CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986/SE3-003

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-510)

APPLICATION #:	**#20986**	**APPLICATION TYPE:**	**NDA: Supplement**
SPONSOR:	**NovoNordisk**	**PROPRIETARY NAME:**	**NovoLog**
CATEGORY OF DRUG:	**Diabetes** **Insulin analogue**	**USAN / Established Name:** **ROUTE:**	**X-14, Insulin aspart** **SQ infusion via external pump**
MEDICAL REVIEWER:	**Elizabeth Koller**	**REVIEW DATE:**	**12/20/01**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/20/00	12/21/00	SE3-003	
2/7/01	2/8/01	SE3-003 C	
2/28/01	2/28/01	SE3-003 IN	
3/6/01	3/6/01	SE3-003 IN	
3/7/01	3/7/01	SE3-003 IN	
3/22/01	3/23/01	N-000 C	Comments on spreadsheet request
6/21/01	6/22/01	SE3-003 BM	EXCEL spread sheets
8/29/01	8/29/01	SE3-003 IN	
10/5/01	10/5/01	P-004	Adverse event reports suggesting injection/infusion site reactions, insulin instability, and infusion set occlusion
10/24/01	10/25/01	SE3-003 BL	
10/25/01	10/26/01	SE3-003 BC	
12/11/01	12/13/01	SE3-003 BL	
12/12/01	12/13/01	SE3-003 BL	
12/17/01	12/17/01	SE3-003 IN	
12/18/01	12/20/01	SE3-003 C	
12/19/01	12/20/01	SE3-003 BL	
12/21/01	12/21/01	SE3-003 IN	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
12/21/99	NDA #20563 SE3-024	Pump supplement
Multiple	NDA #20563 Periodic reports	Adverse events
Multiple	IND [redacted]	[redacted]

Overview of Application/Review:

Three, randomized, open-label, parallel-design studies of varying lengths were conducted in the U.S. in adult patients with variable degrees of diabetic control. Pump studies comparing glycemic control (HgbA1c) using different types of insulin were conducted in IDDM patients already familiar pump therapy. Studies in NIDDM patients new to intensive insulin therapy were conducted to compare glycemic control (HgbA1c) using X-14 injection versus X-14 infusion therapy. The design of the clinical studies differed substantively from standard

medical practice and typical use in real life, with more frequent changes of insulin, infusion sets, and infusion sites, Glycemic control and rates of hypoglycemia were comparable for the various treatment arms in all three studies. The data from the smallest study (018; n=29) suggested that the time to infusion set failure/occlusion was shorter and the number of infusion set changes greater in the X-14 treatment arm than in the buffered human insulin arm. Although data on infusion set changes were also collected in the two, larger studies, these data were not provided. In addition, even though *in vitro* data indicated that X-14 consistently failed in the Mini-Med 506 pump on day 3, no correlation with the clinical data could be made because there were no records of the specific pumps used by individual patients.

Outstanding Issues:.

1-X-14 can be approved for use in specific pumps with specific infusion sets. Approval cannot be extrapolated to other equipment. The X-14 insulin, infusion sets, and infusion sites may be used for up to 48 hours.

2-Because the design of the clinical studies differed substantively from standard medical practice and typical use in real life, with more frequent changes of the insulin, infusion sets, and infusion sites, the consequences of such deviations from recommendations should be delineated in both the physician and patient labels. Because current standard practice reflects the large reservoir size, the software restrictions for reducing the amount of insulin inserted into the reservoir, and pump manufacturers' printed instructions (including changing tubing every three days), the physician and patient labels must clearly indicate that the directions for the specific use of X-14 in pumps supercede the manufacturers' general guidelines.

3-The sponsor should collect information on actual-use either in a phase four study in which insulin and infusion sets are not provided or via collection of adverse event data systematically using a questionnaire specifically designed to identify the causes of pump-insulin problems.

4-New pump guidelines should be developed.

Recommended Regulatory Action:

New Clinical Studies: _____ **Clinical Hold** _____ **Study May Proceed**

NDAs:

Efficacy / Label Supp.: with label changes & appropriate follow-up of pump/insulin malfunction **Approvable**

_____ _____ **Not Approvable** _____

Signed: **Medical Reviewer:** /S/ Elizabeth Koller, M.D. **Date:** 12/2101

Medical Team Leader: _____ **Date:** _____

APPEARS THIS WAY
ON ORIGINAL

1.-Medical Officer Review

1.1.-Administrative summary

1.1.1.-NDA: #20986 SE3

1.1.2.-Review: #1

1.1.3.-Submissions:

1.1.3.1.-Paper submission:12/21/00

1.1.3.2.-CANDA submission: none

1.1.3.3.-Major amendment: none

1.1.3.4.-Other submissions:

2/7/01 SE3-003 C
2/28/01 SE3-003 IN
3/6/01 SE3-003 IN
3/7/01 SE3-003 IN
3/22/01 N-000 C comments on spread sheet request
6/21/01 SE3-003 BM Excel spread sheets
8/29/01 SE3-003 IN
10/5/01 P-004 adverse event reports suggesting skin reactions, insulin instability, & infusion set occlusion
10/24/01 SE3-003 BL
10/25/01 SE3-003 BC
12/11/01 SE3-003 BL
12/12/01 SE3-003 BL
12/17/01 SE3-003 IN
12/18/01 SE3-003 C
12/19/01 SE3-003 BL
12/18/01 SE3-003 IN

1.1.3.5.-Review completed: 12/21/01

1.2.-Drug name

1.2.1.-Generic name: insulin aspart

1.2.2.-Trade name: NovoLog

1.3.-Sponsor: NovoNordisk

1.4.-Pharmacologic category: diabetes, insulin analogue

1.5.-Proposed indication: use in external pumps for subcutaneous infusion

1.6.-Dosage form and route-of administration:

1.6.1.-Dosage form: vials for extraction of insulin that is to be put into a pump reservoir

1.6.2.-Dosage: to be titrated using pre-prandial boluses and basal rates of continuous infusion

1.6.3.-Route-of-administration: subcutaneous infusion

1.7.-NDA drug classification: standard

1.8.-Important related drugs: human insulin (semi-synthetic and recombinant)
Lilly buffered human insulin, BR
(approved; no longer marketed)
NovoNordisk buffered human insulin, Velosulin
lispro

1.9.- Related reviews: NDA #20563 pump reviews and adverse event reports

1.10.-Materials reviewed:

1.10.1.-NDA #20986

12/20/000 SE3-003 (38 volumes)
2/7/01 SE3-003 C
2/28/01 SE3-003 IN
3/6/01 SE3-003 IN
3/7/01 SE3-003 IN
3/22/01 N-000 C comments on spread sheet request
6/21/01 SE3-003 BM Excel spread sheets
8/29/01 SE3-003 IN
10/5/01 P-004 adverse event reports suggesting skin reactions, insulin instability, & infusion set occlusion
10/24/01 SE3-003 BL
10/25/01 SE3-003 BC
12/11/01 SE3-003 BL
12/12/01 SE3-003 BL
12/17/01 SE3-003 IN
12/18/01 SE3-003 C
12/19/01 SE3-003 BL
12/18/01 SE3-003 IN

1.10.2.-Other

Draft pump guidance (1985) (appendix 1)
Velosulin label
Pump questionnaire developed by Dr. Koller in response to questions raised by A. Morrison (Devices) and adverse event reports; 10/10/99
Internal e-mail regarding composition of tubing and needles for various infusion sets (P. Cricenti and V. Nakayama; 11/28/00)
Mini-Med pump video and print information
Disetronic pump video and print information
Pump chat room

1.10.3.-Safety update: none submitted

1.11.-Table of contents

.-Executive summary

The Diabetes Control and Complications Trial (DCCT) determined that good glycemic control decreased the risks for long-term complications in patients with Type 1 diabetes mellitus (IDDM). Intensive therapy was associated with lower HgbA1c values and better clinical outcomes than conventional therapy. Intensive therapy involves pre-prandial dosing with a more rapid-acting insulin. The insulin is delivered either as a subcutaneous injection or a bolus infused subcutaneously by pump. Basal insulin needs are addressed with injections of longer-acting insulin or continuous low rates of insulin infusion. Although comparable glycemic control can be obtained with either multiple injections or pump infusion, some patients prefer pump therapy because of the ability to program low flow rates during sleep or exercise and because of the easy access to insulin for bolusing to manage both spontaneous and planned meals. Some patients are unable or unwilling to undertake the complexities of pump use and/or the associated costs of insulin administration. Initial pump costs are in the [redacted] Replacement of an infusion set costs approximately [redacted]. Furthermore, unlike intensive therapy with multiple injections, intensive therapy with pump infusion depends on the complex interaction of numerous variables including:

a.—user skills.

b.—accuracy, reliability, and other engineering features of the pumps.

c.—reliability of the insulin in an atypical environment:

i.--non-refrigerated and exposed to variable (and perhaps alternating) temperatures determined, in part, by the ambient temperature, pump location e.g., axilla vs waist pocket, and heat absorption because of the color of the pump case or cover,

ii—agitation that may precipitate drug aggregation,

iii.—exposed to variable lengths/areas of plastic and/or teflon cannula/tubing/insulin reservoir surfaces that may absorb drug/drug preservative, and kink or otherwise impair insulin flow, and

iv.—exposed to low or absent flow rates because of programming or use of catheter-tubing devices that can be temporarily disconnected from the infusion site.

d.--skin changes that may occur at the infusion site because of antigenicity of the insulin or the infusion set components.

e.--altered residence times in the SQ tissue that may affect the risk for hyperglycemia and ketosis in the event of pump and/or insulin failure. Residence time may be a property of the insulin itself or the skin changes induced by the insulin.

Some of the complex interactions between pumps, infusion sets, and their insulins were recognized in the 1980s and delineated in a 1985 draft guidance. Additional *in vitro* testing was required. Because it was known that inadequate buffering of human insulin resulted in frank occlusion, these guidelines emphasized buffer assessment. Only limited clinical testing was required because the chemistry parameters that impacted on the clinical safety of the drug had been identified. Since the development of these draft guidelines, however, there have been many changes in the pumps, infusion sets, and insulin products. Because patients and physicians were anxious to utilize the increased rate of insulin absorption to permit more rapid adjustment of blood glucose, rapid-acting analogues were used off-label in pumps. Data from lispro, the first rapid-acting insulin analogue, however, suggest that the clinical and *in vitro* guidelines developed for human

insulin in pumps are not sufficient for insulin analogues, e.g. infusion site reactions (pump bumps) are not uncommon, and, e.g., temperature changes alter pH and the stability.

