papilla. There was no comparison of attempts with and without the use of secretin.

[redacted]

c. Eleven patients received SPS for diagnosis of gastrinoma but only five had a histologically confirmed gastrinoma.

3. CRC97-3: This is an ongoing double blind, randomized, placebo-controlled study of secretin for prophylactic use at the time of ERCP for the prevention of post-ERCP pancreatitis. As of the date of submission 250 out of an anticipated 1500 patients have completed the protocol. Safety data are the only relevant data for review at the time of submission.

4. CRC 98-1 This was a study to compare the results of the secretin stimulation test in patients with a history of an abnormal test and a clinical diagnosis of chronic pancreatitis using the approved BPS and the proposed SPS. Variability in response to secretin stimulation in clinical subjects with pancreatic disease was assessed as well. Safety data were also collected.

5. CRC 98-2 This was a pharmacodynamic study comparing synthetic porcine and synthetic human secretin. The data from this study form part of the safety database since the comparative data do not relate to the proposed indications for the sponsor's SPS.

7.1 Post marketing experience: None

7.2 Literature: Extensive literature exists on the structure and function of secretin, particularly biologically derived porcine secretin. Studies of synthetic porcine secretin date back at least to the 1970s. No published data were found on the sponsor's product during a PUBMED search using the search terms- porcine secretin. There were no published reports comparing the several sources of SPS and the Ferring BPS in the setting of the proposed indications for the sponsor's SPS. The diagnostic accuracy of the Ferring BPS itself has not been defined well in the literature as noted during the advisory committee meetings for the product in 1978. The literature since that time does not further characterize the diagnostic accuracy parameters of BPS. It is therefore important to adequately characterize the sponsor's product.

8 Clinical studies

8.1 Indication: Diagnosis of Pancreatic Exocrine Disease

Two trials were conducted by the sponsor to characterize their product in the setting of the secretin stimulation test for the assessment of pancreatic exocrine function. The initial study, CRC 97-1 was a dose ranging study on healthy volunteers to identify the dose of SPS that most approximated the activity of the approved Ferring product (which is associated with the most extensive database of clinical information). The goal of the study was to identify the dose producing the maximal pancreatic stimulation and the activity of this dose in comparison with the approved dose of the Ferring BPS. This small study containing twelve subjects was adequate to achieve the stated purpose.

CRC 98-1 was a pharmacodynamic study in 12 subjects using the optimal dose of SPS identified by the sponsor in study CRC97-1 to compare with the Ferring BPS in patients with a history of chronic pancreatitis. The small size of this study is problematic. The range of abnormality of pancreatic secretion associated with chronic pancreatitis suggests that a larger study population would be desirable to adequately assess pathologic responses and compare the SPS and BPS. Thoughtful review of the data will be needed to assess whether this small study is adequate and whether other supportive data adequately supports this small database.

The NDA submission contained no adequate or well-controlled studies of SPS for the diagnosis of gastrinoma or for the facilitation of — during ERCP. These indications were therefore not filed.

8.1.1 CRC 97-1 A double blind, randomized four treatment latin square crossover, pharmacodynamic dose response study of intravenously administered synthetic and extracted porcine secretin for the use as a diagnostic agent to evaluate exocrine pancreatic function in normal healthy subjects

8.1.1.1 Objective/Rational: As stated by the sponsor :

1. To assess the safety and tolerance of 3 doses of synthetic porcine secretin in normal healthy subjects

2. To assess the pharmacologic effect on pancreatic secretion of 3 doses of synthetic porcine secretin in these subjects

3. To define the pharmacologic response and variability in normal subjects between synthetic and biologically extracted porcine secretin

8.1.1.2 Design:

This was a double blind, randomized, single center, dose response study. There was no placebo control in this study described as a phase one study by the sponsor. [redacted] performed the study at the [redacted] monitored the study. [redacted] was the statistician.

The blinding was performed by the research pharmacologist who reconstituted the labeled vials of ChiRoClin SPS or Ferring BPS into identically appearing syringes at a volume of 0.1 ml/kg before delivery to the investigator. The total volume for all doses of SPS and the BPS was identical.

According to the sponsor, subjects were to be randomly assigned to a specific sequence of administration of the four treatments using a randomization code generated at ChiRoClin, Inc. **The original protocol described the study as a "four treatment latin square crossover design. The study was not actually conducted this way. The final report indicates that it was a combination of two, 2-treatment crossover periods. The first two study periods were randomly assigned to the 0.2 μg/kg SPS treatment and the BPS treatment. The second two study periods were randomly assigned to the 0.05 and 0.4 μg/kg.** The randomization scheme from the protocol appears in table 3. The randomization as actually reported appears in table 4.

Table 3

(protocol defined randomization schedule)

RANDOMIZATION TABLE

SUBJECT #	BLOCK	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
1	1	A	B	C	D
2	1	B	D	A	C
3	1	C	A	D	B
4	1	D	C	B	A
5	2	A	B	C	D
6	2	B	D	A	C
7	2	C	A	D	B
8	2	D	C	B	A
9	3	A	B	C	D
10	3	B	D	A	C
11	3	C	A	D	B
12	3	D	C	B	A

Treatment A-12 subjects-Synthetic Porcine Secretin-0.2 μg/kg (0.1 mL/kg)
Treatment B-12 subjects-Synthetic Porcine Secretin-0.4 μg/kg (0.1 mL/kg)
Treatment C-12 subjects-Extracted Porcine Secretin-1 CU/kg (0.1 mL/kg)
Treatment D-12 subjects-Synthetic Porcine Secretin-0.05 μg/kg (0.1 mL/kg)

Table 4 (Actual Randomization schedule)

		RANDOMIZATION			
SUBJECT #	BLOCK	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
1	1	C	A	D	B
2	1	A	C	D	B
3	1	C	A	B	D
4	1	A	C	B	D
5	2	C	A	D	B
6	2	C	A	B	D
7	2	A	C	B	D
8	2	A	C	D	B
9	3	C	A	D	B
10	3	A	C	D	B
11	3	A	C	B	D
12	3	C	A	B	D

The division requested clarification of this discrepancy from the sponsor. The response received in communication dated November 4, 1999 stated that "The randomization scheme in the protocol on page 3227 is an ***example*** of a Latin-Square randomization. Since the study was double blinded, the actual randomization scheme appearing on page 3270 was sent only to the pharmacist who maintained the blind of the study." The response is inadequate and does not address this apparent protocol violation. The sponsor did not comment on the potential impact of the order of testing on the results.
An additional protocol violation was identified. The study report stated that the washout period was "at least one week" (page3223). Review of the case report forms revealed that seven out of twelve patients did not have a 1-week washout period between all study periods.

Patient 4A: 5 day washout between periods B and D

Patient 6: 3 day washout period between periods C and A; 4 day washout between periods A and B

Patient 7: 4 day washout between periods A and C; 3 day washout between periods C and B and 3 day washout between periods B and D

Patient 8: 2 day washout between periods C and D

Patient 9: 5 day washout between period C and A; 2 day washout between periods A and D; 2 day washout between periods D and B

Patients 10: 1 day washout between periods C and A; 6 day washout between periods A and B; 1 day washout between periods B and D

Patient 12: 1 day washout between periods A and B; 6 day washout between periods Band D

*This reviewer requested a justification for the protocol violations from the sponsor as well as an assessment of the impact of these violations on the results of the study. The sponsor provided a rationale supported by consultants that the **physiologic** exocrine response of the pancreas recovers within hours of a physiologic meal challenge to allow **optimal** digestion in healthy subjects. This response is logical, however, the SST is a test of **maximal** response to a **nonphysiologic** stimulus. It is of concern that this reviewer identified these protocol violations independently rather than having them identified by the sponsor in the study report.. It must be assumed that there was a rationale for the sponsor to choose a weeklong washout period. A retrospective justification of a significant protocol violation citing the lack of need for a washout period is suspect. Although no well-documented assessment of an appropriate washout period has been presented, this flaw is not serious enough to suggest to this reviewer that the results are invalid.*

8.1.1.3 Protocol

Normal healthy volunteer subjects were examined sequentially with three different doses of SPS, 0.05, 0.2 and 0.4 μg/kg given as an intravenous infusion over 60 seconds compared to the approved 1 μg/kg dose of Ferring BPS for the assessment of pancreatic exocrine function. Pre-specified parameters of study included total volume (TV), bicarbonate concentration (BC) and total bicarbonate output (TBO). The washout period was at least 24 hours between each study group.

Inclusion Criteria

As listed below, the subjects had to meet all of the inclusion criteria to be enrolled in the study.

1) Males or Females of non-childbearing potential (s/p hysterectomy, at least one of the following medically approved contraceptive methods: oral contraceptives, injectable long-acting progestin, Norplant™, tubal sterilization, or IUD).
2) Age 18-65.
3) Weight 40 to 120 kg and within 20% of ideal body weight (Metropolitan Life Height and Weight Tables, Appendix A of clinical protocol).
4) Subjects must have been in good health based on medical history, physical exam and routine laboratory tests.
5) Subjects must not have used tobacco products for one year prior to study screening
6) Subjects must abstain from alcohol 72 hours prior to each treatment.
7) Subjects must have been willing and able to sign written, informed consent.

