.0928X		67
				120	Y= 97.1713-0.0928X		50
Potency	800,000 ATU		2-sided 95% CL	All			81
Related Proteins	-		Upper 95% CL	114	Y=2.9859+ .0899X	S*	30
				116	Y=2.4134+0.0899X		36
				120	Y=2.9984+0.0899X		30

S*: Separate intercepts and common slope
LS*: common intercept and common slope

APPEARS THIS WAY
ON ORIGINAL

III Conclusion

The sponsor proposed a 24-month expiry date based on 24-month data for Refludan stored at temperatures +10°C and +25°C is supported by these data using both the sponsor's analysis and verified by this reviewer.

APPEARS THIS WAY
ON ORIGINAL

Moh-Jee Ng
/S/
Operation Research Analyst

Concur: Dr. Huque /S/
for Dr. Smith /S/ 5/28/97
Dr. Nevius 5/28/97

APPEARS THIS WAY
ON ORIGINAL

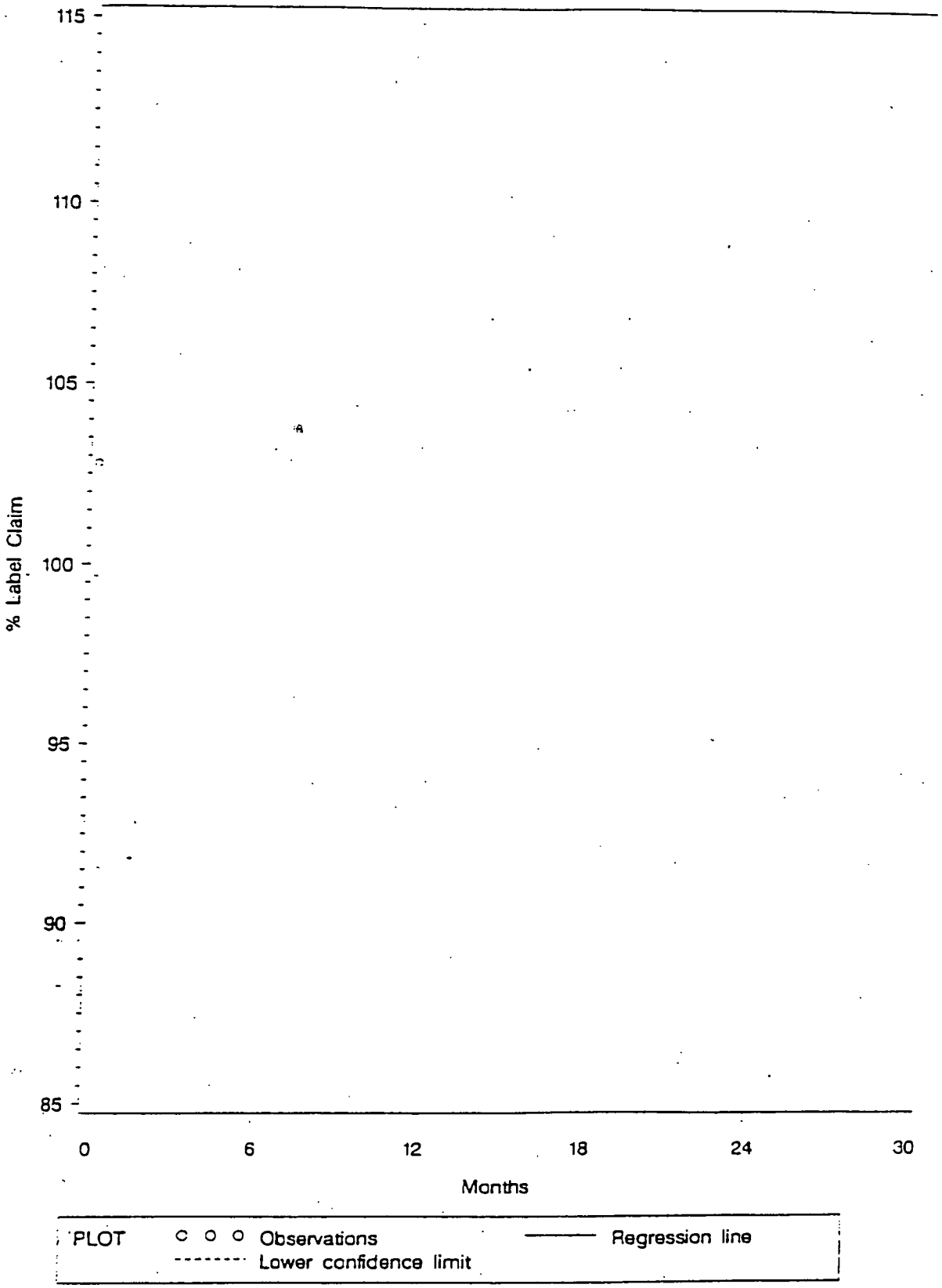
cc:
Orig. NDA 20-807
HFD-180/ Division Files
HFD-180/ Dr. Talarico
HFD-180/ Mr. Folkendt
HFD-180/ Dr. Ysern
HFD-720/ Dr. Smith
HFD-720/ Dr. Huque
HFD-715/ Division File, Chron
HFD-715/ Dr. Nevius, Ms. Ng