In the current submission, the sponsor provided data on Mini-Med 506 and Disetronic H-TRON pump-insulin function at 37°C and with continuous agitation. The durability and performance of X-14 in the Disetronic pump exceeded that in the Mini-Med pump which repeatedly became occluded on day three and thereafter. The sponsor did not provide information on pump-insulin function after exposures higher than 37°C. The sponsor also did not provide information on insulin stability after temperature cycling. These types of exposures are likely in view of the appliances and actual-use videos that the pump manufacturers provide. Although glycemic control, as measured by HgbA1c, was comparable for buffered human insulin and X-14, the clinical data were collected under optimal conditions. Patients changed insulin, infusion sets (reservoirs, tubing, and catheters), and infusion sites at intervals that did not exceed 48 hours. Patients were given as much insulin and as many infusions sets as needed. The sponsor did not conduct any studies that approached real-life use--with insulin, infusion set, and site changes every three to seven days. The data from the smallest study (018; n=29) suggest that the time to infusion set failure/occlusion was shorter and the number of infusion set changes greater in the X-14 treatment arm than in the buffered human insulin arm. Although data on infusion set changes were also collected in the two, larger studies, these data were not provided. No correlation of the *in vitro* pump function data with the clinical data could be made because there were no records of the specific pumps used by individual patients.

Changing infusion sets and sites are not just cost and convenience issues. They are safety issues. Any insulin instability or predilection for occlusion (whether directly by precipitation or indirectly by infusion site reaction) can result in more hyperglycemia and diabetic ketoacidosis. The rapid onset of hyperglycemia and diabetic ketoacidosis observed with the short-acting insulin analogues is likely to be accentuated with pump use because the insulin reservoir in the skin is smaller than with injections. Any progressive insulin instability may also result in continual upward dose titration complicated by hypoglycemia when the reservoir is refilled with new insulin. Patients who are switched from buffered regular insulin in pumps and patients who are switched from multiple-dose intensive injection therapy with either human insulin or rapid acting analogues may be at particular risk for developing these problems.

The sponsor provided incomplete information in this submission, but there is probably sufficient information to write a narrow label that will provide adequate patient protection. This is an important consideration because the drug is likely to be used off-label, and it would be desirable to avoid the morbidity and mortality observed with lispro. The sponsor should collect information on actual-use either with a phase four study in which insulin and infusion sets are not provided or via collection of adverse event data systematically using a questionnaire specifically designed to identify the causes of pump-insulin problems

3—Introduction

3.1.—Rationale for diabetes management with pump therapy

The Diabetes Control and Complications Trial (DCCT) determined that good glycemic control decreased the risks for long-term complications in patients with Type 1 diabetes mellitus. Intensive therapy was associated with lower HgbA1c values and better clinical outcomes than conventional therapy. Typically, intensive therapy involves pre-prandial dosing with a more rapid-acting insulin in conjunction with a longer acting insulin to provide a basal level of control throughout the day. Four or more injections daily are required. Alternatively, patients can utilize subcutaneous insulin infusions delivered by a pump. A basal rate is based on the anticipated activity level. Insulin boluses are given to cover food consumption. Additional insulin is given in the event of unexpected hyperglycemia. Conversely, insulin rates are reduced in the event of hyperglycemia.

Intensive therapy, whether multiple injection or by pump infusion, requires frequent monitoring of blood glucose. Fingerstick (forearm) sampling is typically performed between four and six times per day. Some patients are unable or unwilling to undertake or continue intensive therapy because of the number of insulin injections, the complexities of pump use, the frequency of glucose monitoring, and/or the associated costs of increased glucose sampling and insulin administration. Replacement of an infusion set costs approximately . The "tight control" that can be achieved with intensive therapy is also associated with an increased risk of hypoglycemia. The frequency or severity of hypoglycemia may be the limiting factor to HgbA1c reduction-either directly through symptoms or indirectly through the subsequent glucose rebound. Although comparable glycemic control can be obtained with either multiple injections or pump infusion, some patients prefer pump therapy because of the ability to program low flow rates during sleep or exercise and because of the easy access to insulin for bolusing to manage spontaneous or planned meals.

3.2.—Issues in the development of insulins for external pumps

Unlike intensive therapy with multiple injections, intensive therapy with pump infusion depends on the complex interaction of numerous variables including:

a.—user skills.

b.—accuracy, reliability, and other engineering features of the pumps.

c.—reliability of the insulin in an atypical environment:

i.--non-refrigerated and exposed to variable (and perhaps alternating) temperatures determined, in part, by the ambient temperature, pump placement e.g., axilla vs waist pocket, and heat absorption because of the color of the pump case or cover,

ii—agitation that may precipitate drug aggregation,

iii.—exposed to variable lengths/areas of plastic and/or teflon cannula/tubing/insulin reservoir surfaces that may absorb drug/drug preservative, and kink or otherwise impair insulin flow, and

iv.—exposed to low or absent flow rates because of programming or use of catheter-tubing devices that can be temporarily disconnected from the infusion site.

d.--skin changes that may occur at the infusion site because of antigenicity of the insulin or the infusion set components, e.g., nickel, or infection that may occur because of extended insulin storage without refrigeration and with alterations in bacteriostatic

additives.

e.--altered residence times in the SQ tissue that may affect the risk for hyperglycemia and ketosis in the event of pump and/or insulin failure. Residence time may be a property of the insulin itself or the skin changes induced by the insulin.

Some of the complex interactions between pumps, infusion sets, and their insulins were recognized in the 1980s and delineated in a 1985 draft guidance. Additional *in vitro* testing was required. Because it was known that inadequate buffering of human insulin resulted in frank occlusion, the guidelines emphasized buffer assessment. Only limited clinical testing was required because the chemistry parameters that impacted on the clinical safety of the drug had been identified. Since the development of these draft guidelines, however, there have been many changes in the pumps, infusion sets, and insulin products. Some pumps operate on a time basis, e.g, Disetronic pumps every three minutes. Others operate on a volume basis, e.g., Mini-Med pumps in 1/10 insulin unit increments. Tubing can now be over 100 cm to facilitate distal placement. Appliances permit pumps to be used in the sauna or shower. Data from another insulin analogue suggests that temperature changes alter pH and the stability of the insulin. Given this proliferation of change, it is quite possible that the *in vitro* criteria used to assess buffered human insulins are not adequate predict problems that could arise with insulin analogues in the clinical setting. Furthermore, because pump therapy is so equipment intensive, it is possible that clinical trials will not identify problems that could arise in the setting of less supervision or less replacement equipment/insulin.

3.3.—Rationale for the development of X-14 (insulin aspart; NovoLog) in pumps
X-14 is a modified insulin. The substitution of aspartic acid for proline in position 28 of the B-chain reduces aggregation of the insulin molecule with other insulin molecules and facilitates the absorption of the modified insulin through the skin. This pharmacokinetic property is most evident when compared to more concentrated human insulin (U100 and U500). It is less evident with less concentrated human insulin (U40). Because the volume of infused insulin is relatively small at any given time, the insulin concentration in the skin is low, and the pharmacokinetic differences between X-14 and human insulin could be expected to be less pronounced in pump patients than in injection patients. Nonetheless, the sponsor believes that the pharmacokinetic-pharmacodynamic (PK-PD) profiles are sufficiently distinct that patients will find convenience in bolus dosing immediately prior to meals.

4.—Prior agreements

4.1.—Draft guidelines
Draft guidelines were developed in 1985 prior to the development of insulin analogues. (See appendix 1.)

4.2.—Other
In a three telecommunications and two letters between 3/17/99 and 4/27/99, the sponsor was informed that the FDA did not have guidelines in addition to those proposed in 1985, but that some clinical data suggested that the proposed guidelines might not be sufficient for insulin analogues. Potential stability problems with heat were discussed with Dr. Poul

Strange. Devices that could be used during the clinical trials to assess of maximum temperature exposure was also discussed. Assessment of the pump in real life setting was encouraged because it is known that financial constraints limit changes in tubing and reservoirs to three to seven day intervals. The sponsor attempted to address this by having patients use a single infusion set during the seventh and final week of a small study (018).

The sponsor did not request a pre-NDA meeting. No advance notice of the NDA-supplement was provided prior to its arrival.

5.—Objectives
The sponsor has sought to show that the insulin analogue, X-14, can be used in external pumps for continuous subcutaneous administration without additional modification of the drug substance or excipients.

6.—CANDA
There was no CANDA submission. Supplement data were provided on EXCEL spread sheets 6/21/01.

7.—Financial disclosure
The sponsor stated that there were no financial interests to disclose (Volume 1).

8.—Pediatric waiver
No pediatric waiver was requested.

9.—Data integrity
Most of the investigators were boarded in endocrinology-although some were pediatric endocrinologists. The curriculum vitae were short or truncated-limiting assessment of qualifications. The investigator examining the insulin for crystals and pH changes was not a chemist. The DSI inspections at two sites ( ) were reportedly unremarkable.

10.—Chemistry issues
Recombinant X-14 insulin analogue has the empirical formula $C_{257}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8. Each milliliter contains X-14 (100 units), glycerin (16 mg/ml), phenol (1.50 mg/ml), m-cresol (1.72 mg/ml), zinc 19.6 (ug/ml), disodium hydrogen phosphate dihydrate (1.25 mg/ml), sodium chloride (0.58 mg/dl). The pH is 7.2 to 7.6. The insulin was previously approved for use as an injectable. The insulin was not modified for the proposed pump indication. The size of the pump reservoirs is 3 ml. The software in some pumps encourages patients to fill the reservoir completely.

The chemistry testing was most notable for the decrease in the cresol, which serves as a preservative and anti-microbial agent, and the pump stoppages with the Mini-Med equipment. (See table 1.) The stoppages were recurrent on day three and thereafter. There were also increases in B28isoX-14 and other X-14 related substances over time so that some samples did not meet release limits at six days.