This space intentionally left blank

Exclusion criteria:

1) Ongoing, active acute pancreatitis.
2) History of vagotomy.
3) History of inflammatory bowel disease.
4) History of liver disease.
5) History of alcohol or drug abuse.
6) Known sensitivity or adverse reaction to secretin.
7) Used medication, within one month of screening, known to cause pancreatitis.
8) Used anticholinergics, within one month of screening.
9) Pregnant woman, nursing mothers, or women of child bearing potential (as defined in Section 3.1).
10) Known diagnosis of pancreas divisum.
11) Known or suspected diagnosis of gastrinoma.
12) Positive screen for Hepatitis B or HIV.
13) Any pretreatment laboratory value outside the normal range, except for minor deviations considered not to be clinical significant by the investigator.
14) Used any drugs (other than hormone replacement or oral contraceptives) within 72 hours of study entrance.
15) Allergy to pork.

Table 5

ASSESSMENT SCHEDULE

Evaluation	Screen	Day –1 [a]	Day 1[a]										
	Up to Day –7	-12 Hour	-20 to-10 Min	-10 to 0 Min	-1 Min	0 Hour	5 Min	10 Min	20 Min	40 Min	60 Min	120 Min	240[c] Min
Medical History	X												
Physical Exam	X												
Chemical Profile	X												
CBC	X												
HIV	X												
Hepatitis B	X												
Urine Drug Screen	X												
Pregnancy Test[a]	X	X											
ECG	X												
Vital Signs	X	X			X	X	X	X	X	X	X	X	X
Height/Weight	X												
Admit to Clinic		X											
Informed Consent	X												
Fasting		X											
Secretin Test Dose					X								
Drug Administration						X							
Adverse Events						X	X	X	X	X	X	X	X
Fluid Samples			X	X		X		X	X	X			
Release from Clinic													X

Only patients that completed all four secretin stimulation tests (SST) were to be included in results. Safety data was to be included on all patients however.

The SST was performed as described in the Ferring product package insert.

> A Dreiling type, radiopaque, double-lumen tube is passed through the mouth following a 12 – 15 hour fast. The proximal lumen of the tube is placed in the gastric antrum and the distal lumen just beyond the pailla of Vater with the aid of fluoroscopic guidance. The positioning of the tube must be confirmed and the tube secured prior to secretin testing. A negative pressure of 25 – 40 mmHg is applied to both lumens and maintained throughout the test. Interruption of suction at 1 minute intervals improves the reliability of fluid collections. When uncontaminated duodenal contents are obtained, i.e. when these secretions are clear, although possibly bile stained, and have a pH of ≥ 6.0, a baseline sample of duodenal fluids is collected for 2 consecutive 10 minute periods. Subsequent to the baseline collections, the study Drug is injected intravenously in approximately 1 minute. Duodenal fluid is then collected for 60 minutes after secretin administration. The aspirate is fractioned into four collection periods, the first two at 10 minute intervals, and the last two at 20 minute intervals. The duodenal lumen of the tube is cleared with an injection of air after collection of each fraction. Wide variation in volume of the aspirate will be indicative of incomplete aspiration or contamination. Each fraction of duodenal fluid is to be chilled and subsequently analyzed for volume and bicarbonate concentration.

8.1.1.3.2 Endpoints

The endpoints were those associated with the standard secretin test as outlined in the package insert for the approved Ferring BPS:

1. Total pancreatic output volume for two ten minute intervals and two twenty minute intervals
2. Bicarbonate concentration for each interval
3. In addition, the sponsor calculated total bicarbonate output.

8.1.1.3.3 Statistical considerations

The sponsor only planned a descriptive statistical analysis. The small number of observations severely limits the value of any statistical analysis.

The reviewing medical and statistical teams assessed the data in a descriptive statistical manner independent of the sponsor's approach.

8.1.1.4 Results

Fifteen subjects were enrolled. Two subjects withdrew from the study following failed attempts at intubation with the Dreiling tubes before the first study period. No data were generated for these patients. One subject could not tolerate intubation during study period #2 and withdrew. The single data set from this patient was not included in the results. Patients were added to the study to achieve the goal of 12 subjects.
Table 6 displays the result of the study.

Table 6

EXOCRINE PANCREAS RESPONSE TO SYNTHETIC AND BIOLOGICALLY DERIVED PORCINE SECRETINS

Drug + Dose (µg/kg or CU/kg)	Parameter Mean (SD)	Collection Period (minutes)						
		-20 to -10	-10 to 0	0 - 10	10 – 20	20 – 40	40 - 60	Comb 0 - 60
Synthetic 0.05	Total Vol. (mL)	27.2 ± 17.0	19.7 ± 11.6	43.0 ± 21.9	35.9 ± 14.6	49.6 ± 21.7	41.3 ± 26.5	169.8 ± 54.1
	HCO_3 Con. (mEq/L)	2.8 ± 7.6	3.4 ± 11.8	59.6 ±33.2	104.7 ± 19.0	106.1 ±15.7	89.3 ± 16.6	92.5 ± 16.7
	HCO_3 (mEq)	0.09 ± 0.25	0.10 ± 0.33	3.01 ± 2.35	3.69 ± 1.49	5.26 ± 2.45	3.69 ± 2.45	15.65 ± 5.87
Synthetic 0.2	Total Vol. (ml.)	19.9 ± 19.6	9.8 ± 8.9	49.9 ± 21.6	40.5 ± 25.0	77.8 ± 39.2	67.2 ± 40.3	235.5 ± 92.2
	HCO_3 Con. (mEq/L)	3.3 ± 8.1	5.3 ± 11.3	64.9 ± 24.1	91.2 ± 21.0	104.9 ± 6.3	100.6 ± 12.5	94.5 ± 7.4
	HCO_3 (mEq)	0.02 ± 0.05	0.05 ± 0.11	3.49 ± 1.99	3.67 ± 2.54	8.25 ± 4.25	6.75 ± 4.01	22.16 ± 9.12
Synthetic 0.4	Total Vol. (ml.)	17.7 ± 16.5	12.8 ± 11.1	46.1 ± 30.4	38.9 ± 23.0	83.3 ± 32.7	100.3 ± 27.7	268.6 ± 67.5
	HCO_3 Con. (mEq/L)	2.6 ± 5.2	3.9 ± 7.0	56.5 ± 32.7	93.6 ± 13.3	101.1 ± 12.0	98.4 ± 14.2	91.5 ± 13.8
	HCO_3 (mEq)	0.09 ± 0.20	0.04 ± 0.07	3.21 ± 2.48	3.86 ± 2.54	8.32 ± 3.10	9.75 ± 2.51	25.14 ± 7.74
Biological 1 CU	Total Vol. (mL)	21.8 ± 25.3	11.8 ± 9.0	45.2 ± 17.6	47.7 ± 20.8	76.0 ± 37.5	76.0 ± 44.5	244.8 ± 101.7
	HCO_3 Con. (mEq/L)	5.3 ± 8.8	9.0 ± 10.7	76.0 ± 11.0	102.7 ± 6.8	106.6 ± 6.9	103.3 ± 9.8	99.7 ± 3.6
	HCO_3 (mEq)	0.13 ± 0.20	0.10 ± 0.15	3.52 ± 1.64	4.92 ± 2.24	8.00 ± 3.73	7.62 ± 4.09	24.05 ± 9.93

APPEARS THIS WAY
ON ORIGINAL

Table 6 shows that of the three dose levels of SPS, the 0.2 µg/kg was the most closely correlated to the 1CU BPS dose. The relationship between the 0.2 µg/kg SPS and the 1CU BPS was consistent: the mean SPS values were lower than the BPS means for all three parameters of volume, bicarbonate concentration and total bicarbonate. The 0.4 µg/kg SPS was less consistent than the 0.2 dose in its relation to the BPS results.

Table 7 shows the results of the peak bicarbonate concentrations for each individual subject. The peak concentrations for each patient are above 95 with a dynamic range of [illegible] to [illegible] for the SPS and [illegible] to [illegible] for the BPS. This table shows the variability in the time period associated with the maximal bicarbonate output. Thus, no one period can be used in isolation. Results of the entire 4 period study are needed to obtain the optimal sensitivity and specificity.

Table 7

Pt. #	Peak Bicarbonate Concentration (mEq/L) (period #)		Lowest Bicarbonate Concentration (mEq/L) (period #)	
	BPS (µg/kg)	SPS (0.2 mcg/kg)	BPS (1 µg/kg)	SPS (0.2 mcg/kg)
1	[illegible]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

Sponsor's Conclusions:

In this study of healthy subjects:

1. Over the dose range tested there was a modest dose response for pancreatic juice volume but a near maximal stimulation of bicarbonate concentration at all doses tested.

2. Total bicarbonate output for the entire 60-minute collection period were "***not different***" for the 0.2 and 0.4 µg/kg doses of SPS and the 1µg/kg of BPS

having impaired pancreatic function based on bicarbonate concentration in response to SPS 0.2 μg/kg while 0/12 would be considered impaired based on the results using the BPS. These results represent a specificity of 75% for the SPS and 100% for the BPS. Using volume (ml/kg/hr) as the parameter of comparison and the definitions in the current label, 2/12 healthy subjects during the 0.2 μg/kg SPS test and 1/12 healthy subjects during the 1 μg BPS test would be classified as impaired. These results represent a specificity of 83% for SPS and 92% for BPS.