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

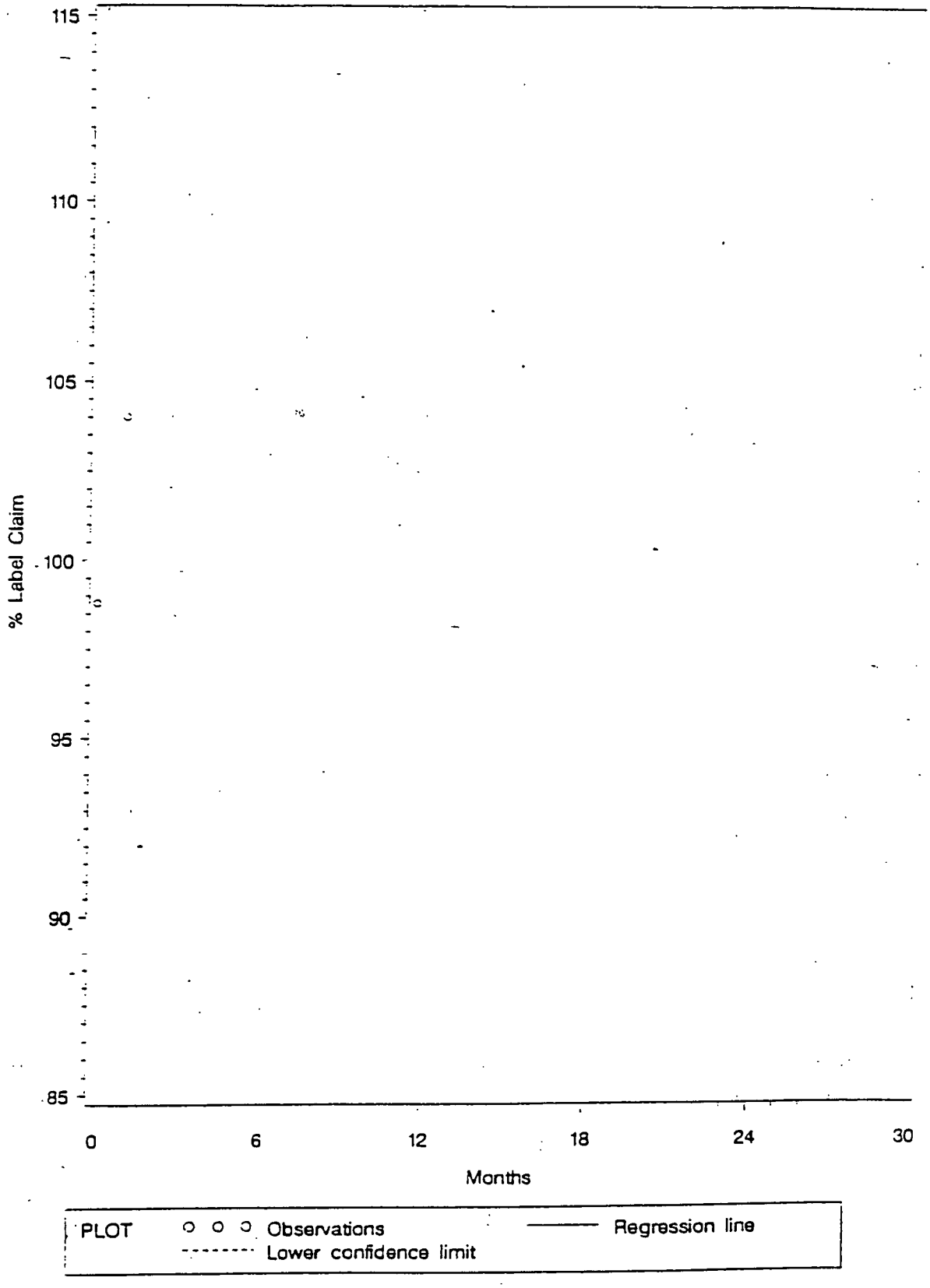
Content of finished product
Behringwerke AG

r – Hirudin 10 deg Celsius
BATCH = 114



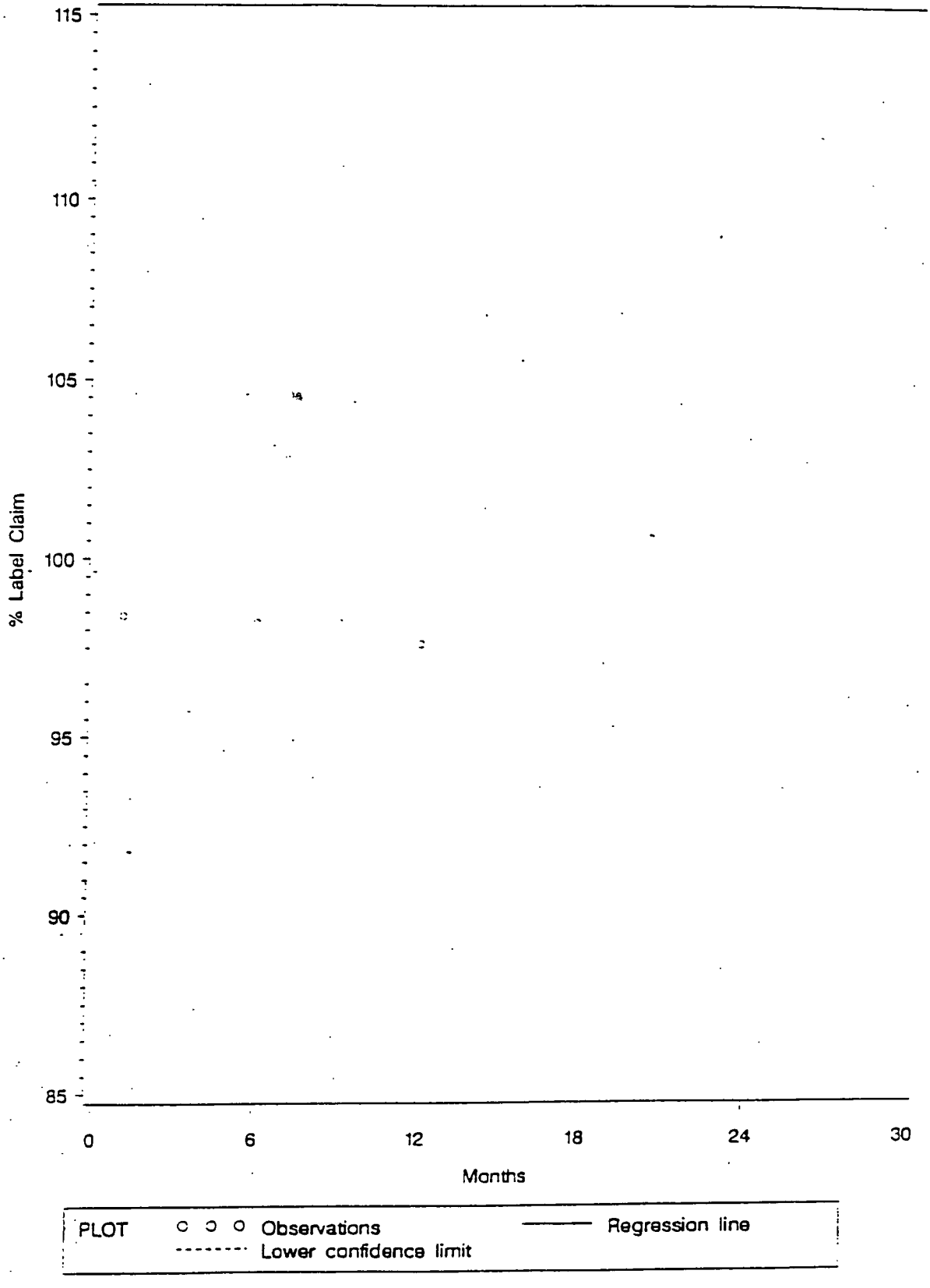
Content of finished product
Behringwerke AG