Table 1 Chemistry Testing for X-14 as a Pump Insulin

Potency, Purity, Degradants	Disetronic Pump (H-tron) Classic tubing 80 cm Tenders tubing 80 cm	Mini-Med Pump (506) Polyfin tubing 106 cm Sof-set Polyfin tubing 106 cm
	3 insulin lots 0.9 U/hr + 3 6U boluses/day At 37°C Tubing change at days 2 & 6 Agitation throughout study	3 insulin lots 0.9 U/hr + 3 6U boluses/day At 37°C Tubing change at days 2 & 6 Agitation throughout study
Appearance	Increase in particles in elute & especially the syringe. Meets USP.	Increase in particles in elute & especially the syringe. Meets USP.
Volume	[redacted] No leakage reported	[redacted] No leakage reported
pH	Increase 0.07 U by day 1 No further increase day1 to 6 Range [redacted] pH delta does not ->particulates	Increase 0.05 U by day 1 No further increase day1 to 6 Range [redacted] pH delta does not ->particulates
Microbial Growth (Tested using pooled sampled from agitated syringes)	No sterility assessment M-cresol decreased over 4 days, but still above limits at 7days.	No sterility assessment M-cresol above limits at 2 days, below limits at 7 days ~~(Loss greater if evaporation from~~ infusion system is permitted.)
Degradants	[redacted]	[redacted]
Leachables	[redacted]	[redacted]
Pump Function	No pump stoppages.	Pump stoppages with bolus dosing on day 3 with both catheter types. Once stoppages occurred they could not be attenuated
Temperatures >37°C	Not done	Not done
Thermocycling	Not done	Not done
Very Low Flow rates	Not done	Not done
Use with Diluent	Not done	Not done

11.—Pharmacology-toxicology issues

Alterations in the infusion sites have been observed in pigs (which have the skin most similar to that of human beings) with another insulin analogue. No animal data were submitted for this application.

12.—Pharmacokinetic-pharmacodynamic issues

No PK-PD studies were submitted. The sponsor did not assess potential PK-PD changes that could occur in conjunction with infusion site changes.

13.-Study design

13.1.-General

Three randomized, open-label, parallel-design studies of varying lengths were conducted in the U.S. in adult patients with variable degrees of diabetic control (Tables 2 and 3). Pump studies using different types if insulin were conducted in IDDM patients already familiar pump therapy. Studies in NIDDM patients new to intensive insulin therapy were compared X-14 injection versus X-14 infusion therapy (Table 3). Patients used a variety of pumps and infusion sets (Table 4). Records of the types of pump equipment were not maintained. Patients were to change their insulin, infusion sets (reservoir, tubing, catheter) and infusion sites every 3 days at a minimum. The number of infusion set changes and episodes of hyperglycemia and DKA particularly unexpected hyperglycemia along with the number of episodes of hypoglycemia. Infusion sites were inspected weekly for study 018 and every 2 to 4 weeks for studies 023 and 024. The insulin and infusion sets were visually inspected in study 018. Although infusion sets were changed every 48 hours or sooner, in the final week of study 018, infusion sets were retained until failure. Various parameters of glycemic control were also assessed.

Table 2 Design Features of Studies

Study	Diabetes	Drug-Delivery	Design	Blinding	Randomization	Duration	Location	#Sites
018	Type 1	Velosulin—Pump[1]	Parallel	No	X-14:V 2:1	6/7 wks[3]	U.S.	1
		X-14—Pump[1]						
023	Type 2	X-14--Pump	Parallel	No	Pump:Inject 1:1	16 wks	U.S.	14
		X-14—Injection[2]						
024	Type 1	Velosulin--Pump	Parallel	No	X-14:V:LP 2:2:1	16 wks[4]	U.S.	13
		X-14--Pump						
		Lispro—Pump[1]						

1 Velosulin (V) dosed 30 minutes before meals; Lispro (LP) and X-14 dosed ≤15 minutes before meals.
2 NPH used as basal insulin once or twice daily.
3 The 7th week was used to assess the time interval an infusion set could be used before obstruction or hyperglycemia
4 Patients were familiarized with more intensive therapy over 4 weeks. An 8 week dose titration phase post-randomization preceded the 16 week treatment phase.

Table 3 Selected Entry Criteria

Study	Naïve to X-14	Naïve to CSII*	Entry HgbA1c (% units)	Entry Age (yrs)
018	?	No-use for ≥3 mo	<12	18-60
023	?	Yes-but not naïve to insulin use→ 2 mo run-in w CSII	≥7; <12	≥35
024	?	No-use for ≥3 mo; 4 wk run-in with Velosulin	≥6.5; <9	≥18

*CSII=continuous subcutaneous insulin infusion=pump.

Table 4 Pump Equipment Parameters

Study	Pump Type	Pump Site*				Infusion Set Type	Tubing Length	Infusion Set Changes		Infusion Site Checks
		A	B	W	O			Planned	Actual	
018	Mini-Med 506, 507, 507c	?	?	?	?	?	?	≤48 hrs	X-14 428 Velosulin 213	q1 wk
023	Mini-Med 507c	?	?	?	?	?	?	≤48 hrs	Collected; not given	q2 wks x2 mo-> q4 wks x2 mo
024	? (1 site used only Disetronic)	?	?	?	?	?	?	≤48 hrs	Collected; not given	q4 wks

*A=axilla; B=breast; W=waist or hip; O=other.

13.2.-Demographic features and patient disposition

No special patient populations were studied. The patients with NIDDM were older than the patients with IDDM (Table 5). They also had higher HgbA1c values, which may reflect their prior treatment-which was conventional therapy, not intensive insulin therapy. There were different proportions of male and female patients in the different studies and sometimes between treatment groups within a study. There were similar numbers of patients in each treatment group who discontinued. The reasons for discontinuation were similar for the various treatment groups. Curiously, the number of days in the study was highly variable. Multiple patients continued in studies several weeks after the scheduled termination.

Table 5 Demographic Features and Patient Disposition of Randomized Patients

Study	Drug	# Randomized (Ethnic Distribution)	Gender	Age (yrs)	HgbA1c (% units; n)	# DCed[1]	Days in Study (mean; range)
018	Velosulin	10 (C10)	F5 M5	33.8	7.18 (10)	0	50.0 (49-51)
	X-14	19 (C19)	F6 M13	37.7	7.17 (19)	1	48.3 (15-55)
023	Injected	61 (C50 B8 O3)	F26 M35	56.0	8.00 (60)	7	164.2 (39-204)
	Infused	66 (C53 B8 O5)	F24 M42	55.1	8.21 (65)	6	162.5 (1-217)
024	Velosulin	59 (C58 A1)	F40 M19	43.1	7.47 (58)	9	106.2[2] (1-141)
	X-14	59 (C58 B1)	F36 M23	42.4	7.34 (58)	5	113.9 (32-180)
	Lispro	28 (C26 A1 O1)	F19 M9	39.9	7.29 (28)	1	121.1[3] (78-177)

1 DC=discontinued; did not have a HgbA1c value at the final study visit.
2 versus X-14; p=0.12.
3 versus X-14; p=0.13.
C=Caucasian; B=Black; A=Asian; O=other.
F=female; M=male.

13.3.-Efficacy variables

The primary efficacy variables were HgbA1c and changes in HgbA1c. Secondary variables depended on self-collected glucose measurements at 8 points during the day. Mean glucose values at various times of the day were determined as were glucose excursions, mean glucose profiles, and variation from the mean glucose. Fructosamine values were assessed in study 018-primarily to determine if there was a progressive change in glycemic control during the final week of the study when the insulin, infusion set, and infusion site were not changed until failure.

13.4.-Safety variables

Safety variables included the number of infusion set changes and episodes of hyperglycemia and DKA (particularly unexpected hyperglycemia) along with the number of episodes of hypoglycemia. The insulin and infusion sets were visually inspected for precipitation and the insulin pH tested in study 018. The time to infusion set failure was monitored in study 018. Injection or infusion site reactions were also monitored.

14.-Efficacy results

Glycemic control as measured by HgbA1c did not change substantially in IDDM patients treated with pumps regardless of the insulin used (Table 6). Glycemic control as measured by HgbA1c improved in NIDDM patients switched to intensive therapy, but did not differ by mode of delivery (injection versus pump). The self-collected glucose measurements, particularly the change in mean glucose profile, correlated poorly with the more rigorous HgbA1c parameters so no further assessments of the self-collected values were performed.

Table 6 Glucodynamic Assessments

Study	Drug	HgbA1c (% units; n)		Glucose Profile (mg/dl; n)*		Correlation (r; n) HgbA1c vs Profile	
		At Exit	Delta	At Exit	Delta	At Exit	Delta
018	Velosulin	7.06 (10)	-0.12 (10)	152.6 (10)	8.5 (10)	0.75 (10)	0.62 (10)
	X-14	6.86 (18)	-0.31 (18)	150.1 (19)	3.5 (19)	0.26 (18)	-0.002 (18)
023	Injected	7.53 (59)	-0.46 (59)	160.4 (60)	-10.2 (59)	0.50 (59)	0.55 (58)
	Infused	7.59 (63)	-0.62 (62)	153.5 (66)	-23.7 (63)	0.59 (63)	0.47 (59)
024	Velosulin	7.63 (53)	0.15 (52)	158.1 (58)	-0.6 (58)	0.25 (53)	0.11 (52)
	X-14	7.36 (58)	-0.004 (57)	154.0 (58)	-1.3 (58)	0.55 (58)	0.17 (57)
	Lispro	7.47 (28)	0.18 (28)	159.4 (28)	4.2 (27)	0.54 (28)	0.64 (27)

* Serial, glucometer values self-collected over the course of a day with the collection days determined by the patient; all patients did not take 100% of measurements at all timepoints

15.-Safety results

15.1.-Clinical trials

Hypoglycemia did not differ between treatment groups, and hypoglycemia was not clearly correlated with HgbA1c or changes in HgbA1c (Table 7). Major increases in total insulin doses were not required to obtain comparable glycemic control with X-14 compared to Velosulin (Table 8). Episodes of hyperglycemia and DKA were not more common in any particular treatment group. Because these episodes of hyperglycemia did not correlate well with HgbA1c, they were likely very transient (Table 9). Curiously, there were more hyperglycemic episodes per patient in the study with the lowest HgbA1c levels (018). Data from study 018 suggest that more infusion sets changes were required to maintain glycemic control in patients who used X-14 ($p \leq 0.05$). Unfortunately, although comparable data were collected in the subsequent studies, they were not presented (Table 10). The time-to-infusion set failure during the seventh week of study 018 was also shorter for patients who used X-14 ($p \leq 0.05$) (Table 10). The numbers of "unplanned infusion set changes for unexpected hyperglycemia" could not be interpreted because of the subjective nature of the determination. There were no clear differences in the infusion site reactions by treatment group, but monitoring was limited (Table 10).