Peak bicarbonate concentration during any one of the 4 collection periods of the secretin stimulation test may be the best parameter to use in considering pancreatic function. Variability in response time to the injection and the inherent limitations of attempting to suction all of the pancreatic fluid produced during a given interval make this parameter appealing. **Using this parameter, all twelve healthy subjects had at least one of the four collection periods with a bicarbonate concentration of greater than 90 mEq/L with both SPS and BPS. The specificity of the Secretin stimulation test using the 90 mEq/L peak concentration is 100 percent in a small population of 12 subjects with no evidence of pancreatic disease. This specificity cannot be extrapolated to other populations such as patients with clinical presentations that lead to an assessment of pancreatic function.**

The peak bicarbonate concentration (mEq/L) values for each individual patient from studies 97-1 and 98-1 are displayed in Figure 1. The statistical reviewer Dr. Chen prepared this figure. The letter H (for healthy) on the plot designates the 97-1 patients and the BPS derived values for each patient are plotted against the SPS for the same patient. The line through the figure has a slope of one, the theoretical pharmacodynamic equivalence of the two tests. The healthy patients hover close to the line. 8/12 have lower values with the SPS compared to the BPS based secretion tests; 3 subjects straddle the line and only one is slightly above the line. This suggests that there may be systematic pattern of lower pharmacodynamic potency of the SPS compared to the BPS. This pattern is displayed in a tabular form in table 2.3.1 of the statistical review. This table shows the 95% confidence limits for the difference in group mean (SPS-BPS). The predominance of negative values indicates that the BPS is associated with higher pharmacodynamic values than the SPS. The other two parameters studied (volume and total bicarbonate) do not show the same pattern. These two variables show much greater variance as reflected by the lower and upper bounds of the 95% confidence interval for the ratio of the SPS and the BPS expressed as a percentage. This table displays the lower specificity associated with these parameters compared to the peak bicarbonate parameter.

The dynamic range for the secretin stimulation test for both SPS and the BPS for the 12 healthy volunteers is above the dynamic range for the 8 pancreatitis patients.
The letter R (for recovered) indicates patients with a past history of chronic pancreatitis that had normal range results using the BPS based secretin stimulation test. These subjects are informative in terms of test sensitivity and will be discussed in the review of study 98-1.

3. The 0.05 µg/kg dose resulted in a ***"significantly lower"*** volume and total bicarbonate output than the other doses.

4. 0.2 µg/kg dose was ***"statistically equivalent"*** to the 1µg/kg dose of BPS in terms of pharmacologic stimulation of pancreatic exocrine function as measured by volume, bicarbonate concentration and total bicarbonate output over a 60-minute collection period. These products both produced near maximal stimulation of the exocrine pancreas and the 0.2 µg/kg dose of SPS is on the plateau of the dose response curve.

5. Both the SPS and the BPS were safe and well tolerated at all doses tested.

In summary, according to the sponsor, SPS at 0.2 µg/kg produces an ***"equivalent"*** physiologic compared to 1CU of BPS and will be ***"equivalent"*** for the evaluation of exocrine pancreatic function.

Reviewers comments

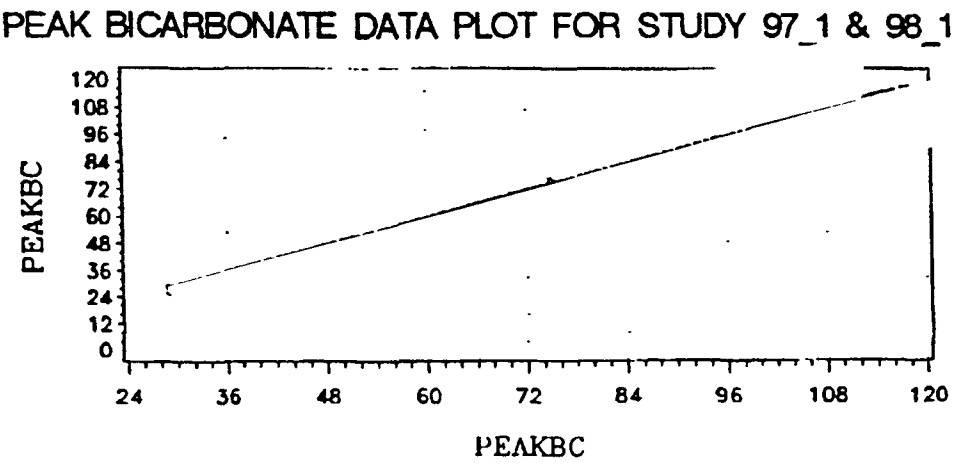
1. The reviewer does agree with the sponsor that 0.2 µg/kg dose was the closest match to the 1 µg BPS for use in testing in patients with pancreatic disease. The sponsor assumed that equivalence could be defined as difference of no greater than 20% in the numeric group mean pharmacodynamic values of the two products studied. This definition of equivalence may not be the most appropriate way to evaluate a diagnostic test that relies on a binary test result. If a significant degree of specificity, sensitivity and diagnostic accuracy is lost by a 20% higher or lower pharmacodynamic effect of the test, the tests are not equivalent. The statistical analysis, as pointed out by the statistical reviewer, was based on the null hypothesis of showing a difference. This is not the same as showing equivalence.

2. Diagnostic equivalence is the endpoint of interest. Such a comparison would require a much larger sample size of subjects with both normal and abnormal pancreatic function. Despite requests by the Division to supply such data, the sponsor chose to submit an NDA with only pharmacodynamic data. The issue of diagnostic accuracy will be addressed in the review of study 98-1. The analysis of this study does provide information on the optimal dose selection for further study of the diagnostic value of the secretin stimulation test in the assessment of pancreatic exocrine function. The statistical review of this NDA points out a trend towards lower peak bicarbonate levels with the SPS compared to the BPS for both healthy and chronic pancreatitis subjects. The effects of this trend will be discussed in the review of study 98-1.

3. While population means for the healthy subjects in study 97-1 are descriptively close between 0.2 µg/kg SPS and the 1 µg dose of BPS, the variability of results and outliers are important parameters in assessing the value of a diagnostic test. The label of the currently approved BPS states that " A volume response of less than 2 ml/kg/hr, bicarbonate concentration of less than 90 mEq/kg/hr and bicarbonate output of less than 0.2 mEq/kg/hr are consistent with impaired pancreatic function." Using these criteria, 4/12 normal patients studied in Study 97-1 would be classified as

Figure 1

Peak bicarbonate concentration (mEq/L) for subjects in study 97-1 and 98-1



Note: PEAKBC in vertical axis is peak bicarbonate concentration from sPS treatment; PEAKBC in horizontal axis is peak bicarbonate concentration from bPS treatment.

s (sick) = chronic pancreatitis patient
h = healthy subjects
r (recovered) = patients with a history of chronic pancreatitis and abnormal SST in the past but normal SPS and BPS based SSTs at the time of NDA study

4. These results were achieved under the ideal conditions in a small number of patients. As noted earlier in this review, physicians with extensive experience with the secretin stimulation test will obtain the best results. Physicians or laboratories performing few tests may have meaningfully less reliable results than those obtained by the investigator in the current study, Philip Toskes M.D.

8.1.1.4.3 Safety

Safety information was collected during the SST and for 4 hours after infusion of secretin.

One patient experienced flushing for five minutes after receiving 0.2 and 0.4 µg/kg SPS and 1 µg/kg BPS. That individual did not have a reaction in response to the lowest dose of SPS (0.05 µg/kg).

There were no deaths or serious or severe adverse events reported.
The sponsor identified no significant changes in vital signs or laboratory safety parameters by comparing pre and post values. One of the twelve patients had a hypertensive blood pressure response at the end of the 60 second infusion of the lowest dose of SPS (0.05 µg/kg). That subject's blood pressure rose from 99/48 pre-dose to 152/113 immediately post-dose. Within five minutes the blood pressure had returned to baseline range of 98/61. There was no significant change in pulse during this interval. No such change occurred with any of higher doses in this subject. The data suggest no pharmacologic relationship between this one event and the study drug.

8.1.1.5 Reviewer's conclusions of study results

1. The peak bicarbonate concentration is the parameter with the most consistent and reproducible results across subjects and between products tested.

2. The specificity of the secretin test in a small sample of 12 healthy subjects with no clinical signs or symptoms of pancreatitis or pancreatic exocrine insufficiency is 100% when using the peak bicarbonate concentration cutoff of either 80 or 90 mEq/L.

3. This small study suggests that there may be a small difference in pharmacodynamic potency between the SPS 0.2 µg/kg dose and BPS 1 µg when used to test pancreatic exocrine function in healthy patients. The available data are insufficient to assess the full impact of this possible difference on the diagnostic value of SPS compared to BPS.

8.1.2 98-1 A randomized, crossover study evaluating synthetic porcine secretin and biologically derived porcine secretin for the assessment of exocrine pancreatic function in patients with a diagnosis of chronic pancreatitis

8.1.2.1 Objective:

To obtain comparative pharmacological and safety data for 0.2 µg/kg synthetic porcine secretin and 1 µg/kg biologically derived porcine secretin as diagnostic agents in patients with a diagnosis of chronic pancreatitis.

The hypothesis tested was that SPS and BPS at the doses tested will produce similar exocrine pancreas responses in terms of volume and bicarbonate concentration.

8.1.2.2 Design:
Randomized crossover two treatment study

The dose chosen was based on the results of study 97-1. In that study the results of the 0.2 µg/kg were closest to the 1 µg-dose results using the BPS. The study was not blinded as the study nurse who reconstituted the study drug and dispensed the dose to the investigator knew the identity of the test being administered. This may have potentially affected the results of the protocol. The prior knowledge of the results of the first test may have affected interpretations of the second test. The methodology of measuring volume of pancreatic secretion may be susceptible to bias. Checking for tube patency, timing of collection intervals, patient positioning all may impact on the results.
The sponsor stated that the patient assignment was carried out randomly to one of two possible sequences of administration of the two study drugs. The randomization schedule appears below in table 8. This sequence is not random.