r-Hirudin 10 deg Celsius
BATCH=116



Content of finished product
Behringwerke AG

r – Hirudin 10 deg Celsius
BATCH = 120



Potency of finished product
Behringwerke AG

r – Hirudin 10 deg Celsius
BATCH = All

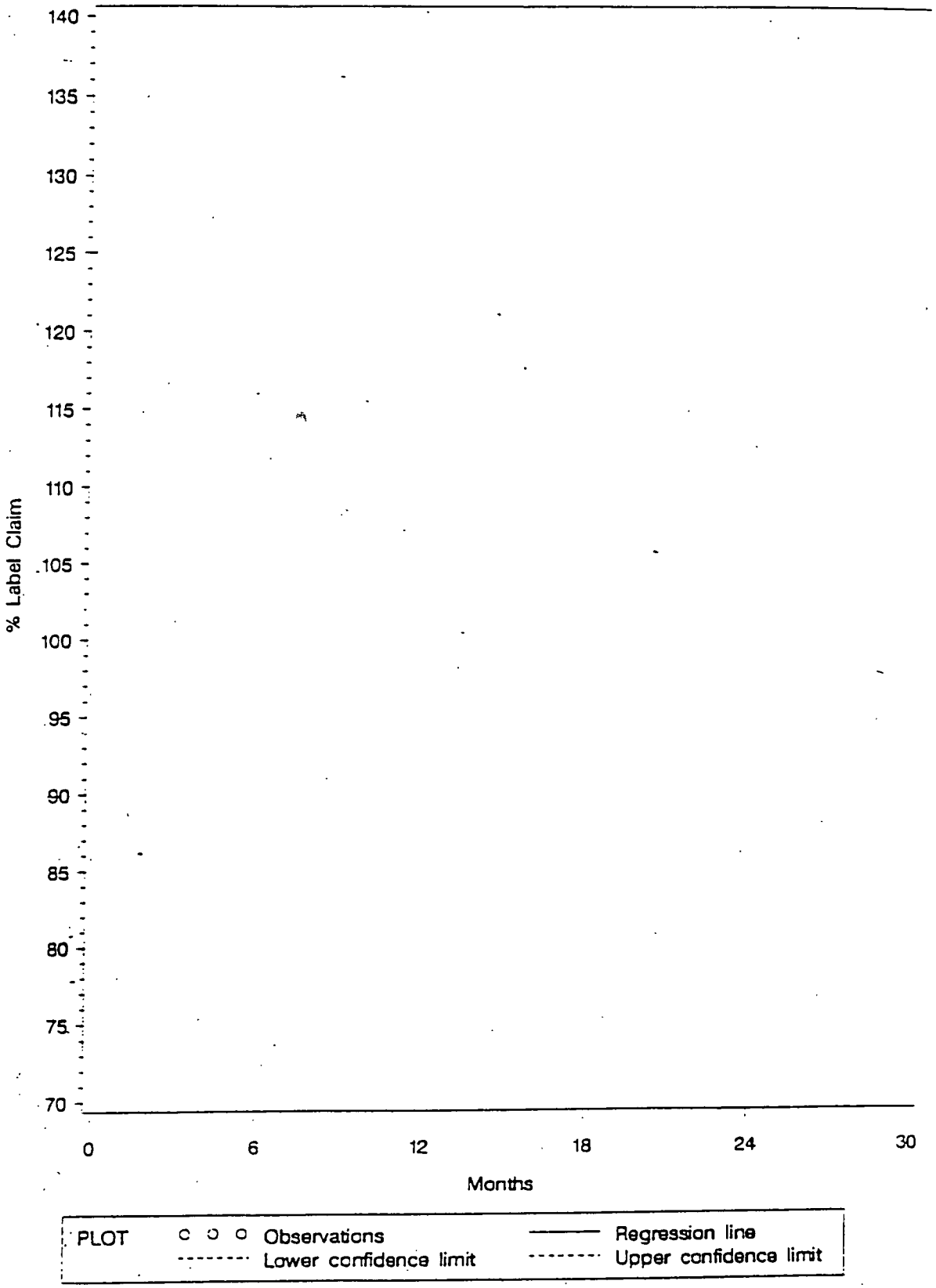
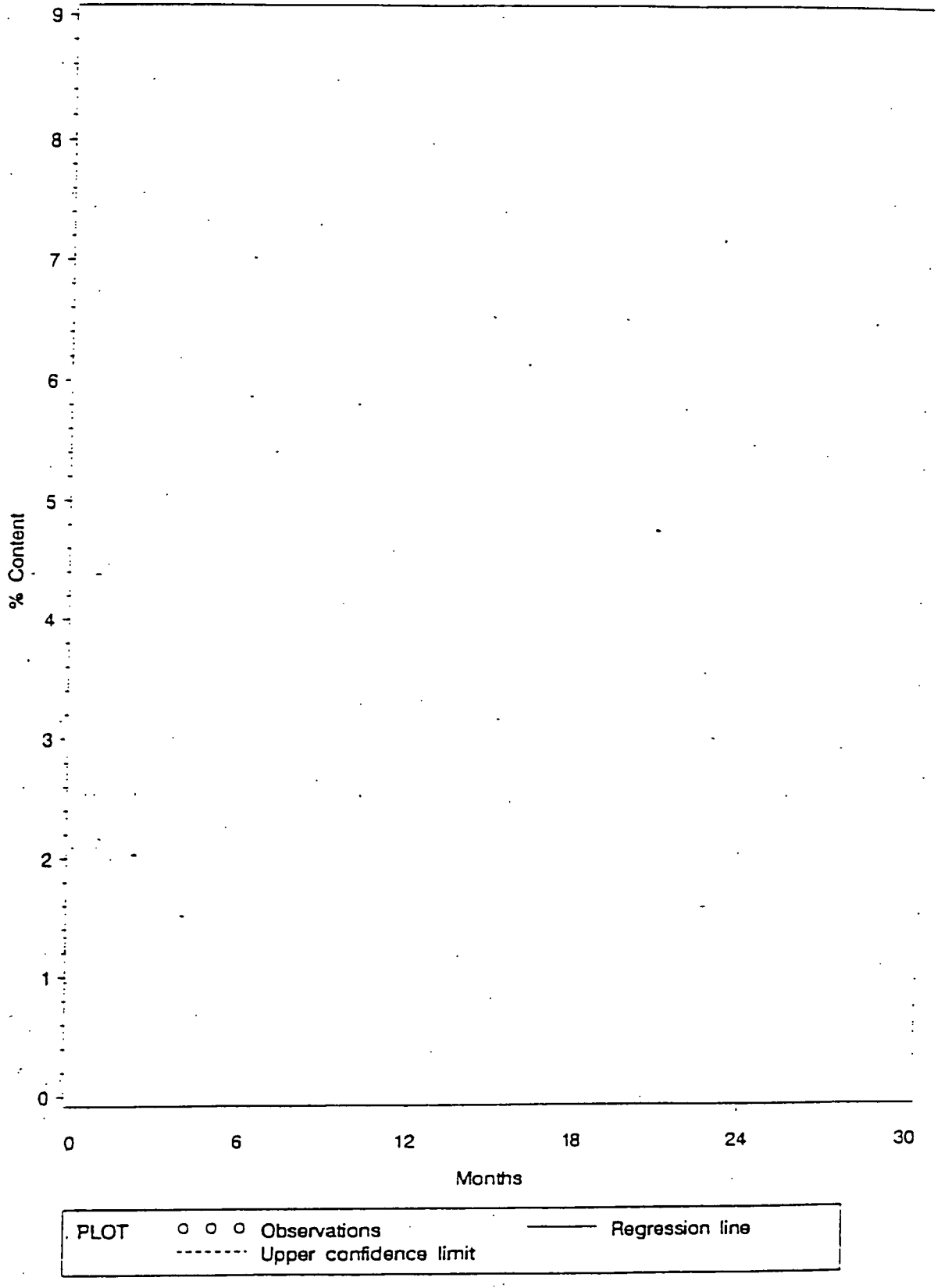