One of the 205 patients treated with X-14 was discontinued because an allergic reaction. The patient was on injection therapy. No patients using buffered regular insulin were discontinued for allergic-type reactions. The differences in cross-reacting anti-insulin antibodies and alkaline phosphatase there were observed in previous studies were present here as well (Table 11).

15.2.-Other

There have been only limited numbers of adverse events for X-14. These numbers may reflect the relatively small distribution the sponsor has in the domestic insulin market. The submitted reports suggest that:

1- rash may occur after X-14 use in the pump (report number 210150). The patient had a similar response requiring lispro discontinuation.

2-infusion site reactions may occur within 48 hours of starting a new site and take several days to resolve (report number 210279). These reactions can also occur with injections (report number 210432).

3-particular vials of X-14 are sub-potent (report number 210946)(report number 210757; normalization of glucose values required switching to another insulin).

4-insulin that has been refrigerated and initially is potent can become sub-potent after being put into a pump (report 210493 in an 8 year old patient; occurred with three separate vials).

5—hyperglycemia and frank occlusion can occur on a repeated basis with X-14 and lispro, but not with buffered regular insulin when used in a pump. Insulin extracted from the X-14 vial and injected SQ lowered glucose levels appropriately (report number 210156).

Table 7 Glycemic Control in the Context of Hypoglycemia

Study	Drug	HgbA1c (% units; n)		Hypoglycemia[1]			Correlation (r: n) Hypo vs HgA1c	
		At Exit	Delta	Mean	Total # Events	N Affected	At Exit	Delta[2]
018	Velosulin	7.06 (10)	-0.12 (10)	3.4	34	6	-0.77 (10)	0.50 (10)
	X-14	6.86 (18)	-0.31 (18)	1.7	32	12	-0.26 (18)	0.02 (18)
023	Injected	7.53 (59)	-0.46 (59)	0.43	26	8	-0.05 (59)	0.05 (57)
	Infused	7.59 (63)	-0.62 (62)	0.35	23	13	-0.02 (63)	-0.17 (62)
024	Velosulin	7.63 (53)	0.15 (52)	2.07	122	29	-0.10 (53)	-0.10 (52)
	X-14	7.36 (58)	-0.004 (57)	1.03	61	27	-0.24 (58)	-0.17 (58)
	Lispro	7.47 (28)	0.18 (28)	1.5	42	15	-0.36 (28)	-0.31 (28)

1 Hypoglycemia defined as a glucose </=36 mg/dl and/or requiring third party intervention.

2 Delta HgbA1c vs number of hypoglycemic episodes.

Table 8 Glycemic Control in the Context of Insulin Dose

Study	Drug	HgbA1c (% units; n)		Insulin Dose (U/kg; n)		Correlation (r; n) HgbA1c vs Dose[2]	
		At Exit	Delta	At Exit	Delta	At Exit	Delta
018	Velosulin	7.06 (10)	-0.12 (10)	0.60 (10)	0.40 (10)	-0.04 (10)	0.04 (10)
	X-14	6.86 (18)	-0.31 (18)	0.54 (19)	-0.03 (19)	0.35 (18)	0.67 (18)
023	Injected	7.53 (59)	-0.46 (59)	0.91 (57)	0.21 (57)[1]	0.19 (56)	0.04 (56)
	Infused	7.59 (63)	-0.62 (62)	0.85 (60)	0.10 (60)[1]	0.31 (60)	-0.43 (59)
024	Velosulin	7.63 (53)	0.15 (52)	0.58 (55)	0.02 (55)	-0.08 (53)	-0.01 (52)
	X-14	7.36 (58)	-0.004 (57)	0.68 (57)	-0.006 (55)	0.12 (57)	-0.06 (54)
	Lispro	7.47 (28)	0.18 (28)	0.53 (28)	-0.005 (25)	-0.28 (28)	0.16 (25)

1 Baseline dose data were not included in the electronic spreadsheet. Data were collected, but reflect early dosing or changes in dosing in patients who may have been on insulin+oral agents.The data were extracted from volume 14.

2 Exit HgbA1c vs exit insulin dose and delta HgbA1c vs delta insulin dose.

Table 9 Assessment of the Effect of Insulin-Pump Function on Glycemic Control

Study	Drug	HgbA1c (% units; n)		Hyperglycemia[1]			Correlation Hyper vs HgA1c[2] (r; n)		DKA[3]
		At Exit	Delta	Mean	Total # events	Total N	At Exit	Delta[1]	
018	Velosulin	7.06 (10)	-0.12 (10)	21.8	218	10	0.48 (10)	0.02 (10)	0
	X-14	6.86 (18)	-0.31 (18)	20.0	381	19	0.55 (18)	-0.09 (18)	0
023	Injected	7.53 (59)	-0.46 (59)	8.3	506	53	0.17 (59)	0.17 (59)	0
	Infused	7.59 (63)	-0.62 (62)	6.9	454	57	0.44 (63)	-0.16 (62)	0
024	Velosulin	7.63 (53)	0.15 (52)	8.6	507	56	0.31 (53)	-0.03 (52)	0
	X-14	7.36 (58)	-0.004 (57)	7.2	424	57	0.47 (58)	0.30 (57)	0
	Lispro	7.47 (28)	0.18 (28)	8.2	230	28	0.39 (28)	-0.03 (28)	0

1 Glucometer readings >/=250 mg/dl. It is not known if a particular pump type, episode of heat exposure, or period of low insulin flow was associated with hyperglycemic episodes.

2 Delta HgbA1c vs number of hyperglycemic episodes.

3 DKA=diabetic ketoacidosis

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Table 10 Other Assessments of the Effect of Insulin-Pump Function

Study	Drug	Obstructions/ Leakages[1,2] (events; n)	Infusion Set Change[2]			Time to Set Change[3] (hours; n)	Injection Site Reaction[7] (events; n)
			Unplanned (events; n)	Actual -Total (events)	Expected -Total (events)		
018	Velosulin	5 (4)	52 (10)	213[5]	210[5]	154.5 (10)[6]	0
	X-14	37 (12)	131 (18)	428[5]	388[5]	128.8 (18)[6]	0
023	Injected	Not applicable	0	0	0	Not applicable	0
	Infused	270 (46)	346 (51)	Collected; not given	5362[4]	Not collected	15 (8)
024	Velosulin	136 (35)	213 (39)	Collected; not given	3133[4]	Not collected	2 (1)
	X-14	158 (37)	208 (42)	Collected; not given	3360[4]	Not collected	6 (6)
	Lispro	81 (21)	103 (24)	Collected; not given	1695[4]	Not collected	1 (1)

1 Only Study 018 reported leakages.
2 It is not known if a particular pump type, episode of heat exposure, or period of low/high insulin flow was associated with obstructions, leakages, or infusion set changes.
3 Extrapolated from the data presented on page 67, volume 3. X^2 $p \leq 0.05$.
4 Calculated from the mean duration of treatment x # patients/ expected infusion change q2 days.
5 Infusion sets not changed until failure during the last week (7^{th} week) of the study.
6 p=0.04
7 Unclear whether these numbers included additional cases of cellulitis.

Table 11 Other Safety Assessments

Study	Drug	HgbA1c (% units; n)		Weight (kg; n)		Alkaline Phosphatase (U/L; n)		Cross-reacting Antibodies (% specific binding; n)	
		Exit	Delta	Exit	Delta	Exit	Delta	Exit	Delta
018	Velosulin	7.06 (10)	-0.12 (10)	72.2 (10)	-0.42 (10)	78.0 (10)	.60 (10)	Collected; not given[3]	Collected; not given[3]
	X-14	6.86 (18)	-0.31 (18)	81.0 (18)	-0.19 (18)	71.3 (18)	-0.17 (18)	Collected; not given[3]	Collected; not given[3]
023	Injected	7.53 (59)	-0.46 (59)	92.4 (59)	0.16 (59)	84.5 (57)	2.30 (57)	Not collected	Not collected
	Infused	7.59 (63)	-0.62 (62)	94.1 (62)	0.16 (61)	88.0 (59)	0.92 (59)	Not collected	Not collected
024	Velosulin	7.63 (53)	0.15 (52)	75.1 (52)	-0.004[1] (52)	73.7 (52)	-0.22[2] (49)	Not collected	Not collected
	X-14	7.36 (58)	-0.004 (57)	77.5 (58)	0.06 (58)	78.6 (53)	4.16[2] (50)	Not collected	Not collected
	Lispro	7.47 (28)	0.18 (28)	76.5 (28)	0.83[1] (28)	79.3 (27)	7.08 (26)	Not collected	Not collected

1 Velosulin vs lispro p=0.14.

2 Velosulin vs X-14 p=0.04.

3 The sponsor acknowledged that cross-reacting antibody levels were higher in those treated with X-14, but did not provide the levels. The sponsor provided scattergram data to show the absence of a relationship between antibodies and obstructions.

15.-Reviewer's commentary

Human insulin that has been highly buffered has been successfully used in external, subcutaneous-infusion pumps. Such preparations are stable and appear to tolerate higher temperatures-even though this attribute was not specifically evaluated with *in vitro* testing. The occurrence of infusion site reactions that might result in secondary occlusion also appears to be low. These features have permitted pump manufacturers to utilize reservoirs that contain enough insulin (300 U) for approximately one week in adults. Some patients have successfully limited the number of infusion set and infusion site changes to one or two times per week. Pediatric patients have been able to dilute buffered regular insulin to permit low infusion particularly during sleep and exercise. Patients do not rapidly progress to ketosis if there are occlusions or insulin stability problems because there is a larger subcutaneous reservoir with human insulin than with insulin analogues. Fewer changes of insulin, infusion sets, and infusion sites have resulted in more convenience and reduced monetary cost without significant clinical consequences.