Table 9

RANDOMIZATION

SUBJECT #	BLOCK	PERIOD 1	PERIOD 2
1	1	A	B
2	1	B	A
3	2	A	B
4	2	B	A
5	3	A	B
6	3	B	A
7	4	A	B
8	4	B	A
9	5	A	B
10	5	B	A
11	6	A	B
12	6	B	A

Treatment A Synthetic Porcine Secretin, 0.2 µg/kg

Treatment B Biologically Derived Porcine Secretin, 1 CU/kg

8.1.2.3 Protocol

The protocol was similar to that of 97-1 except that the pre and post injection pancreatic fluid collection periods were of 15 minute rather than 10 and 20 minute durations used in 97-1 that also appears on the current label of BPS. This difference may impact the ability to compare results of peak bicarbonate concentrations between the healthy subjects in 97-1 and the patients with chronic pancreatitis in 98-1.

The study population is defined below. Unfortunately the sponsor gave no definition of a clinical diagnosis of pancreatitis.

Inclusion Criteria

The study enrolled patients who met all of the inclusion criteria as listed below.

1) Males or females of non-childbearing potential (if childbearing potential must be using a medically approved contraceptive method).
2) Patients with a diagnosis of chronic pancreatitis documented by a prior secretin stimulation test with bPS and by clinical and laboratory findings consistent with this diagnosis.

These inclusion criteria are appropriate to assess the similarity in performance during the secretin stimulation test between the two forms of secretin. The absence of a prespecified definition that excludes the test under study (the secretin stimulation test) has produced a potential verification bias into the study and may affect the value of this study in assessing the diagnostic accuracy of the test. Review of the case report forms reveals that 10/12 subjects had clinical grounds that could justify consideration of the diagnosis independent of the SST. 1/12 subjects (#6) did not have compelling support for the diagnosis of chronic pancreatitis independent of the SST. The sponsor did not provide the clinical data requested on subject #12 in order to assess the diagnosis of pancreatitis. Table # 10 shows the extent of data presented. Thus, despite the absence of any prespecified criteria for the diagnosis of pancreatitis, 10/12 subjects had compelling data to support their inclusion in this study. The inclusion of the other two subjects is less well supported.

Exclusion Criteria

The study enrolled patients who did not exhibit any of the exclusion criteria listed below.

1) Active acute pancreatitis
2) Use of anticholinergic medications within one week of testing
3) Known sensitivity or adverse reaction to secretin
4) Pregnant or nursing female
5) Any medical condition, which in the judgment of the investigator would prevent the patient from safely undergoing the secretin stimulation test as described in Appendix A of the Protocol (Appendix 15.1 of Study Report).

8.1.1.3.2 Study Endpoints

Pharmacological and Safety Measurements

This study evaluated the following pharmacological, diagnostic efficacy, and safety variables.

1. Pharmacological variables
   - Volume of pancreatic juice during specified time periods post secretin dosing
   - Bicarbonate concentration of pancreatic juice during these time periods
   - Total bicarbonate output for one hour post secretin dosing
2. Diagnostic variable (efficacy)
   - Positive diagnosis of chronic pancreatitis based on peak bicarbonate concentration < 80 mEq/L
3. Safety variables
   - Adverse events during each treatment period
   - Vital signs pre and post secretin dosing

Unfortunately the sponsor did not prespecify the variables of primary importance. The time interval of interest was not defined. The medical literature includes several diagnostic criteria for use in relation to the secretin stimulation test. It would be important to specify a priori whether volume or bicarbonate concentration is to be considered the primary endpoints pharmacodynamic endpoint. Total 1-hour results or peak results can also be used and should have been part of the prespecified endpoints. The analysis is therefore essentially hypothesis generating. The assessment must therefore be qualitative rather than quantitative. In the study report the sponsor retrospectively defined a peak bicarbonate concentration during any collection period of 80 mEq/L as the "diagnostic outcome for chronic pancreatitis".

Primary Efficacy Variable

The primary diagnostic efficacy variable was the diagnosis of chronic pancreatitis in these patients with a documented diagnosis of chronic pancreatitis. The comparison of diagnostic results with sPS and bPS was analyzed.

This primary efficacy endpoint cannot be adequately assessed due to the small number of cases. This represents a major problem.

The statistical reviewer Dr. Chen evaluated the ability of such a small database to provide statistical information regarding the diagnostic accuracy of the proposed product. This analysis appears in the reviewer's comments and conclusions section.

8.1.1.3.3 Statistical Plan

The statistical plan outlined in the original protocol is unclear:

" The study is a two-way Latin square in which the treatments are synthetic porcine formulation 0.2 μg/kg (Treatment A) and extracted porcine secretin 1 μg/kg (Treatment B). The GLM procedure from SAS will be used to test for treatment and carryover effect. Multiple comparisons and regressions will be utilized to compare treatments A and B. Summary and descriptive statistics will be provided for the treatment effects.

The HCO_3 content in mEq/L will be utilized to calculate the power of the study to detect the treatments at alpha = 0.05."

No statistical hypothesis was defined. The retrospective definition of 80 mEq/L for any period of study as the "diagnostic outcome for pancreatitis" may have been appropriate if the study population had been large enough to independently serve as an adequate database to use in defining a diagnostic range for the test. As performed however, with only 8 subjects meeting the sponsor's post hoc definition of chronic pancreatitis, there is

no way to assess the independent ability of the final chosen diagnostic criterion to accurately diagnose pancreatic insufficiency when applied to the proposed product.

8.1.1.4 Results:

8.1.1.4.1 Demographics:

Table 10

DEMOGRAPHIC CHARACTERISTICS

Pat #	Initials	Date Enrolled	DOB (Age)	Height (cm)	Weight (kg)	Age	Gender	Race
1		09/15/98		139.7	43.5	52	F	B
2		09/17/98		160.0	60.2	56	F	C
3		09/22/98		185.5	75.7	56	M	C
4		09/24/98		172.5	79.3	63	F	C
5		10/01/98		157.5	58.0	61	F	B
6		10/13/98		167.5	71.6	51	F	C
7		10/27/98		165.0	68.0	69	M	C
8		10/29/98		170.0	57.3	39	F	C
9		11/05/98		165.0	88.6	56	F	C
10		11/12/98		178.0	84.0	37	M	C
11		11/17/98		157.5	100.0	69	F	C
12		12/01/98		178.0	93.2	64	M	C

Table 11

MEDICAL HISTORY OF PANCREATITIS

Pat #	Date Chronic Pancreatitis Diagnosed	Secretin Stimulation Test		Elevated Biochemical Markers		Ultrasound		Other		
		Yes	No	Yes	No	Yes	No	Yes	If yes, specify	No
1	1984	✓				✓		✓	ERCP, abdominal x-rays, CT scan	
2	08/04/88	✓						✓	CT scan	
3	09/11/98	✓			✓			✓	trypsin	
4	1993	✓		✓				✓	CT scan, trypsin	
5	06/18/84	✓			✓	✓		✓	abdominal x-ray	
6	10/21/97	✓								
7	04/01/97	✓			✓			✓	ERCP	
8	10/03/96	✓								
9	04/10/92	✓		✓				✓	laboratory work	
10	05/31/95	✓		✓				✓	serum trypsin	
11	04/17/97	✓		✓				✓	MRI, ERCP, amylase	
12	11/19/98	✓		✓						

***Reviewer's comment**: The initial submission did not contain any primary source documents related to the diagnosis of chronic pancreatitis. Several of the case report forms included short handwritten phrases describing the basis upon which the subjects carried the diagnosis of chronic pancreatitis. The division requested further documentation. A submission from the sponsor dated January 28, 2000 included Forms titled "Clinical data related to pancreatitis". The clinical basis for the initial diagnosis was presented but unfortunately the information on the current clinical status of these subjects was not provided. Therefore no correlation between the clinical manifestations of "chronic pancreatitis and the SST can be made.*

The forms provided by the sponsor were reviewed. Forms for 1/12 subjects were missing. 4/12 dates of diagnosis were inconsistent with such data that appears in table 10 above. If the indication of SPS were to include that specific diagnosis of chronic pancreatitis rather than pancreatic exocrine function, the lack of specific inclusion criteria and the missing clinical information and inconsistencies would be critical inadequacies of this study. As the primary reference for assessing the SPS is based on comparisons with BPS, these issues are disturbing but do not negate the results of the study.

8.1.1.4.2 Efficacy endpoint outcome:

The sponsor did not prespecify primary efficacy endpoints. The analysis provided by the sponsor is reproduced in tables 12 and 13.