Figure 5

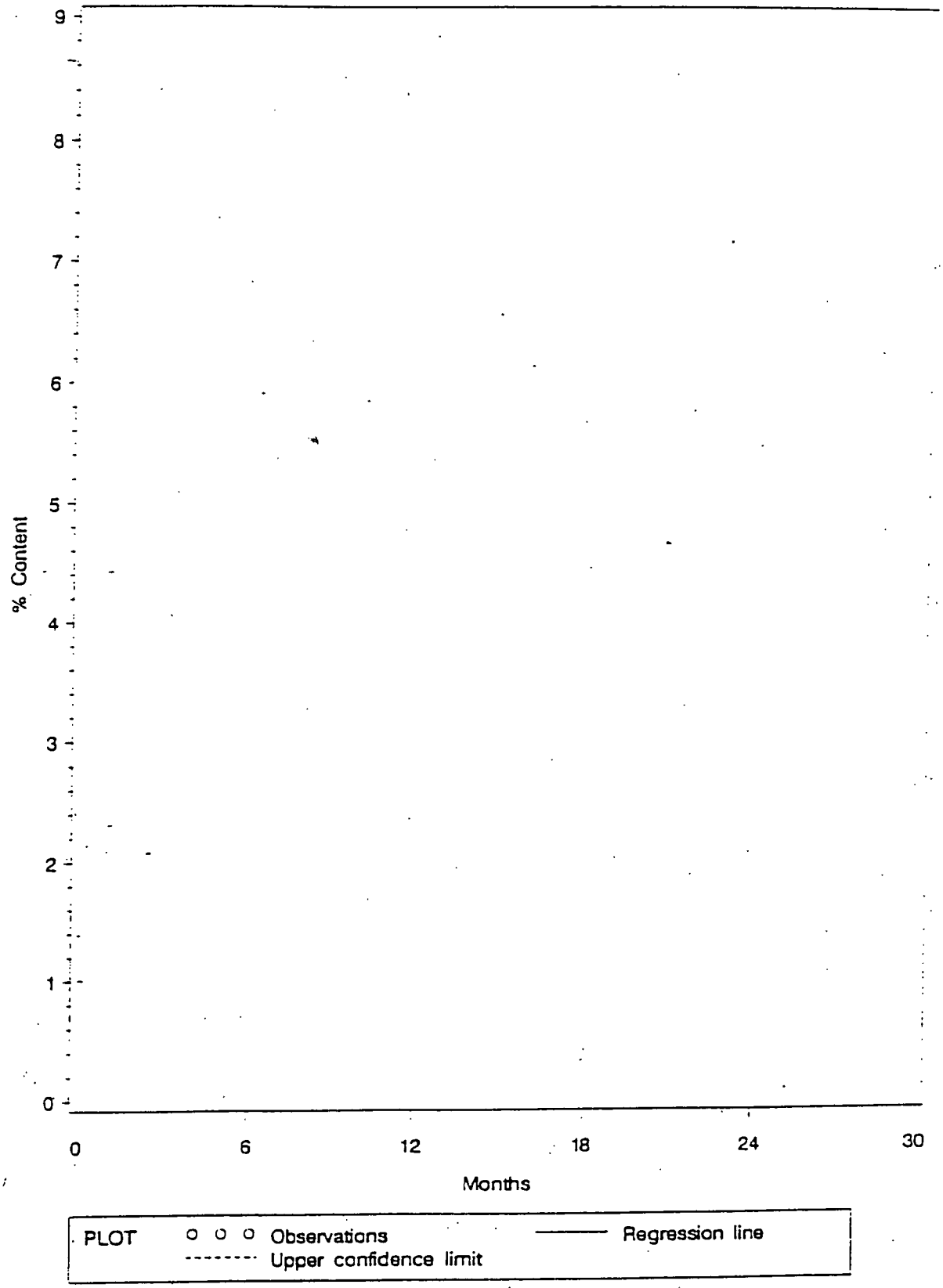
Related proteins in finished product
Behringwerke AG