With the advent of insulin analogues, many patients and physicians were anxious to utilize the increased rate of absorption to permit more rapid adjustment of blood glucose levels. Lispro was the first insulin employed for this purpose-albeit off-label. Adverse event reports suggested that pump site reactions (pump bumps) were not uncommon and that the insulin was less stable in warm weather and/or under conditions of low flow, e.g. with exercise out-of-doors. Patients have attempted to remedy these perceived problems by mixing buffered regular insulin and lispro. Subsequent data from Mini-Med has demonstrated that temperature elevations result in pH changes. Furthermore, much of the equipment associated with continuous infusion has changed substantively since the mid

1980s. Some pumps work on a volume basis (Mini-Med pumps time insulin releases to 0.1 U increments; others work on a time basis (Disetronic pumps release insulin every three minutes). Moreover, the newly available Animas pump has never been assessed in pump insulin studies. (It delivers insulin every three minutes in increments of 0.05 U.) The plastics in the tubing also have changed along with the available lengths of tubing.. Consequently, there may be over 18 units of insulin in the dead space of tubing. Pump appliances now permit pumps to be worn in a variety of body sites and under a variety of conditions that may increase an insulin's exposure to excessive ambient or radiant heat. Insulin in pumps worn in the axilla is warmer than insulin in pumps carried in a pocket. Insulin in pumps carried in a pouch for the sauna or shower is warmer than pumps disconnected for such activities. Insulin in waterproof pumps with black sport cases worn outside the clothing while at the beach is warmer than insulin in pumps in an air-conditioned environment. Because of these changes in equipment and insulin, it is likely that the guidelines-both clinical and *in vitro*-that were developed for human insulin in pumps are not sufficient for insulin analogues.

In the current submission, the sponsor provided data on Mini-Med 506 and Disetronic H-TRON pump-insulin function at 37°C and with continuous agitation. The durability and performance of X-14 in the Disetronic pump exceeded that observed in the Mini-Med pump, which repeatedly became occluded on day three and thereafter. The sponsor did not provide information on pump-insulin function after exposures higher than 37°C. The sponsor also did not provide information on insulin stability after temperature cycling. These types of exposures are likely in view of the appliances and actual-use videos that the pump manufacturers' provide. The clinical data were also collected under optimal conditions. Patients were instructed to change insulin, infusion sets (reservoirs, tubing, and catheters), and infusion sites at a minimum of every 48 hours. Patients were given as much insulin and as many infusions sets as needed. The data from study 018 suggest that patients using X-14 required more infusion set changes than did patients using Velosulin; $p \leq 0.05$. This veracity and clinical significance of this finding could not be assessed in the other two, larger and longer studies because, although data on the number of infusion sets were collected, they were not provided in the NDA submission. Assessment of the interaction between specific pumps and insulin function could not be done because there were no records of the specific pumps used by each patient .

The cost of changing the insulin, infusion set, and infusion site every 48 hours or less may be prohibitive to many patients. The sponsor did not conduct any studies that approached real-life use in which insulin, infusion set, and site are changed every three to seven days. The sponsor did have the small number of patients (n=28) in study 018 retain their insulin, infusion set, and infusion site until failure during the final and seventh week of the study. The investigator, not a chemist, also visually inspected and tested the pH of the infusion sets. The time-to-failure was shorter ($p \leq 0.05$) with X-14. There were no clear differences in fructosamine levels for the two treatment groups during this seventh week, but differences in glycemic control would not be expected if patients promptly changed their insulin, infusion set, and infusion site in response to an alarm or unexpected hyperglycemia. Although the adverse events reported for lispro provided some insight into some of the problems in real-life use and the etiology of these problems was

elucidated, in part, with further chemical testing, a similar assessment of X-14 cannot be done. There are only a few reports suggesting instability of X-14. Putatively, the aspartic acid substitution could help the analogue to retain a lower pH. Alternatively, the lack of reports may reflect the short duration (less than two years) and limited distribution in the U.S. market.

The cost issues may outweigh convenience considerations for some patients. More important, however, are the safety issues. Any insulin instability or predilection for occlusion (whether directly by precipitation or indirectly by infusion site reaction) can result in more hyperglycemia and diabetic ketoacidosis. The rapid onset of hyperglycemia and diabetic ketoacidosis observed with the short-acting insulin analogues is likely to be accentuated with pump use because the insulin reservoir in the skin is smaller than with injections. Any progressive insulin instability may also result in continual upward dose titration complicated by hypoglycemia when the reservoir is refilled with new insulin. Patients who are switched from buffered regular insulin in pumps and patients who are switched from multiple-dose intensive injection therapy with either human insulin or rapid acting analogues may be at particular risk for developing these problems.

The sponsor provided incomplete information in this submission, but there is probably sufficient information to write a narrow label that will provide adequate patient protection. This is an important consideration because the drug is likely to be used off-label, and it would be desirable to avoid the morbidity and mortality observed with lispro.

16.-Regulatory conclusions

1-X-14 can be approved for use in specific pumps with specific infusion sets (Disetronic H-TRON plus V100 with Disetronic Classic or Tender infusion sets; Mini-Med Model 506 with Polyfin or Sof-set infusion sets). Approval cannot be extrapolated to other equipment. The X-14 insulin, infusion sets, and infusion sites may be used for up to 48 hours.

2-Because the design of the clinical studies differed substantively from standard medical practice and typical use in real life, with more frequent changes of the insulin, infusion sets, and infusion sites, the consequences of such deviations from recommendations should be delineated in both the physician and patient labels. Because current standard practice reflects the large reservoir size, the software restrictions for reducing the amount of insulin inserted into the reservoir, and pump manufacturers' printed instructions (including changing tubing every three days), the physician and patient labels must clearly indicate that the directions for the specific use of X-14 in pumps supercede the manufacturers' general guidelines.

3-The sponsor should collect information on actual-use either in a phase four study in which insulin and infusion sets are not provided or via collection of adverse event data systematically using a questionnaire specifically designed to identify the causes of pump-insulin problems. See the enclosed questionnaire. The sponsor has inquired about a mailing to patients that would enable them to learn more about X-14. This questionnaire could be included in such a mailing.

4-New pump guidelines should be developed.

Questionnaire for patients who use external pump to administer insulin:

Pump Manufacturer:_____
Model:_____
Insulin(s):_____ Mixture of insulins:_____
HgbA1c(%):_____
Duration of diabetes (yrs):_____ Pump experience:_____

Describe problem:
In the event of hyperglycemia:

- Did an alarm sound? Yes No
- What was the nature of the alarm?
- Was there visible occlusion of the tubing? Yes No Describe.
- Was there flow from the tubing-even in the absence of a visible obstruction? Yes No
- (Did you need to bolus the insulin to see any flow? Yes No)
- Did the insulin in the reservoir look unusual? Yes No Describe.
- Was there (a) skin reaction/induration at the infusion site? Yes No Describe.
- When was the last time the tubing was changed?
- When was the last time the infusion site was changed?
- When was the last time the insulin in the reservoir was changed?
- When was the last time the insulin vial was changed?
- Provide lot number:
- What was the flow rate?
- What was the ambient temperature?
- What were your activities?
- Do you have an explanation for your hyperglycemia?
- What was the response to rebolusing?
- What was the response to changing the tubing?
- What was response to changing the insulin in the reservoir?
- What was the response to changing the insulin vial and putting it in the pump?
- What was the response to injecting insulin from the reservoir as a subcutaneous injection?
- What was the response to injecting insulin from the source vial of insulin?
- What was the response to injecting insulin from injecting insulin from a new vial of insulin?
- What color is your pump?
- Where do you wear your pump?
- How do you store your source insulin?

17.-Label review

17.1-General comments:

1-X-14 can be approved for use in specific pumps with specific infusion sets. The sponsor has tried to infer that other equipment can be used. The specific pumps and infusion sets should be delineated several places in the label, including indications and usage, because the pump-tubing-insulin were tested as an integral unit.

2-The sponsor has indicated that the insulin may be used for up to 48 hours in pumps. Complete disclosure would actually require the sponsor to describe the frank failure of the Mini-Med pump after three days and the sponsor's inability to provide information on the type of pump that each patient used in the three trials. Complete disclosure would also require the sponsor to provide information on the actual number of tubing changes required for each treatment group.

3-Because the design of the clinical studies differed substantively from standard medical practice and typical use in real-life, with more frequent changes in insulin, infusion set, and infusion sites, the consequences of such deviations should be delineated in both the physician and patient labels. Patients and physicians should be advised temperature may damage X-14 and given examples of when such damage could occur. Patients and physicians should be told that the rapid onset of hyperglycemia and diabetic ketoacidosis observed with the short-acting insulin analogues is likely to be accentuated with pump use because the insulin reservoir in the skin is smaller than with injections and that any progressive insulin instability may also result in continual upward dose titration that may be complicated by hypoglycemia when the reservoir is refilled with new insulin. Patients and physicians should be notified that skin reactions may be more common in patients using insulin analogues-particularly when the infusion site is not changed-and that continued infusion into such sites can change the absorption kinetics of the insulin and result in hyperglycemia and diabetic ketoacidosis. Physicians should be particularly alert to these complications when switching patients from buffered regular insulin in pumps or multiple-dose intensive injection therapy with either human insulin or rapid acting analogues.

4-Because current standard practice reflects the large reservoir size, the software restrictions for reducing the amount of insulin inserted into the reservoir, and pump manufacturers' printed instructions (including changing tubing every three days), the physician and patient labels must clearly indicate that the directions for the specific use of X-14 in pumps supercede the manufacturers' general guidelines.

5-The physician label provides information on the treatment of diabetes during pregnancy. This should be excluded until clinical information reflecting the use of this product pregnancy is available.

6-The current patient label is too long and attempts to teach patients management of diabetes. The label should be focused on the specific features of X-14 that will affect patient management including the more rapid onset of glucose lowering activity and the problems with missing meals as well as the more rapid onset of hyperglycemia and ketoacidosis in the event of missed insulin doses, insulin failure, or pump equipment failure. The reviewer's label addresses these concerns. (For specific comments see label reviews.)