TABLE 12

PANCREATIC STIMULATION RESULTS FOR 15 MINUTE INTERVALS

Synthetic Porcine Secretin vs Biological Porcine Secretin											
TREAT		V_B	BC_B	V_15	BC_15	V_30	BC_30	V_45	BC_45	V_60	BC_60
bPS	Mean	35.08	14.83	57.67	42.92	38.17	64.75	28.82	61.08	40.90	56.50
bPS	STD	45.12	15.49	32.59	16.12	30.33	25.53	25.99	31.01	27.22	31.32
bPS	%CV	128.60	104.39	56.52	37.56	79.47	39.44	90.20	50.77	66.56	55.44
sPS	Mean	24.83	19.00	59.33	45.58	34.60	62.17	36.71	62.92	32.29	54.75
sPS	STD	18.72	17.69	35.28	24.84	28.03	30.46	35.90	32.58	34.98	28.26
sPS	%CV	75.39	93.13	59.46	54.50	81.01	48.99	97.80	51.79	108.33	51.62
	Prob	0.3494	0.3978	0.7976	0.5489	0.5624	0.4227	0.1762	0.622	0.3625	0.8044

BC = bicarbonate concentration (mEq/L)
V = volume (mL)

Table 13

PANCREATIC STIMULATION RESULTS FOR 60 MINUTE SAMPLE

Synthetic Porcine Secretin vs Biological Porcine Secretin					
TREAT		V_1_60	BC_1_60	B_TBC	TBC
bPS	Mean	165.55	55.12	9.59	10.45
bPS	STD	102.67	22.56	9.11	10.38
bPS	%CV	62.01	40.93	94.98	99.35
sPS	Mean	162.93	54.28	10.38	10.85
sPS	STD	122.10	26.58	10.93	11.37
sPS	%CV	74.94	48.96	105.30	104.77
	Prob	0.8848	0.7029	0.4961	0.7099

BC = bicarbonate concentration (mEq/L)
V = volume (mL)
TBC = total bicarbonate (mEq)

The mean BPS and SPS values for the parameters displayed above are quite similar. The variability is quite large however. This is not inconsistent or surprising. There is great biologic variability among subjects with chronic pancreatitis and the test inherently has limited reproducibility. The parameter of importance in assessing this proposed product is the diagnostic accuracy as compared to the approved BPS. Table 13 displays the results for the diagnostic parameters that appear in the current label of secretin.

Table 14

Pt. #	Date of Dx	Date of SST	(0-60 min) cc/kg/hr	Total Bicard mEq/L (0-60 min)	Peak Bicard mEq/L (period)	Peak Bicarb at time of Dx (yr of initial SST)
1A	1984	1998	2.2			
1B			3.3			48 (1997)
2A	1988	1998	2.4			
2B			2.1			68 (1997)
3A	1998	1998	1.0			
3B			2.2			79 (1998)
4A	1993	1998	0.2			
4B			1.5			12 (1997)
5A	1984	1998	1.8			
5B			1.4			68 (1971)
6A	1997	1998	6.0			
6B			6.1			67 (1997)
7A	1997	1998	2.8			
7B			2.2			77 (1997)
8A	1996	1998	4.6			
8B			4.5			77 (1996)
9A	1992	1998	1.1			
9B			1.0			69 (missing)
10A	1995	1998	1.6			
10B			1.7			40 (1996)
11A	1997	1998	0.6			
11B			0.5			63 (1998)
12A	1998	1998	3.6			
12B			2.3			54 (1998)

A= SPS
B=BPS

The Ferring BPS label suggests that peak bicarbonate concentrations of under 90 mEq/L or volume output of less than 2 ml/kg/hr are indicative of impaired pancreatic exocrine function. This suggestion is based on the medical literature available in 1980. Based on peak bicarbonate concentration, 3/12 of the previously diagnosed patients with pancreatic insufficiency no longer fit that category. Based on the volume of secretion 6/12 are no longer insufficient.

The two tests are concordant in all cases using the peak bicarbonate criteria. They are discordant in one case using the volume criteria.

The principal investigator, Philip Toskes M.D., a leader in the field of pancreatitis uses criteria other than those in the label to define an abnormal secretin stimulation test.

His laboratory uses peak bicarbonate concentration of **80 mEq/L** and pancreatic fluid output of **1.5 cc/kg/hr** as the lower range of normal. Using Dr. Toskes criteria, 9/12 patients in this study did not have pancreatic insufficiency based on pancreatic fluid volume and 4/12 did not have pancreatic insufficiency based on peak bicarbonate concentration using the BPS. Using Dr. Toskes criteria there is discordance of diagnosis in 3/12 patients based on volume and 0/12 based on peak bicarbonate concentration. However only 8/12 subjects had pancreatic insufficiency based on the current SST. No clinical information is provided to assess whether they currently have clinical signs of chronic pancreatitis or whether they have "recovered". Interestingly, three of the apparently recovered subjects with a history of pancreatic insufficiency in association with a clinical diagnosis of pancreatitis experienced this pancreatic exocrine recovery within two years of the previously abnormal SST test. This is a very small database to assess for diagnostic comparability.

The underlying practical limitations involved in performing the secretin stimulation test add to the difficulty in accepting the results of the small current database as adequate to assess the diagnostic value of the proposed product approval.

8.1.1.4.3 Safety results

One patient experienced a headache lasting 5 hours during and following the SPS test. This resolved spontaneously without treatment. A second patient experienced a hematoma at the site of the intravenous access site.
No other adverse events were reported.

8.1.1.6 Reviewer's comments and conclusions

1. The limited data base provided suggests good correlation between the approved BPS at a dose of 1 μg/kg and the proposed SPS product at a dose of 0.2 µg/kg when used to assess pancreatic exocrine function. Figure 1 and table 8 of this review provide the qualitative visual and statistical representations of the similarities.

2. The diagnostic accuracy in differentiating chronic pancreatitis from other causes of pancreatic exocrine insufficiency cannot be assessed from the data provided.

3. A probability analysis provided by Dr. Chen is reproduced below:

In order to assess the robustness of the 100% agreement in the results to diagnose pancreatitis by the two diagnostic agents, sPS and bPS, reported by the sponsor for Study CRC-98-1, this reviewer calculates the probability of 100% agreement between sPS and bPS in the diagnosis of pancreatitis using eight sick patients, under the assumption that there exits a certain disagreement probability between these two agents.

Since each patient went through two tests by sPS and bPS, the disagreement probability between these two tests for each patient is the sum of the two probabilities: sPS positive and bPS negative and vice versa. It is noticed that even if the disagreement probability for the two diagnostic agents, sPS and bPS, on each sick patient is 0.25, due to small number of sick patients, the probability for the 100% agreement in the diagnostic results tested by these two agents on the eight sick patients is still 0.10.

This analysis suggests that study 98-1, standing alone would not be adequate statistically to support the use of SPS in place of BPS in the secretin stimulation test for the assessment of pancreatic exocrine function. However, in view of the similarity in physiologic activity on pancreatic secretion between BPS and the SPS and the diagnostic concordance in this study as well as the published medical literature on the SPS product, the secretin stimulation test using the proposed SPS appears to have diagnostic value.

4. As noted by the statistical reviewer, Dr. Chen and graphically represented in figure 1 of this review, the peak bicarbonate concentrations obtained using the BPS are generally higher than those obtained using the SPS. Review of the "dose ranging" data from study 97-1 in table 6 of this review indicates that this difference is not due to the choice of SPS dose. The BPS based SST results are higher than both doses of SPS associated results. These results are counterintuitive. This trend may be meaningful in some instances where the diagnostic results are borderline. This may need to be discussed in labeling.

8.1.2 CRC 98-2 An open label randomized crossover study evaluating synthetic porcine secretin and synthetic human secretin for the assessment of exocrine pancreas function in patients with a diagnosis of chronic pancreatitis

8.1.3.1 Objective:

"To obtain supplemental pharmacological efficacy and safety data in standard clinical use for the diagnostic indications approved for the extracted product".

8.1.3.2 Hypothesis:

"Synthetic human secretin will be a safe and effective diagnostic agent for chronic pancreatitis and produce exocrine pancreas responses in terms of volume and bicarbonate concentration similar to synthetic porcine secretin."

Reviewer's Comment
As noted in the review of study 98-1 no statistical hypothesis was proposed and therefore assessment of study results is limited to descriptive statistics.

8.1.3.3 Design:

The original protocol describes the study as open label. The final study report describes it as a blinded study based on the assumption that a site nurse who was aware of the drug identity was not a study participant. In a secretin stimulation test this may not be a valid assumption.

The design was identical to study 98-1 except that the active comparator was synthetic human secretin 0.2 µg/kg instead of biologic porcine secretin 1 μg/kg.
The "randomization scheme is identical to that used in 98-1 (shown in table 4).

8.1.3.4 Protocol:

The protocol was identical to that of study 98-1.

8.1.3.5 **Results:**

Patient disposition: The first nine patients are duplicate patients from study 98-1.

Table 15

DEMOGRAPHIC CHARACTERISTICS

Pat #	Initials	Date Enrolled	Age	Height cm	Weight kg	Gender	Race
1	[redacted]	1/28/99	53	140	42.2	F	B
2		2/2/99	51	167.5	73	F	W
3		2/4/99	57	160	58.9	F	W
4		2/9/99	64	178	93.2	M	W
5		2/11/99	70	157.5	101	F	W
6		2/16/99	61	157.5	58	F	B
7		2/23/99	56	183	75.9	M	W
8		2/25/99	69	165	69	M	W
9		3/11/99	56	165	84.1	F	W
10		4/8/99	27	178	83.64	M	W
11		5/5/99	68	160	93.2	F	W
12	[redacted]	6/29/99	76	162.5	61.6	F	W

Table 16

MEDICAL HISTORY OF PANCREATITIS

Pat #	Date Chronic Pancreatitis Diagnosed	Secretin Stimulation Test		Elevated Biochemical Markers		Ultrasound		Other		
		Yes	No	Yes	No	Yes	No	Yes	If yes, specify	No
1	1984	✓				✓		✓	ERCP, abdominal X-ray – 92, CT scan	
2	10/21/97	✓				✓		✓	SST – 10/97, US – 1998	
3	08/04/88	✓						✓	CT, ERCP	
4	11/19/98	✓		✓		✓		✓	Abdominal ultrasound – 1996, abdominal CT – 1997 or 1998	
5	04/17/97	✓		✓				✓	MRI, ERCP, amylase	
6	06/18/84	✓			✓	✓		✓	CT scan, ERCP	
7	09/11/98	✓			✓	✓		✓	Abdominal CT, ERCP, trypsin	
8	04/01/97	✓			✓			✓	ERCP	
9	04/10/92	✓		✓				✓	Serum trypsin, lipase, amylase	
10	12/17/94	✓		✓		✓			CT Scan	
11	05/98	✓								
12	1995	✓				✓		✓	Abdominal CT Scan	