r – Hirudin 10 deg Celsius
BATCH = 114



Related proteins in finished product
Behringwerke AG

r – Hirudin 10 deg Celsius
BATCH = 116



Related proteins in finished product
Behringwerke AG

r-Hirudin 10 deg Celsius
BATCH=120

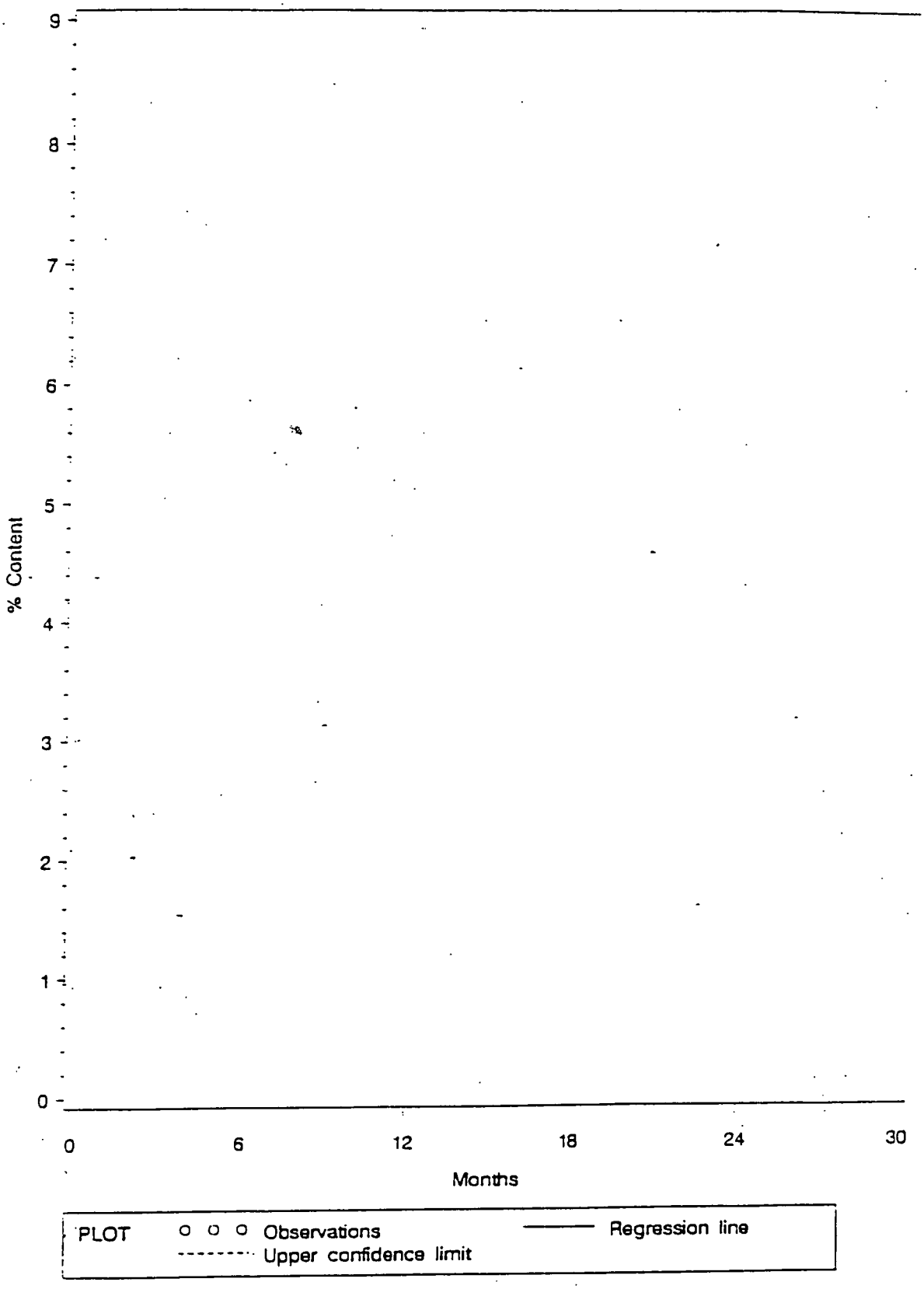
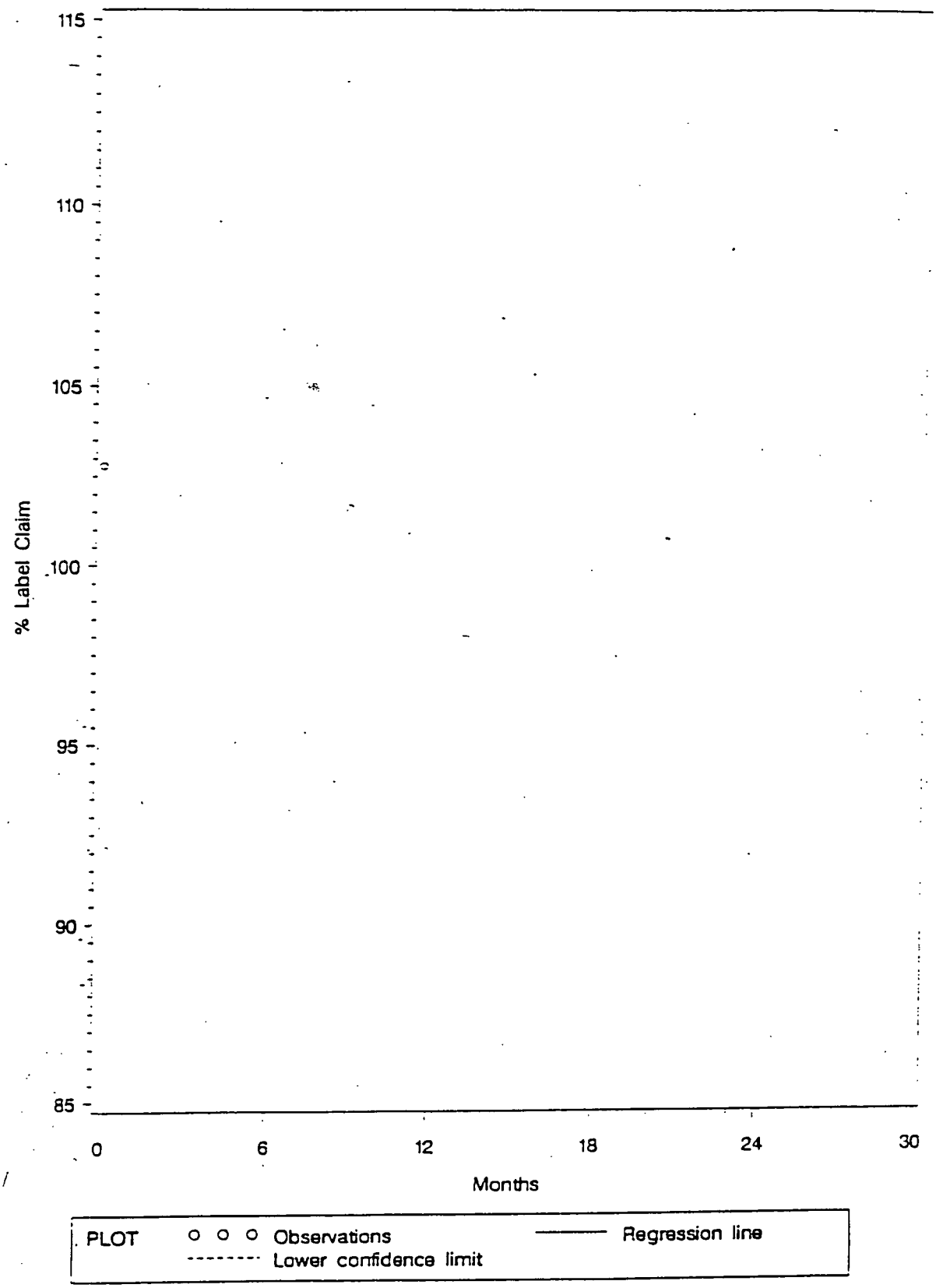