26 pages redacted from this section of the approval package consisted of draft labeling

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FEB 20 1985

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REQUIREMENTS PROPOSED FOR PUMP INSULINS AND INSULIN PUMPS

Division of Metabolism and
Endocrine Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

Division of Gastroenterology-Urology and
General Use Devices
Office of Device Evaluation
Center for Devices and Radiological Health

All regular insulin solutions are approved for subcutaneous or intravenous injection. More recently, regular insulins have been increasingly used for continuous subcutaneous infusion via open-loop external pumps, or occasionally, for intravenous infusion via open-loop implanted pumps. Insulin degradation, precipitation and aggregation as well as failure of pump components and breaks in the infusion pathway have all been reported as causes of clinical complications. Under current Medical Device Regulations, implanted pumps are classified as class III devices requiring premarket approval. However, external pumps are considered class II devices required only to meet performance standards to be established by the Office of Device Evaluation. In view of the risks associated with using pumps for insulin therapy, recently, the Office of Device Evaluation has advised some insulin pump manufacturers to specify in their labeling that the pump reservoir and infusion set be used no longer than 48 hours; reservoirs and infusion sets should be changed every 48 hours or less. Manufacturers of devices designed for longer reservoir use (less frequent reservoir refills or changes) were advised to submit stability data to show that the pump and pump components in contact with insulin have no adverse effects on the insulin.

In order to assure the safety of patients using insulin pumps, safety and efficacy data for insulin pumps and insulin products to be used in these pumps must be developed systematically and consistently. A flow chart (Appendix I) depicts proposed regulatory requirements and specific tests for several external-pump/insulin systems. The tests are described in detail in Appendix II.

Although it is the responsibility of a manufacturer seeking a label claim for a product (pump compatible with a certain insulin or insulin compatible with a certain pump) to submit data to the Office of Device Evaluation and/or Office of Biologics Research and Review, pump and insulin manufacturers should collaborate in conducting studies so that meaningful data can be collected to support proposed label claims. The two Offices of FDA are committed to work together in reviewing and evaluating the data.

Appendix II

Description of the tests

1) Mechanical and engineering testing of the pump The Office of Medical Devices has the responsibility to assure that the pump meets the performance standards or fulfills premarket approval requirements. The submission should include a complete description of the pump and its components, including material (leachables), electronics, energy source, and modes of operation. The precision and accuracy of the pump at different flow rates should be documented. Safety features, including assurance of the sterility of the fluid path, should be demonstrated. The method of sterilization of the insulin reservoir and infusion set should be described.

2) Clinical pharmacokinetic study The pharmacokinetics of the modified insulin product and the original unmodified insulin should be compared in 4-6 normal volunteers. Insulin action can best be assessed with a Biostator or similar closed-loop glucose clamp device which allows precise quantitation of glucose utilization following an injection of insulin. A proposed protocol will be evaluated under an IND by the Division of Metabolism and Endocrine Drug Products.

3) Clinical safety and efficacy study The study should include 15-20 diabetic patients given the modified insulin by the infusion pump. The total duration of the trial should be at least 6 weeks. Clinical data collected should include:

a) For all pumps
Daily insulin dose.
"Mean daily fasting glucose" based on preprandial blood glucose measurements.
Number of episodes of "unexplained" hyperglycemia or hypoglycemia.
Number of serious adverse events (defined under item 7 below).
Unexpected events related to the study drug or conduct of study.

b) For external pumps
Number of catheters used per week.
Number of episodes of infusion set obstruction or leakage.
At least one catheter should be examined each week. Catheter examination should include measurement of the pH of the insulin solution obtained from the reservior and the distal half of the catheter and macroscopic and microscopic examination for the presence of insulin precipitate.

c) For internal pumps
Frequency of catheter occlusion or breakage.
Residual insulin analysis - The physicochemical integrity and sterility of the residual insulin in the reservoir should be assessed when the reservoir is refilled.

4) On-shelf drug stability study. Three lots of the modified insulin product stored in the designated container (e.g. glass vial, plastic syringe, or rubber cassette, etc.) under the recommended storage condition should be studied to establish the expiration date of the drug. The following parameters should be measured periodically to assure that the drug is stable for the entire proposed shelf-life:

a) Clarity and appearance. Macroscopic and microscopic examination should be conducted to examine the formation of particulates. The product should meet USP requirements for injectables.

b) pH. pH values should be in compliance with the USP XXI monograph for insulin injection.

c) Potency. During its entire shelf-life, the potency of the packaged drug must stay within 95-105% of the labelled claim as required by USP XXI. Potency may be assayed by comparing the sample lot with an established reference standard by HPLC.

d) Aggregates and degradation products. The formation of aggregates (dimeric, oligomeric and polymeric insulin) or other modified insulins must be determined quantitatively by SDS polyacrylamide gel electrophoresis, a suitable HPLC system or other suitable methods.

e) Sterility and non-pyrogenicity. It must be shown that the manufacturing and repackaging process of the modified insulin has not introduced microorganisms nor pyrogens. Tests and specifications should comply with USP XX. If preservative effectiveness and the presence of proper amount of the preservatives throughout the shelf life can be demonstrated, these tests need to be conducted only once.

f) Buffering capacity. If inorganic salts have been added to produce a buffered insulin, the acid-neutralizing capacity of this insulin solution should be determined by titrating with an acid.

g) Elastomeric components contents. If the modified insulin will be stored in a plastic or rubber container, the chemical information on the materials used for manufacturing the containers should be provided. The extractable elastomeric components (e.g., monomer, accelerator, vulcanizing agents, etc.) from the materials should be given. The amount of the elastomeric components which may have leached into the insulin solution during the entire proposed shelf-life should be determined.

In any event, the expiration date of the modified insulin should not exceed the expiration date stamped on the vials of the original insulin products.

5) In-vitro in-pump-use stability study. At least three lots should be tested under the condition simulating the actual clinical use. Briefly, insulin should be stored in the pump at elevated temperature (37° C) under agitation. Samples should be collected periodically at the catheter ends for the determination of clarity and appearance, pH, potency, content of degraded and non-monomeric insulins and the amount of the elastomeric components leaching from the reservoir and infusion set. The test methods were described in detail under item 4) above. The frequency of catheter or infusion set

obstruction should be recorded. The solution in the reservoir should be examined for the formation of particulates. The length of the study should be approximately twice the time that the insulin will be stored in the pump in actual clinical use.

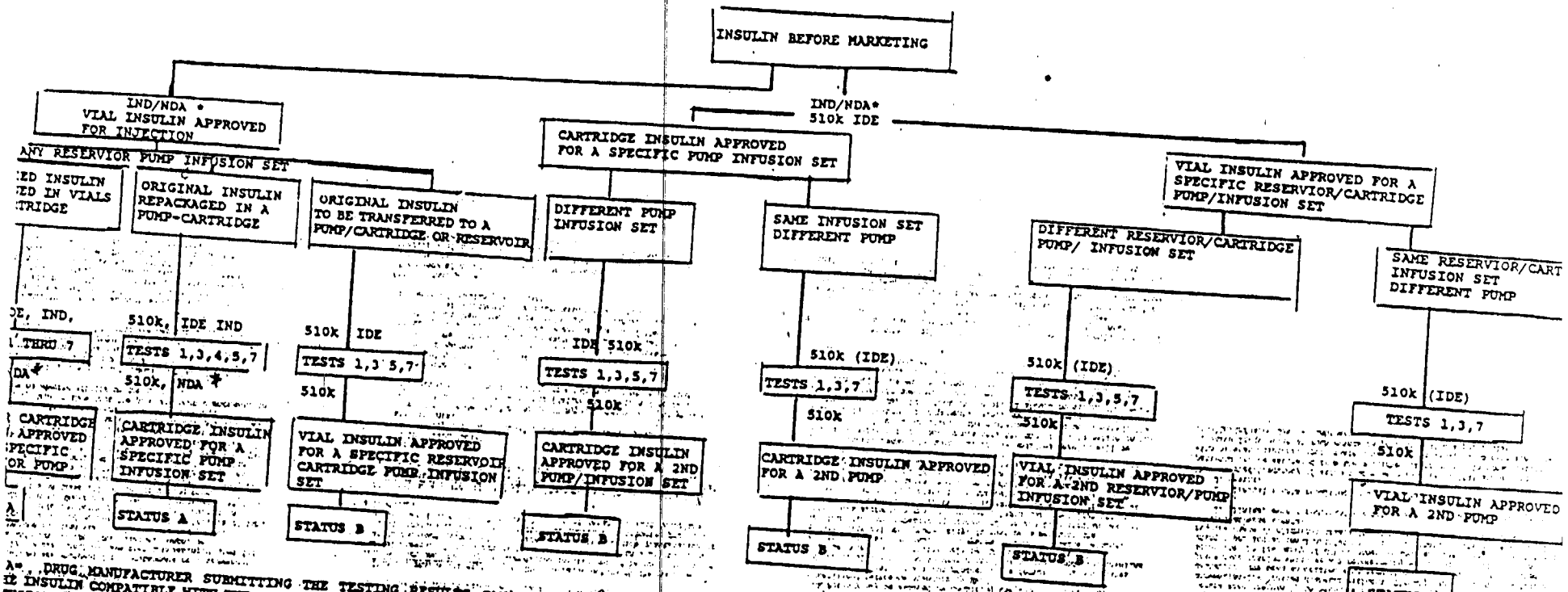
6) Preclinical study. When additives other than inorganic salts and glycerol are used to modify the insulin (e.g. surfactants), animal toxicity data for the additive will be required. In addition, full chemical and manufacturing information on the additive must be provided.

7) Phase IV clinical trials. At the time of approval, the insulin and/or pump manufacturer should submit protocols for post-marketing surveillance. Reports in the medical literature indicate that diabetic ketoacidosis (DKA) occurs more frequently in patients receiving insulin via CSII than among conventionally treated diabetic patients. Blockage and leaking of infusion catheters have been associated with many of these episodes. The limited pre-market testing which we are recommending would not be sufficient to determine the frequency of DKA or other serious adverse events among patients using a particular insulin/infusion device combination. Therefore we shall require Phase IV clicnical trials designed to determine the frequency of serious adverse events.

1. clinical events requiring a visit to a doctor's office or emergency room.
2. clinical events resulting in hospitalization.
3. deaths.

The expected frequency of serious adverse events (e.g. DKA) among pump patients can be estimated from the published literature. In consultation with biostatisticians, appropriate studies may be designed to determine the relative frequencies of such events in patients using a particular insulin/infusion device combination.