Results:

Table 17

PANCREATIC STIMULATION RESULTS FOR 15 MINUTE INTERVALS

Synthetic Porcine Secretin vs Synthetic Human Secretin Study											
TREAT		V_B	BC_B	V_15	BC_15	V_30	BC_30	V_45	BC_45	V_60	BC_60
sHS	Mean	29.58	10.92	54.17	38.08	34.08	55.08	36.08	63.42	41.50	57.33
sHS	STD	34.02	7.84	33.27	20.63	22.35	20.71	25.32	21.01	30.98	15.14
sHS	%CV	115.01	71.86	61.42	54.18	65.58	37.59	70.16	33.13	74.64	26.40
sPS	Mean	27.17	11.58	53.25	40.58	39.42	56.75	38.25	62.17	39.08	54.33
sPS	STD	22.31	11.51	37.49	12.54	23.21	20.08	25.13	20.11	25.19	20.67
sPS	%CV	82.13	99.35	70.40	30.89	58.88	35.39	65.71	32.35	64.46	38.05
	Prob	0.8272	0.8823	0.8997	0.6262	0.5043	0.5878	0.6854	0.5957	0.5878	0.306
sHS = synthetic human secretin											
sPS = synthetic porcine secretin											
B_ = Baseline Corrected											

Table 18

PANCREATIC STIMULATION RESULTS FOR 60 MINUTE SAMPLE

Synthetic Porcine Secretin vs Synthetic Human Secretin Study (CRC98-2)				
TREAT		**V_1_60**	**B_TBC**	**TBC**
sHS	**Mean**	165.83	9.46	9.73
sHS	**STD**	101.56	8.00	8.20
sHS	**%CV**	61.24	84.59	84.27
sPS	**Mean**	170.00	9.72	9.91
sPS	**STD**	87.40	7.99	7.96
sPS	**%CV**	51.41	82.20	80.33
	Prob	**0.8013**	**0.8412**	**0.8896**
BC = bicarbonate concentration (Meq/L)				
V = volume (mL)				
TBC = total bicarbonate (Meq)				

Table 19

Pt. #	Date of Dx	Date of SST	(0-60 min) cc/kg/hr	Peak Bicarb mEq/L (period #)
1A	1984	1999	2.7	
1B			1.4	
2A	1997	1999	5.4	
2B			5.0	
3A	1988	1999	2.7	
3B			2.8	
4A	1998	1999	1.6	
4B			3.6	
5A	1997	1999	0.5	
5B			0.4	
6A	1984	1999	1.9	
6B			1.8	
7A	1998	1999	1.7	
7B			2.7	
8A	1997	1999	3.3	
8B			1.9	
9A	1992	1999	1.2	
9B			1.4	
10A	1994	1999	1.8	
10B			1.9	
11A	1998	1999	1.9	
11B			2.0	
12A	1995	1999	2.7	
12B			2.8	

A= SPS
B=BPS

The current label suggests that peak bicarbonate concentrations of under 90 mEq/L or volume output of less than 2 ml/kg/hr are indicative of impaired pancreatic exocrine. As previously mentioned the laboratory at the University of Florida uses 1.5 ml/kg/hr and 80 mEq/L as the lower range of normal pancreatic exocrine function.

Using the ranges represented in the label, there are 4/12 discordant cases based on volume and 1/12 discordant cases based on bicarbonate concentration. Using the University of Florida criteria there is one discordant case using volume and no discordant cases using the peak bicarbonate concentration. This study supplies three additional cases to the database of Study 98-1 where a ***past*** abnormal peak bicarbonate concentration based on the secretin stimulation test using the BPS is reproduced using the SPS product. Thus the concordance is 15/15 tests in the database.

8.1.3.6 Safety

No clinically significant adverse events were reported

Reviewer's Comment:

Study 98-2 expands the safety and pharmacodynamic database on SPS by only three patients.

Comparisons between synthetic human and porcine secretin are of interest scientifically. Such comparisons however, do not allow for comparisons to the approved BPS. Conclusions about the diagnostic value of SPS must ultimately be supported primarily by data collected on this product. The three new patients in this study (#10,11 and 12) did have results of the peak bicarbonate consistent with chronic pancreatitis based on BPS based secretin stimulation tests in 1994, 1998 and 1995. The current results generated with SPS are consistent with the older BPS generated results. One did not have chronic pancreatitis based on volume criteria of the BPS label. Interestingly, none of three met Dr. Toskes volume based criteria for chronic pancreatitis.

The results from the three new patients should be kept in mind when considering the diagnostic value of the test.

8.2 Uncontrolled open label studies for all proposed indications

Studies 97-1, 98-1 and 98-2 are the only controlled studies of the proposed indications in the NDA submission. 97-2 and 98-4 are open label studies of secretin for all four of the proposed indications. As noted earlier in the review the proposed indications included:

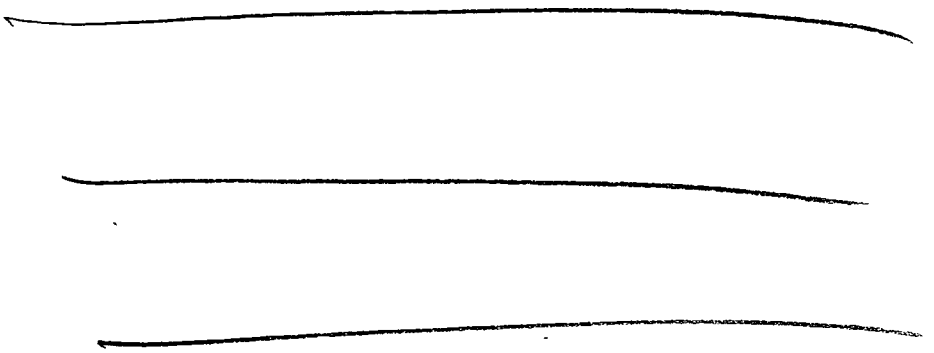
1. Evaluation of exocrine pancreas

Studies 97-1, 98-1 and to a limited extent 98-2 represent the primary basis for the assessment of SPS for the evaluation of pancreatic function. These studies support the

pharmacodynamic similarity of the drugs and to a limited extent the diagnostic similarity when using peak bicarbonate concentration as the endpoint.

Study 97-2 represents supportive data for pancreatic function indication. This data is not controlled and is not the basis for approvability of SPS for the indication of evaluation of pancreatic exocrine function.

[ ]



3. Diagnosis of gastrinoma

At the time of submission there were no data on histologically confirmed cases to review in support of approval for use in the diagnosis of gastrinoma. Six patients were exposed to SPS in the context of testing for gastrinoma. None had a final diagnosis of gastrinoma and the secretin stimulation test was negative in all patients. The Division refused to file the application for this indication based on the inadequacy of data to review. The sponsor was informed of this and at a meeting on September 14, 1999 the division informed the sponsor of the type of data that would be needed to review and consider approval for this indication. The sponsor chose to file over protest for the gastrinoma indication and notified the Division that evaluable data would be submitted for this indication during the review period. A separate NDA for this indication was therefore created administratively. Given the seriousness of the indication it was given priority review status. Review of the evidence for this indication will therefore occur under a different NDA, 21,209.

4. Facilitation of _ during ERCP

Facilitation is not a currently approved usage for BPS. The sponsor has provided no controlled data to support approval for this indication. The sponsor provided material for review from several textbooks and one testimonial letter from an expert in the field, (see appendix 1)

(Bold Italics per reviewer)

"To facilitate orifice identification, secretin can be given intravenously at 0.25 to 1 μg/kg. This generally results in vigorous pancreatic exocrine juice flow and obvious orifice dilatation. During vigorous juice flow, it may be difficult to force contrast media

retrograde to the pancreatic tail, and ***use of such force may precipitate postductography pancreatitis.*** Secretin use should therefore be reserved for difficult cannulation cases. At times, pancreatic juice flow after secretin stimulation may still be inconspicuous." [9]

"The papilla can be made more prominent and the orifice visible if the pancreas is stimulated with secretin (give 25-50 units I.V. and wait three minutes). ***A problem with secretin is that contrast must then be injected against a flow of juice. Whilst this does not appear to be dangerous, it may prove difficult to outline the entire duct system without using excessive pressure.***" [10]

"The orifice of the accessory papilla is transiently prominent during pancreatic secretion. For this reason it is helpful to give the patient an intravenous bolus of the pancreatic secretagogue, secretin. Within three minutes of an intravenous bolus, a brief but often profuse outpouring of bicarbonate-rich fluid begins. The accessory papilla becomes more prominent as fluid accumulates in the dorsal pancreatic duct, then the papilla may "wink" open. There is a brief "window of opportunity" to cannulate the accessory duct before the orifice closes again. ***It can be difficult to fill the duct fully with contrast, which is being injected against a stream of pancreatic juice.***" [11]

"Intravenous secretin in a dosage of 1 unit/kg I.V. has been recommended to increase the prominence of the accessory ampulla and to identify the orifice more clearly. ***In my experience, it has rarely been helpful.***"[12]

Appendix 1 contains a letter by ⟶ . submitted by the sponsor in the NDA. The references and letter provided by the sponsor do not suggest that approval for the indication of facilitation of cannulation of the pancreatic duct is warranted based on literature review.

There are no adequate or well-controlled data to review regarding this indication. Case reports were submitted under study 97-2. These cases do not address the safety of efficacy of secretin in this setting. This indication was not filed due to the lack of adequate data to review.