Figure 8

Content of finished product
Behringwerke AG

r-Hirudin 25 deg Celsius
BATCH=114



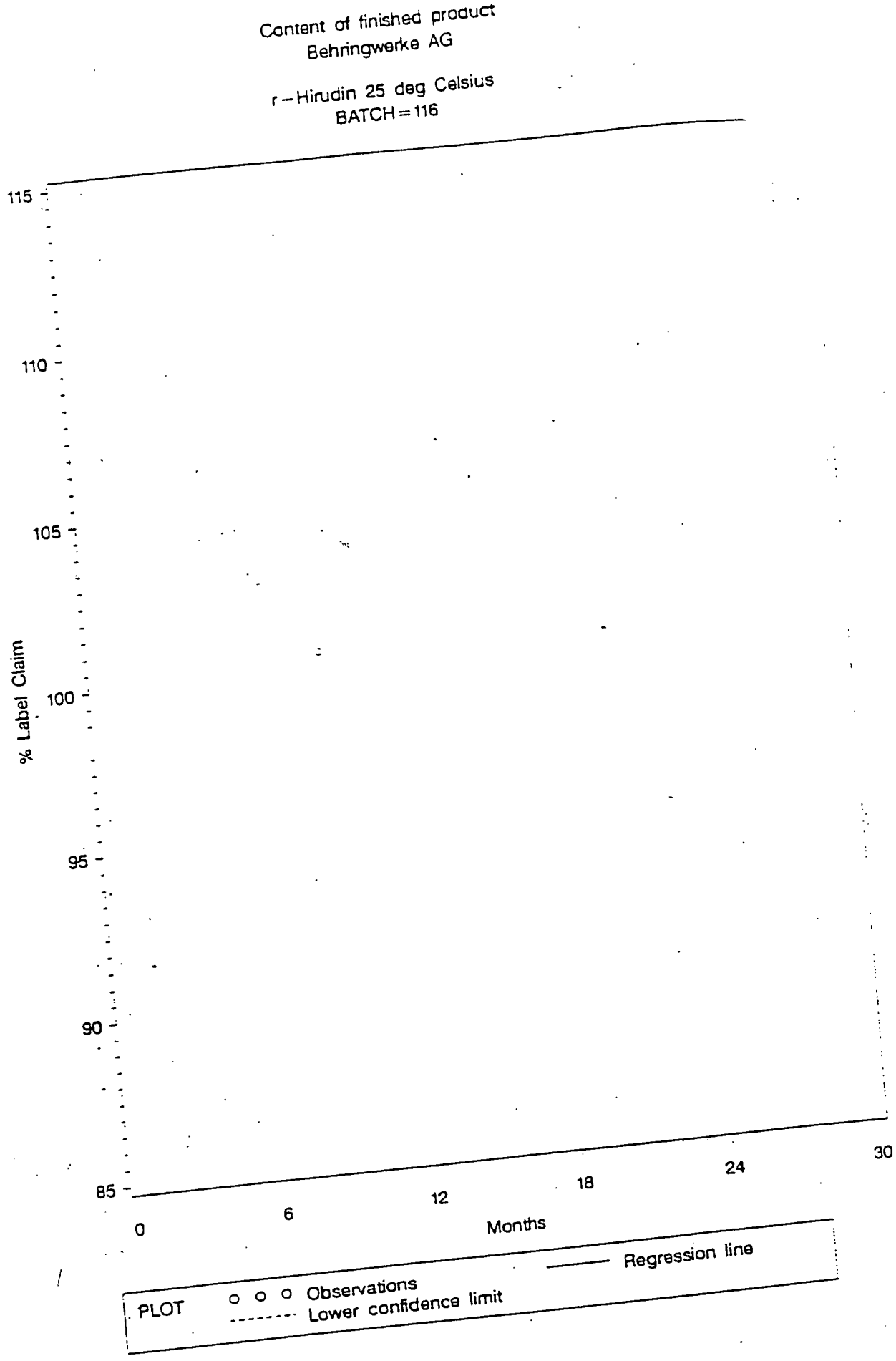
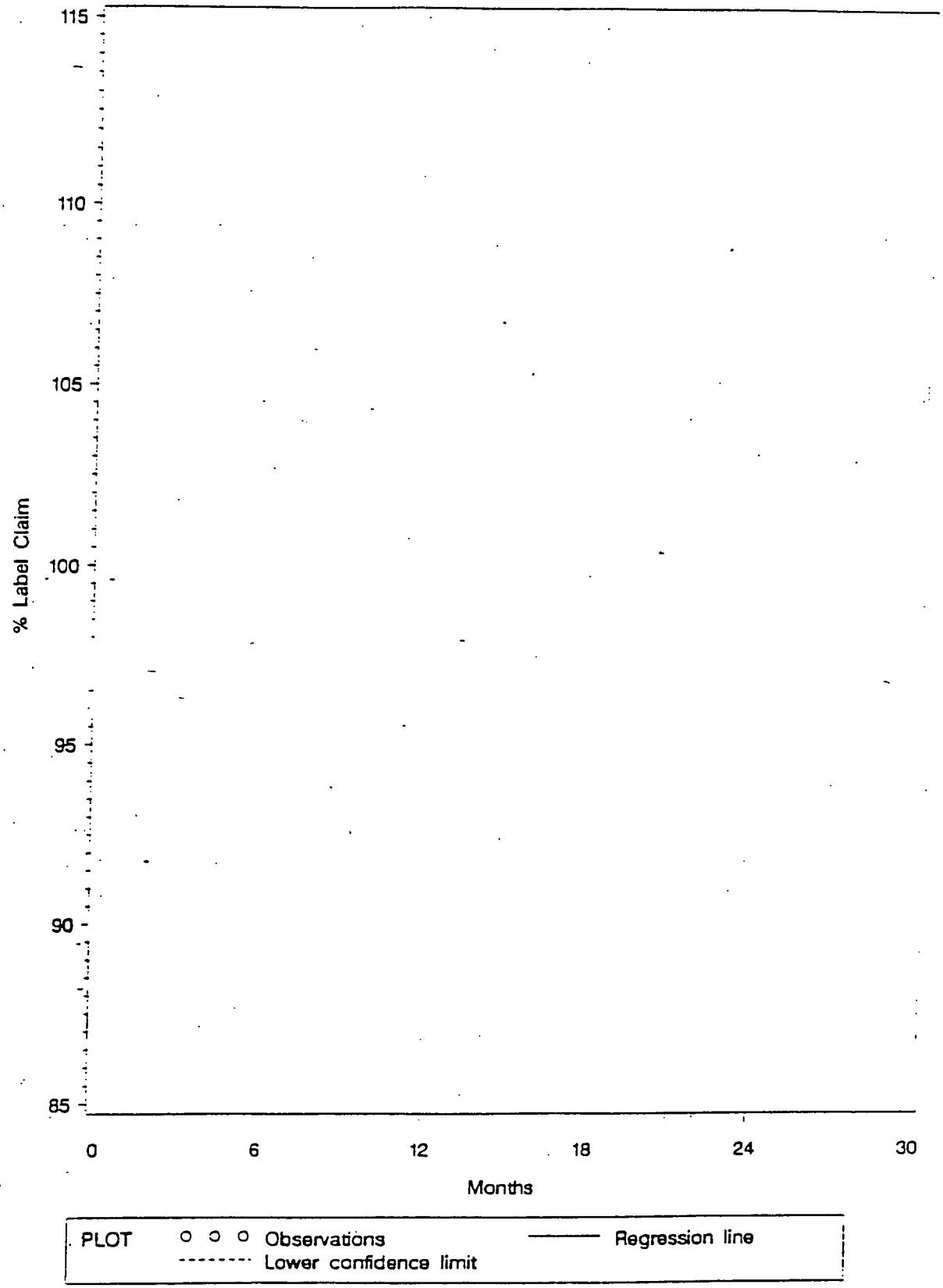