Drafted by Y. Chiu/4-3-84.
Commented by E.B. Rappaport and J.L. Gueriguian and initialed by V. Berliner, D.J. Kertesz and Office of Devices Evaluation.
Last revision by Y. Chiu/01-16-85.
Revised by EBRappaport, 1/24/85



A= DRUG MANUFACTURER SUBMITTING THE TESTING RESULTS CAN
E INSULIN COMPATIBLE WITH THE SPECIFIC RESERVIOR/CARTRIDGE-
FUSION SET SYSTEM, PUMP MANUFACTURER SUBMITTING THE TESTILNG
CAN LABEL THEIR PUMP COMPATIBLE WITH THE INSULIN

B= PUMP MANUFACTURER SUBMITTING THE TERSTING RESULTS CAN
HEIR PUMP. IF DRUG MANUFACTURER WANTS TO LABEL THEIR
THEY MUST SUBMIT TESTING RESULTS THROUGH THE IND/NDA

OF INSULIN MUST BE CERTIFIED BY FDA BEFORE MARKETING

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Division of Metabolism and
Endocrine Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

Division of Gastroenterology-Urology and
General Hospital Devices
Office of Device Evaluation
Center for Devices and Radiological Health

All regular insulin solutions are approved for subcutaneous or intravenous injection. More recently, regular insulins have been increasingly used for continuous subcutaneous infusion via open-loop implanted pumps. Occasionally, for intravenous infusion via open-loop external pumps, or insulin degradation, precipitation and suppuration as well as failure of pump components and breaks in the infusion pathway have all been reported as causes of clinical complications. Under current Medical Device Regulations, implanted pumps are classified as class III devices requiring premarket approval. However, external pumps are considered class II devices required only to meet performance standards to be established by the Office of Device Evaluation. In view of the risks associated with using pumps for insulin therapy, recently, the Office of Device Evaluation has advised some insulin pump manufacturers to specify in their labeling that the pump reservoir and infusion set be used no longer than 48 hours; reservoirs and infusion sets should be changed every 48 hours or less. Manufacturers of devices designed for longer reservoir use (less frequent reservoir refills or changes) were advised to submit stability data to show that the pump and pump components in contact with insulin have no adverse effects on the insulin.

In order to ensure the safety of patients using insulin pumps, safety and efficacy data for insulin pumps and insulin products to be used in these pumps must be developed systematically and consistently. A flow chart (Appendix II) depicts proposed regulatory requirements and possible tests for several external-pump/insulin systems. The tests are described in detail in Appendix II.

Although it is the responsibility of a manufacturer seeking a label claim for a product (pump compatible with a certain insulin or insulin compatible with a certain pump) to submit data to the Office of Device Evaluation and/or Office of Biologics Research and Review, pump and insulin manufacturers should collaborate in conducting studies so that meaningful data can be collected to support proposed label claims. The two Offices of FDA are committed to work together in reviewing and evaluating the data.

Appendix II

Description of the tests

1) Mechanical and engineering testing of the pump. The Office of Medical Devices has the responsibility to ensure that the pump meets the performance standards or Bellille premarket approval requirements. The submission should include a complete description of the pump and its components, including material (formulation) electronics, energy source, and modes of operation. The precision and accuracy of the pump at different flow rates should be documented. Safety features, including assurance of the sterility of the fluid path, should be demonstrated. The method of sterilization of the insulin reservoir and infusion set should be described.

2) Clinical pharmacokinetic study. The pharmacokinetics of the modified insulin product and the original unmodified insulin should be compared in 4-6 normal volunteers. Insulin action can best be assessed with a biostator or similar closed-loop glucose clamp device which allows precise quantitation of glucose utilization following an injection of insulin. A proposed protocol will be evaluated under an IND by the Division of Metabolism and Endocrine Drug Products.

3) Clinical safety and efficacy study. The study should include 15-20 diabetic patients given the modified insulin by the infusion pump. The total duration of the trial should be at least 6 weeks. Clinical data collected should include:

a) For all pumps
Daily insulin doses.
"Mean daily fasting glucose" based on preprandial blood glucose measurements.
Number of episodes of "unexplained" hyperglycemia or hypoglycemia.
Number of serious adverse events (defined under item 7 below).
Unexpected events related to the study drug or conduct of study.

b) For external pumps
Number of catheters used per week.
Number of episodes of infusion set obstruction or leakage.
At least one catheter should be examined each week. Catheter examination should include measurement of the pH of the insulin solution obtained from the reservoir and the distal half of the catheter and macroscopic and microscopic examination for the presence of insulin precipitate.

c) For internal pumps
Frequency of catheter occlusion or breakage.
Residual insulin analysis - The physicochemical integrity and sterility of the residual insulin in the reservoir should be assessed when the reservoir is refilled.

IMPLANTS = 100 SUBJECTS

4) Overall drug stability study. Three lots of the modified insulin product stored in the designated container (e.g. glass vial, plastic syringe, or rubber cassette, etc.) under the recommended storage condition should be studied to establish the expiration date of the drug. The following parameters should be measured periodically to assure that the drug is stable for the entire proposed shelf-life:

a) Clarity and appearance. Macroscopic and microscopic examination should be conducted to examine the formation of particulates. The product should meet USP requirements for injectables.

b) pH. pH values should be in compliance with the USP XXI monograph for insulin injection.

c) Potency. During its entire shelf-life, the potency of the packaged drug must stay within 85-115% of the labelled claim as required by USP XXI. Potency may be assayed by comparing the sample lot with an established reference standard by HPLC.

d) Aggregated and degradation products. The formation of aggregates (dimers, oligomers and polymers insulin) or other modified insulins must be determined quantitatively by HPLC polyacrylamide gel electrophoresis, a suitable HPLC system or other suitable methods.

e) Sterility and non-pyrogenicity. It must be shown that the manufacturing and repackaging process of the modified insulin has not introduced microorganisms nor pyrogens. Tests and specifications should comply with USP XX. If preservative effectiveness and the presence of proper amount of the preservatives throughout the shelf-life can be demonstrated, these tests need to be conducted only generally.

f) Buffering capacity. If inorganic salts have been added to produce a buffered insulin, the acid-neutralizing capacity of this insulin solution should be determined by titrating with an acid.

g) Elastomeric components contents. If the modified insulin will be stored in a plastic or rubber container, the chemical information on the materials used for manufacturing the containers should be provided. The extractable elastomeric components (e.g., monomer, accelerator, vulcanizing agents, etc.) from the materials should be given. The amount of the elastomeric components which may have leached into the insulin solution during the entire proposed shelf-life should be determined. In any event, the expiration date of the modified insulin should not exceed the expiration date stamped on the vials of the original insulin products.

5) In-vitro in-response stability study. At least three lots should be tested under the condition simulating the actual clinical use. Briefly, insulin should be stored in the pump at elevated temperature (37° C) under agitation. Samples should be collected periodically at the catheter ends for the determination of clarity and appearance, pH, potency, content of degraded and non-monomeric insulins and the amount of the elastomeric components leaching from the reservoir and infusion set. The test methods were described in detail under item 4) above. The frequency of catheter or infusion set

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Appendix II

Description of the tests

1) Mechanical and engineering testing of the pump. The Office of Medical Devices has the responsibility to ensure that the pump meets the performance standards or fulfills premarket approval requirements. The submission should include a complete description of the pump and its components, including material (implantable) of construction, energy source, and modes of operation. The precision and accuracy of the pump at different flow rates should be documented. Safety features, including assurances of the sterility of the fluid path, should be demonstrated. The method of sterilization of the insulin reservoir and infusion set should be described.

2) Clinical pharmacokinetic study. The pharmacokinetics of the modified insulin product and the original unmodified insulin should be compared in 4-6 normal volunteers. Insulin action can best be assessed with a Biostator or similar closed-loop glucose clamp device which allows precise quantitation of glucose utilization following an injection of insulin. A proposed protocol will be evaluated under an IND by the Division of Metabolism and Endocrine Drug Products.

3) Clinical safety and efficacy study. The study should include 15-20 diabetic patients given the modified insulin by the infusion pump. The total duration of the trial should be at least 6 weeks. Clinical data collected should include:

a) For all pumps
Daily insulin dose.
"Home daily testing glucose" based on preprandial blood glucose measurements.
Number of episodes of "unexplained" hyperglycemia or hypoglycemia.
Number of serious adverse events (defined under item 7 below).
Unexpected events related to the study drug or conduct of study.

b) For external pumps
Number of catheters used per week.
Number of episodes of infusion set obstruction or leakage.
At least one catheter should be examined each week. Catheter examination should include measurement of the pH of the insulin solution obtained from the reservoir and the distal half of the catheter and macroscopic and microscopic examination for the presence of insulin precipitates.

c) For internal pumps
Frequency of catheter occlusion or breakage.
Residual insulin analysis - The physicochemical integrity and sterility of the residual insulin in the reservoir should be assessed when the reservoir is refilled.

4 IMPLANTS = 100 SUBJECTS

2

4) Ex-vivo/in vitro drug stability study. Three lots of the modified insulin product stored in the designated container (e.g. glass vial, plastic syringe, or rubber cosmetic, etc.) under the recommended storage condition should be studied to establish the expiration date of the drug. The following parameters should be measured periodically to ensure that the drug is stable for the entire proposed shelf-life:

a) Clarity and appearance. Macroscopic and microscopic examination should be conducted to examine the formation of particulates. The product should meet USP requirements for injections.

b) pH. pH values should be in compliance with the USP XXI monograph for insulin injection.

c) Potency. During its entire shelf-life, the potency of the packaged drug must stay within 90-120% of the labelled claim as required by USP XXI. Potency may be assayed by comparing the sample lot with an established reference standard by HPLC.

d) Aggregated and degradation products. The formation of appropriate (dimeric, oligomeric and polymeric insulin) or other modified insulins must be determined quantitatively by HPLC polyacrylamide gel electrophoresis, a suitable HPLC system or other suitable methods.

e) Sterility and non-pyrogenicity. It must be shown that the manufacturing and repackaging process of the modified insulin has not introduced microorganisms nor pyrogens. These and specifications should comply with USP XX. If preservative effectiveness and the presence of preservative throughout the shelf-life was to be demonstrated, these tests need to be conducted only

f) Buffering capacity. If isoionic salts have been used to produce a buffered insulin, the acid-neutralizing capacity of this insulin solution should be determined by titrating with an acid

g) Elastomeric components contents. If the modified insulin will be stored in a plastic or rubber container, the chemical information on the materials used for manufacturing the container should be provided. The extractable elastomeric components (e.g., monomers, vulcanizing agents, etc.) from the materials should be given. The amount of the elastomeric components which may have leached into the insulin solution during the entire proposed shelf-life should be determined. In any event, the expiration date of the modified insulin should not exceed the expiration date stamped on the vials of the original insulin products.