9. Overview of efficacy:

9.1 Evaluation of pancreatic exocrine function

In studies 97-1 and 98-1 the sponsor has provided comparative pharmacodynamic effects of SPS and BPS in healthy subjects and subjects with a history of pancreatic exocrine insufficiency based on the SST using BPS in association with a clinical history of chronic pancreatitis. The results of statistical comparison of group means and variance (as reflected in standard deviation) are discussed in detail in the statistician's review. The relatively large inter and intra-individual variance associated with the results of the numerous parameters studied must be attributed at least in part to biologic variability between different subjects and limitations inherent in the test methodology (sampling of duodenal contents via a nasoduodenal or oroduodenal tube). The small sample size

amplifies the degree of variability between BSP and SPS. Statistical equivalence is not proven as noted in the analysis by Dr. Wen Jen Chen. However, as noted by Dr. Chen, the reviewing statistician, the clinical setting, performance parameters and biologic basis of this test require a qualitative interpretation as well. The clinically relevant questions in this review are:

1. Does SPS have biologic activity in the assay (SST).
2. Does the SST using SPS have a meaningful diagnostic role in the assessment of pancreatic exocrine insufficiency associated with chronic pancreatitis similar to that using BPS.
3. Can one quantify the diagnostic value of the SST using SPS.

The sponsor has demonstrated the presence of assay activity of the SPS based SST. The "meaningfulness" of activity requires a subjective assessment. The Agency and the medical community made this assessment two decades ago with the approval of BPS. Usage during the interval has confirmed the value of the SST. Parameters of diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) are important for the physician to know if the test is to be properly interpreted. The advisory committee and reviewers in 1980 did not feel that adequate data existed to define diagnostic accuracy. The intervening years have allowed for additional research data and clinical experience with this diagnostic tool. This reviewer feels that such information for the physician is important. In the regulatory sense, the label must contain adequate instruction for the proper use/interpretation of an approved drug. This reviewer feels that the qualitative similarity between the SPS and BPS products in the healthy, recovered and persistently insufficient subjects examined in studies 97-1 and 98-1 is adequate to consider the two drugs "similar" diagnostically.

The recommended diagnostic parameter for the SST in much of the literature is the peak bicarbonate concentration. This is supported by the current database which showed the least variability and the highest accuracy when compared to volume of pancreatic fluid secretion and total bicarbonate secretion over 1 hour post dose. The available literature suggests that 80 mEq/l is the best cutoff to discriminate pancreatic insufficiency. The current label does not give a cutoff value and displays a table (with much less data than the current NDA database) from which the physician may independently define a cutoff.

Using the current database to support studies in the published literature, this reviewer feels that 80 mEq/l is the most useful cutoff value. A true sensitivity and specificity analysis cannot be defined using a contingency table due to the 0 value in 2 of the cells.

Table 20

Subjects with PBS over 80 (healthy)	Subjects with BPS under 80 (pancreatic insufficiency)
16	0
0	8

The total concordance between the two products in defining pancreatic insufficiency is noteworthy. Dr. Chen has pointed out however in his review that the small number of subjects prevents a statistically robust analysis. The confidence intervals for the difference between the SPS and the BPS in the two populations studied are displayed in tables 21 and 22 below. The population means are also displayed in these tables. Although the 95% confidence intervals for diagnostic concordance is not calculated, the differences between the means of the healthy subjects and those with pancreatic insufficiency is quite wide and suggests that diagnostic accuracy would not be meaningfully affected by the change from BPS to SPS. The meta-analysis in appendix 2 would suggest this as well. The diagnostic accuracy in the studies in this meta-analysis was not meaningfully affected by the difference in the source of secretin used in the various studies.

Table 21

Supportive Study CRC97-1 (Twelve Healthy Patients)

VARIABLES	95% CONF. INT.[a] LWR. BND.[1]	UPR. BND.[2]	BPS SAMPLE MEAN	PERCENTAGE LB/BPS M.[3]	UB/BPS M.[4]
PEAKBC	-7.46	1.79	110.92	-6.7%	1.6%
TBC	-4.35	0.57	24.28	-17.9%	2.3%
V_1_60	-33.23	14.5	244.83	-13.6%	5.9%

[a]: Confidence Interval; [1]: Lower Bound; [2]: Upper Bound; [3]: Lower Bound/bPS Sample Mean;
[4]: Upper Bound/bPS Sample Mean.
PEAKBC = peak bicarbonate concentration (mEq/L); V=volume (mL); TBC=total bicarbonate (mEq).

Table 22

Table 2.3.1 The 95% confidence intervals on the differences of two treatment effects (sPS – bPS)
Pivotal Study CRC98-1 (Eight Sick Patients)

VARIABLES	95% CONF. INT.[a] LWR. BND.[1]	UPR. BND.[2]	BPS SAMPLE MEAN	PERCENTAGE LB/BPS M.[3]	UB/BPS M.[4]
PEAKBC	-11.50	5.03	55.75	-21%	9%
TBC	-3.47	4.14	5.45	-64%	76%
V_1_60	-74.84	57.10	126.88	-59%	45%

The database does not allow for an assessment of diagnostic accuracy of the SST in diagnosing chronic pancreatitis as it was the "gold standard" used by the investigators in defining pancreatic exocrine insufficiency in patients with suspected chronic pancreatitis. **It must be stated that other causes of pancreatic exocrine insufficiency as measured by the SST, such as pancreatic cancer or duct obstruction due to stricture or stones may not be differentiated from chronic pancreatitis. The population tested in the current NDA submission contained only patients with chronic pancreatitis (based on previous SST using the Ferring product and clinical suspicion). It is clear that the test may give abnormal results in other conditions, such as cancer and cystic fibrosis and therefore cannot be assumed to differentiate between the many causes of pancreatic insufficiency.**

10. Overview of safety:

The safety database of SPS within the controlled trials(97-1, 98-1and 98-2) and open label trial (97-2) suggests minimal toxicity when used for the assessment of pancreatic exocrine function at a dose of 0.2 μg/kg bolus over 1 minute.

Studies 97-1, 98-1 and 98-2

Of the 27 patients in the controlled database one experienced flushing with both the 0.2 and 0.4 μg/kg dose as well as with the BPS product. This patient did not have such a reaction to the lowest dose of SPS 0.02 μg/kg. The reaction was therefore dose related and likely to be drug related. Another patient experienced a headache that was self limited and lasted five hours. The placement of a nasogastric tube during the SST may have caused this headache and it is unclear whether this adverse event was drug related. One patient out of forty-six was reported as to have nausea associated with the use of SPS in the open label use study 97-2.

Study 97-3

Study 97-3 was a randomized placebo-controlled study of intravenous SPS, 16 and 8 μg over one minute prior to ERCP for the prevention of post ERCP pancreatitis.
The sponsor is not currently seeking approval for this indication and the study is therefore not reviewed for efficacy. At the time of the current NDA submission the study was described as ongoing with an interim analysis performed after 250 patients had been enrolled. However, it was not identified as an ongoing trial at the time of the NDA quarterly safety update or IND annual report.

This randomized, placebo-controlled study may however be used for safety assessment. 119 subjects received SPS and 118 received placebo.

Interim analysis of efficacy data after the enrollment of 250 patients revealed that 11 subjects in the SPS and 9 subjects in the placebo group developed pancreatitis. Additionally, 8/9 of the adverse events occurred in the SPS group. The adverse event table 20 is reproduced from the NDA submission. These events were associated not only

with the administration of SPS but also interventions that included parenteral sedation and analgesia as well as invasive instrumentation. Thus the causality of adverse events is difficult to assess.

Table 22

ADVERSE EVENTS

Pat #	Treat-ment	Event	Onset Time	End Time	Con-tin-uing	Sever-ity	Relation-ship to Study Drug	Action	Out-come
6	Secretin	Abdominal discomfort	10:00	10:00		Mild	Unlikely	None	Resolved
16	Secretin	Drop in blood pressure	9:59	11:00		Mild	Possible	Normal saline IV kept in place – no fluids given	Resolved
19	Secretin	Endoscopic perforation	12:20	16:00		Mild	Unlikely	Wire perforation of tumor region. Antibiotics only. Overnight observation.	Resolved
34	Secretin	Diarrhea	11:49	3 days		Mild	Unlikely	Lomotil prescribed	Resolved
34	Secretin	Cramps	11:49	3 days		Mild	Unlikely	Lomotil prescribed	Resolved
127	Secretin	Abdominal pain	12:00	3 days		Mild	Unlikely	Hospital observation; 3 days	Resolved
127	Secretin	Low grade fever	12:00	3 days		Mild	Unlikely	Hospital observation; 3 days	Resolved
127	Secretin	Diaphoresis	12:00	3 days		Mild	Unlikely	Hospital observation; 3 days	Resolved
133	Placebo	Leukocyto-clastic vasculitis	9/20/98	Unk.		Mild	Unlikely	Likely due to contrast allergy. Patient had received steroids prior to procedure. Skin biopsy: negative for bacteria and fungi	Resolved
142	Secretin	Immediate bleeding	Unk	11:37		Mild	Unlikely	GI bleeding: Site cleaned. Patient sent to observation. Observation 2 days	Resolved
145	Secretin	Allergic reaction-hives	12:20	Unk		Mild	Unlikely	Patient developed allergic reaction to sedation or antibiotics. Diphenhydramine hydrochloride 25mg administered upon development of hives. Reaction resolved prior to the administering of secretin.	Resolved
210	Secretin	Endoscopic perforation	Unk	Unk		Mild	Unlikely	Antibiotics administered	Resolved

Of concern are 2 endoscopic perforations, a potentially serious complication, which occurred, in the treated group. No perforations occurred in the placebo group. While instrumentation is undoubtedly related to these events, it is not clear whether the physiologic effects of secretin may have played a role. The references provided by the sponsor and reproduced on page 47 of this review suggest the possibility of adverse events associated with the increased intraductal pressures that would be expected with the administration of secretin. Both events were biliary rather than pancreatic duct perforations. This makes a physiologic relationship to secretin much less likely. The rate

of post ERCP pancreatitis was higher in the treated group as was the rate of endoscopic perforation as noted above. An additional patient in the secretin group had abdominal pain and cramps that required hospitalization. Another patient in the secretin group had cramps and diarrhea that required several hours of observation following the procedure. None of the placebo treated patients had any similarly significant adverse events. Thus, there is a worrisome imbalance between the two groups in adverse events that required hospital observation or reached the pancreatitis endpoint (16/119 in the SPS group and 9/118 in the placebo group). It is possible that this imbalance is random or related to endoscopist decision making in response to seeing a gush of pancreatic juice from the papilla. Complication rates during ERCP have been associated in the past with the amount of contrast used. Endoscopists may have been emboldened to prolong the procedure and inject cumulatively higher volumes of contrast in subjects receiving secretin. This issue requires clarification before the safety of secretin in the setting of ERCP can be addressed.