Content of finished product
Behringwerke AG
r-Hirudin 25 deg Celsius
BATCH=116
115
110
105
100
95
90
85
% Label Claim
0
6
12
18
24
30
Months
PLOT
Observations
Lower confidence limit
Regression line

Figure 10

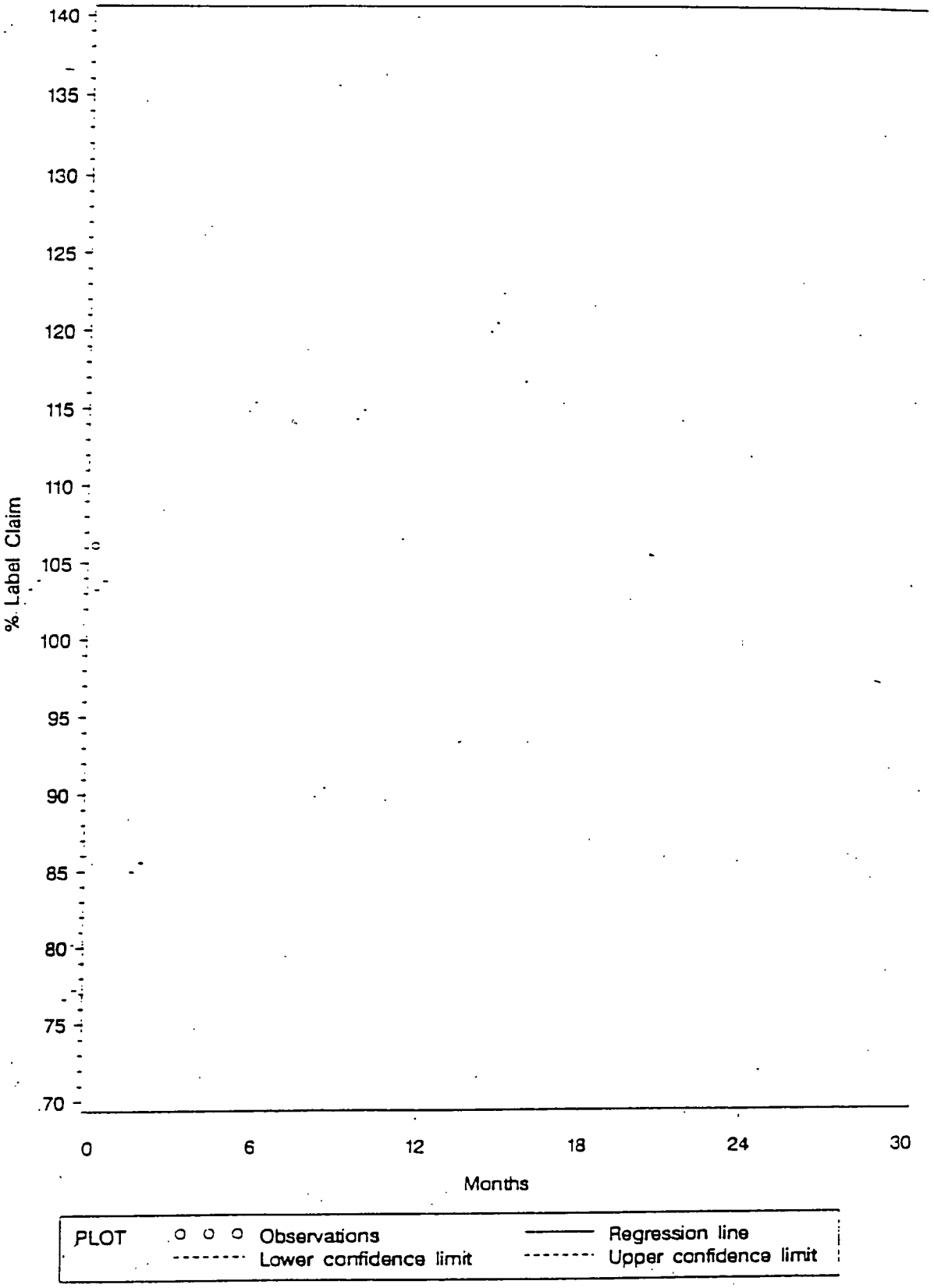
Content of finished product
Behringwerke AG