5) In-vitro in-process stability study. At least three lots should be tested under the condition simulating the actual clinical use. Briefly, insulin should be stored in the pump at elevated temperature (37° C) under agitation. Samples should be collected periodically at the catheter ends for the determination of clarity and appearance, pH, potency, amount of degraded and non-monomeric insulins and the amount of the elastomeric components leaching from the reservoir and infusion set. The test methods were described in detail under item 4) above. The frequency of catheter or infusion set

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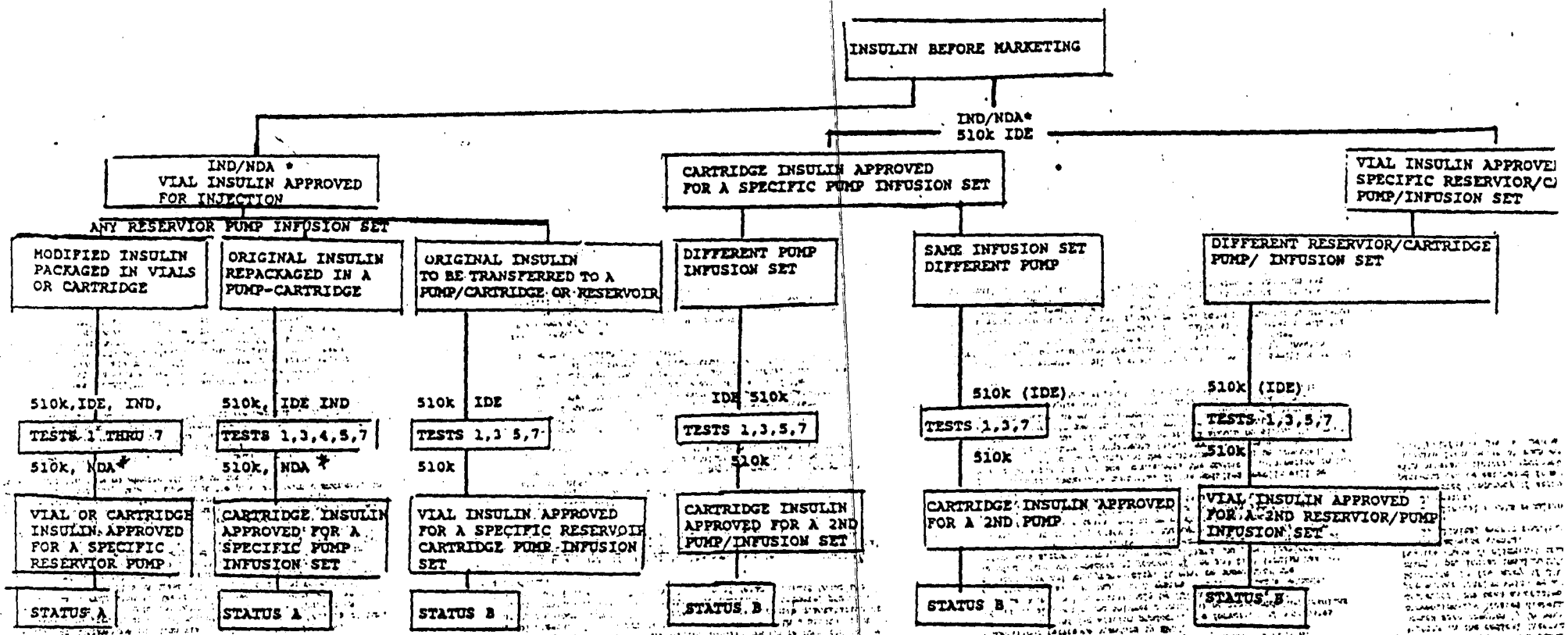
obstruction should be recorded. The solution in the reservoir should be examined for the formation of particulates. The length of the study should be approximately twice the time that the insulin will be stored in the pump in actual clinical use.

6) Preclinical study. When additives other than inorganic salts and glycerol are used to modify the insulin (e.g. surfactants), animal toxicity data for the additive will be required. In addition, full chemical and manufacturing information on the additive must be provided.

7) Phase IV clinical trials. At the time of approval, the insulin and/or pump manufacturer should submit protocols for post-marketing surveillance. Reports in the medical literature indicate that diabetic ketoacidosis (DKA) occurs more frequently in patients receiving insulin via CSII than among conventionally treated diabetic patients. Blockage and leaking of infusion catheters have been associated with many of these episodes. The limited pre-market testing which we are recommending would not be sufficient to study a particular insulin/infusion device combination. Therefore we shall require Phase IV clinical trials designed to determine the frequency of serious adverse events.

1. clinical events requiring a visit to a doctor's office or emergency room.
2. clinical events resulting in hospitalization.
3. deaths.

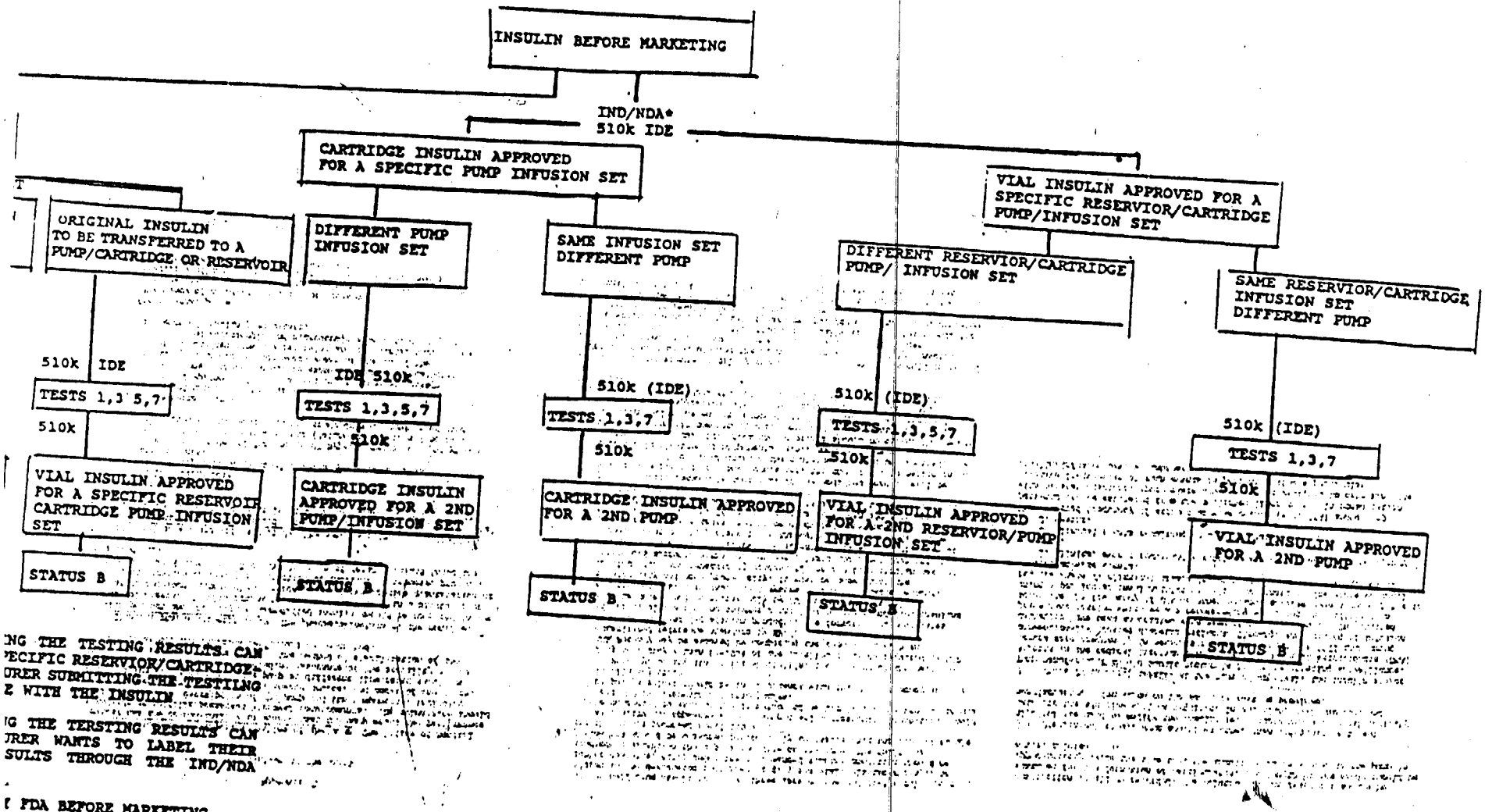
The expected frequency of serious adverse events (e.g. DKA) among pump patients can be estimated from the published literature. In consultation with biostatisticians, appropriate studies may be designed to determine the relative frequencies of such events in patients using a particular insulin/infusion device combination.



STATUS A= DRUG MANUFACTURER SUBMITTING THE TESTING RESULTS CAN LABEL THE INSULIN COMPATIBLE WITH THE SPECIFIC RESERVIOR/CARTRIDGE-PUMP INFUSION SET SYSTEM, PUMP MANUFACTURER SUBMITTING THE TESTING RESULTS CAN LABEL THEIR PUMP COMPATIBLE WITH THE INSULIN.

STATUS B= PUMP MANUFACTURER SUBMITTING THE TERSTING RESULTS CAN LABEL THEIR PUMP. IF DRUG MANUFACTURER WANTS TO LABEL THEIR INSULIN, THEY MUST SUBMIT TESTING RESULTS THROUGH THE IND/NDA PROCESS.

* EACH LOT OF INSULIN MUST BE CERTIFIED BY FDA BEFORE MARKETING



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