r – Hirudin 25 deg Celsius
BATCH = 120



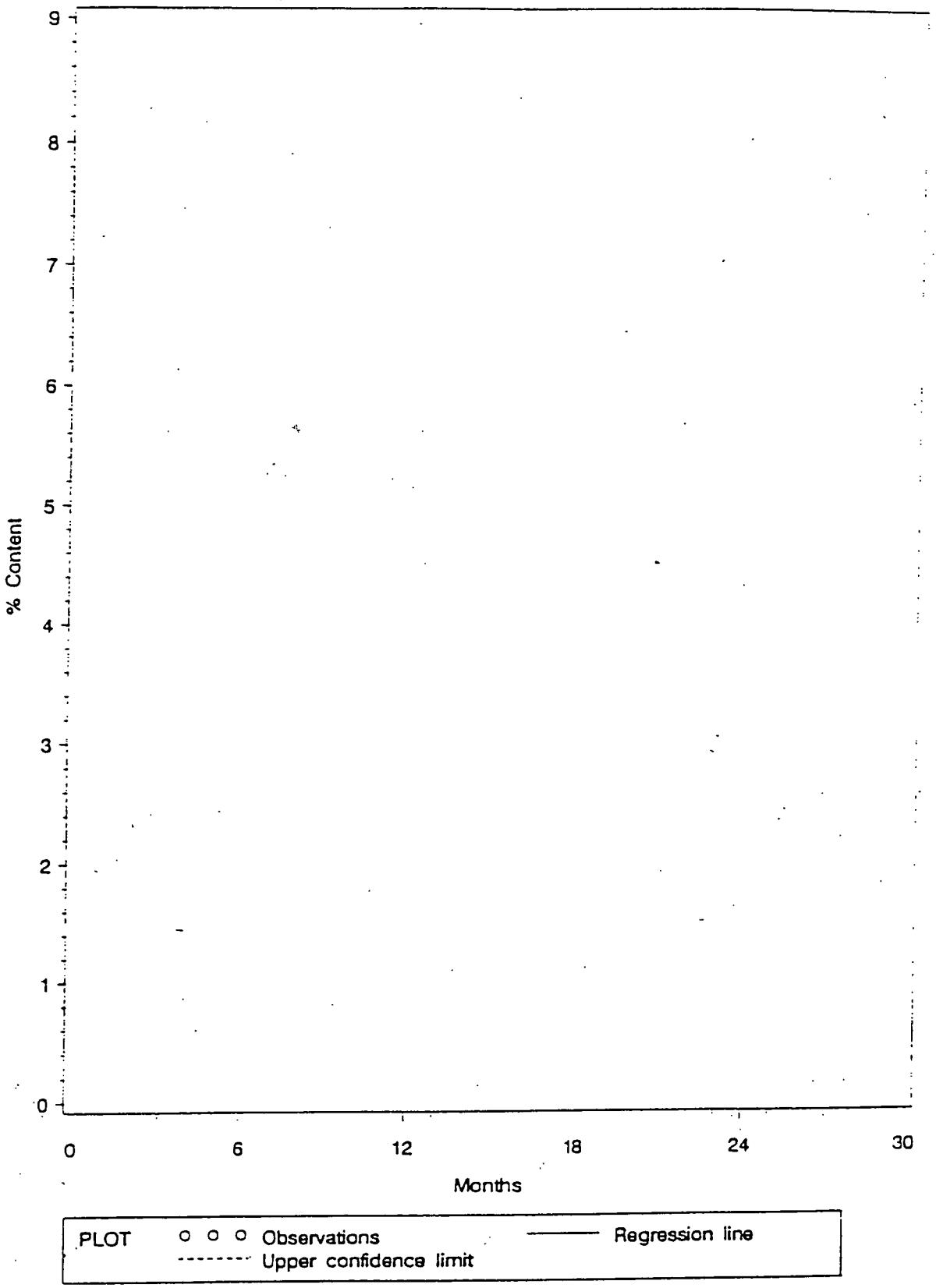
Potency of finished product
Behringwerke AG

r – Hirudin 25 deg Celsius
BATCH = All



Related proteins in finished product
Behringwerke AG

r-Hirudin 25 deg Celsius
BATCH = 114



Related proteins in finished product
Behringwerke AG

r-Hirudin 25 deg Celsius
BATCH=116

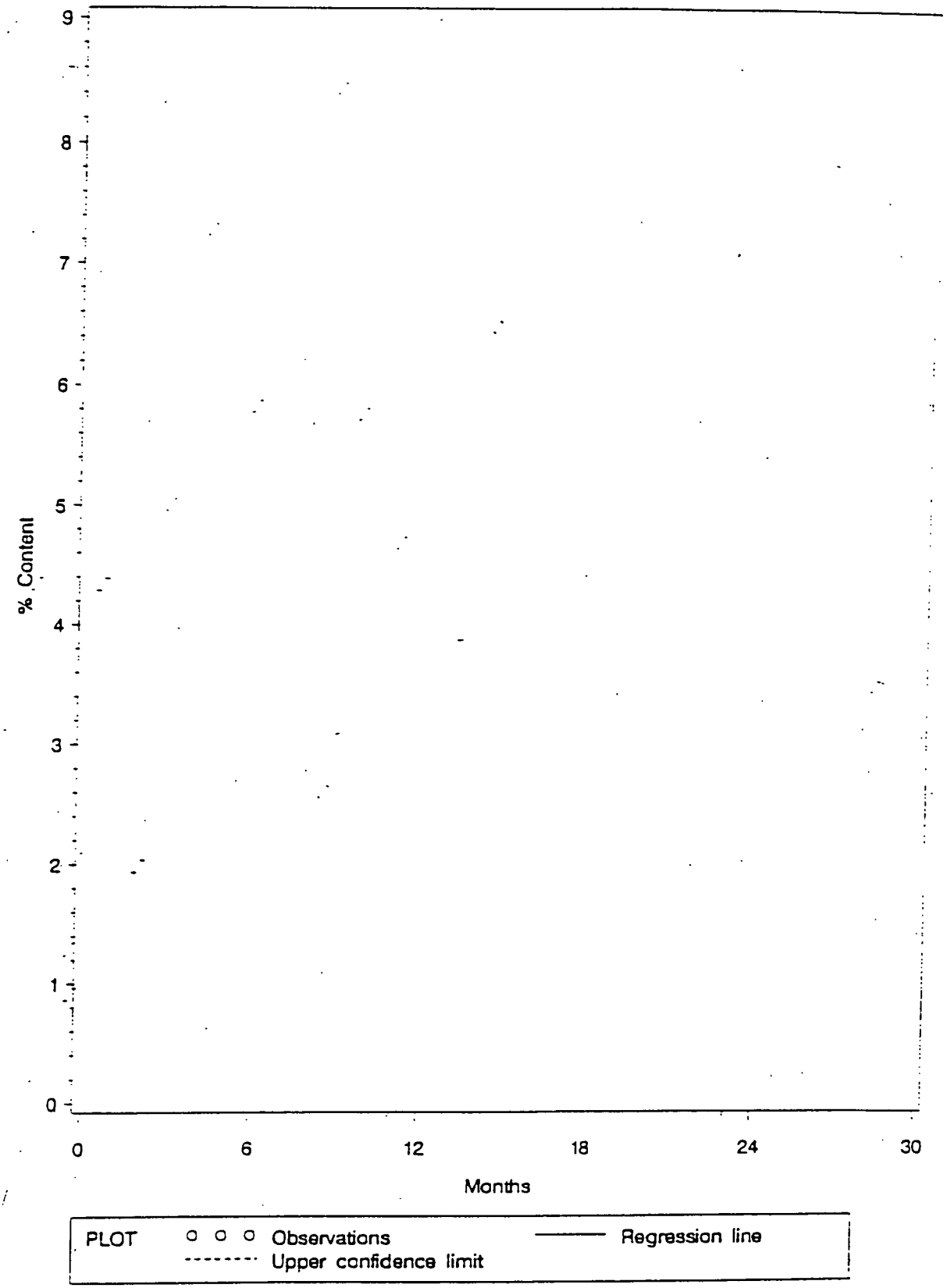


Figure 14

Related proteins in finished product
Behringwerke AG

r-Hirudin 25 deg Celsius
BATCH=120