Additional safety data are available from [redacted] Study 98-3B is a completed double blind placebo controlled study of the safety and efficacy of secretin for the treatment of autism and related pervasive developmental disorders. This single dose study included placebo, low (0.2 μg/kg) and high (0.4 μg/kg) dose groups of 10 subjects each.

Temporally related vasodilatation or flushing occurred in 2/10 subjects receiving the low dose and 1/10 patients receiving the high dose SPS. 0/10 subjects in the placebo group reported temporally related vasodilatory symptoms on the day of treatment.

In a second phase of this study all thirty subjects received the high dose of SPS; 2/30 subjects in this group experienced temporally related vasodilatation of the hands, face, neck and trunk. Although the proposed synthetic porcine secretin was not used in this study, one cannot rule out the possibility that this event may be physiologic and occur in association with porcine secretin. There was one patient in the synthetic porcine secretin database that experienced flushing following secretin administration. The small database and manipulation with nasogastric tubes and endoscopes in the current NDA studies may obscure efficient ascertainment of this event. It is however, a mild self-limited event. The database of the large placebo controlled pancreatitis prevention study (97-3) was examined for hypotensive effects that may be associated with a clinically relevant vasodilatory effect. The results appear in table 21. While there was a consistent trend towards more hypotension in the SPS group, this difference was small and of questionable statistical or clinical relevance.

Table 21

	Secretin	Placebo
Greater than 9 point drop in systolic BP	48/89 (54%)	43/86 (50%)
Greater than 19 point drop in systolic BP	34/89 (38%)	30/86 (35%)
Greater than 9 point drop in diastolic BP	43/89 (48%)	31/86 (36%)
Greater than 19 point drop in diastolic BP	20/89 (22%)	14/86 (16%)

There are missing blood pressure data on 36/125 (29%) of the secretin treated patients and 39/125 (31%) of the placebo treated patients. This is surprising since this is a clinically mandated measurement on any patient undergoing ERCP. The small trend is of note but no conclusions can be made regarding the hypotensive effect of secretin. It is clear however that the underlying treatment of all subjects with sedatives and analgesics accounts for the majority, if not all of the hypotensive effects seen in the study.

Safety Summary

1. Synthetic human secretin may cause mild vasodilatation in up to 20 % of subjects receiving a single 0.2-μg/kg injection. This effect was seen in association with synthetic porcine secretin.

2. A modest hypotensive effect of secretin may exist. This is unlikely to be of clinical significance unless superimposed upon other hypotensive agents in a patient with marginal circulatory reserve.

3. Secretin usage may be associated with clinically moderate to severe adverse events in the setting of ERCP. Although the sponsor is not proposing the use of secretin in the setting of ERCP, any future study of secretin in this setting will need to address concerns raised based on review of the database thus far collected.

4. No safety information is available regarding repeated dose exposure or exposure above 0.4 μg/kg.

5. No data on drug-drug interaction is available. Currently available knowledge would not suggest any such interaction, other than possibly transient enhancement of the hypotensive effects of concomitant hypotensive therapy.

11. Conclusions:

1. The database for evaluating the diagnostic efficacy of the secretin stimulation test in evaluating pancreatic exocrine function within this NDA is extremely small and is limited to subjects with an established diagnosis of chronic pancreatitis and pancreatic exocrine insufficiency. Therefore this reviewer cannot independently assess the diagnostic value of the sponsor's synthetic porcine secretin product.

2. The database does allow for qualitative comparisons between the Ferring biologic porcine secretin and the Sponsor's synthetic product. The two products demonstrated adequate similarity in the parameter of peak pancreatic fluid bicarbonate concentration during any one of four 15-minute periods of study, to consider them diagnostically interchangeable for purposes of that parameter. This is true despite the fact that there appears to be a slightly lower activity of the synthetic product compared to the biologic product. The two products were less consistent quantitatively in comparisons of the parameters of pancreatic fluid volume and total bicarbonate output, which lacked the high degree of concordance of diagnosis seen with the peak bicarbonate concentration parameter. The current database as well as the historical database that served as the basis of approval of the Ferring biologic product does not support claims regarding the diagnostic value of the secretin stimulation test in differentiating pancreatic exocrine insufficiency due to chronic pancreatitis and other potential causes of pancreatic exocrine insufficiency.

3. The sponsor has not demonstrated the diagnostic value of using secretin to [redacted] The published medical literature and previous secretin NDA 18-290 do not provide adequate or controlled data in this regard either.

4. The adverse event profile in the setting of pancreatic exocrine function assessment using the secretin stimulation test is acceptable. The database of all exposure suggests that flushing, abdominal cramps, nausea, and mild transient hypotensive effects may occur.

   In the off label use setting of ERCP, the use of secretin may be associated with significant adverse events. These events may include post ERCP pancreatitis, endoscopic perforation, and post-ERCP abdominal pain. The results are not conclusive and the association may be based on endoscopists behavior in response to seeing the pancreatic fluid output after secretin injection, a pharmacologic effect of secretin or a secretin related increase in pancreatic duct pressure. These results represent the largest database of its kind. Study 97-3 is not completed and the comparative safety data from this study is not relevant to the proposed indications and too preliminary for inclusion in the proposed label.

Recommendation for regulatory action

11.1

11.1.1 This reviewer recommends that SPS be approved for use in the SST for the diagnosis of pancreatic exocrine dysfunction based on submitted clinical studies 97-1 and 98-1 supported by published medical literature.

11.1.2 This reviewer recommends that SPS not be approved for ——— . The sponsor should be informed that adequate and well-controlled studies showing diagnostic advantage associated with the use of secretin in the setting of ——— .

11.1.3 Adequate labeling should include graphic and tabular information from the data base that reflects individual subject results in relation to the state of pancreatic function as determined by BPS as well as group means with presentation of variability.

11.1.4 Labeling should include pharmacokinetic data when available. Approval should not await such data.

11.1.5 Outstanding chemistry issues should be addressed.

11.2 Labelling

11 Draft Labeling Page(s) Withheld

[redacted]

(5)

Lawrence Goldkind, M.D.

cc:
NDA 21-136
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia (5)
HFD-180/HGallo-Torres (5)
HFD-180/LGoldkind
HFD-181/CSO
HFD-180/JChoudary
HFD-180/LZhou
r/d 3/9/00 jgw
f/t 3/15/00 jgw
N/21136003.0lg

References

1. Garvey TQ. Supplementary medical review of NDA for secretin NDA #18-290

2. McGuigan JE et al. Secretin injection test in the diagnosis of gastrinoma. Gastroenterol 1980; 79: 1324-31

3. Kolts BE et al . Radioimmunoassay measurement of secretin half-life in man. Gastroenterol 1977; 72: 55-60

4. Christ A et al. Human secretin: biologic effects and plasma kinetics in humans. Gastroenterol 1988; 94: 311-16

5. Dreiling DA The technique of the secretin test. J Mt. Sinai Hosp 1955; 21: 363-72

6. Petersen H. the effects of pure natural secretin on the bicarbonate secretion into the duodenum in man Scand J of Gastroent 1970; 5: 105-111

5. Gutierrez LV et al. A comparison of Boots and GIH secretin as stimuli of pancreatic secretion in human subjects with and without chronic pancreatitis

6. Gyr K, et al. Comparison of the biologic potency of a new synthetic preparation of secretin with that of natural porcine secretin in the dog. Gut 1978; 19: 355-7

7. Clinics of North America January 1998, Volume 8 Sherman S. page 62

8. Practical Gastrointestinal Endoscopy, Third edition, Blackwell Scientific Publications. Chapter 6, page 96

9. Gastrointestinal Endoscopy, basic principles and practice, John Baille, Butterman, Heineman publisher page 121

10. ERCP, Diagnostic and Therapeutic Applications Ira M. Jacobson editor, Elsevier Publishers page 31

11. Lankisch PE, Function tests in the diagnosis of chronic pancreatitis. International Journal of Pancreatology 1993; 14: 9-17

Appendix 1

WITHHOLD 1 PAGE (S)

August 10, 1999

Dr. Seymour Fein
ChiRhoClin Inc.
15500 Gallaudet Avenue
Silver Spring, MD 20905

RE: Use of secretin during ERCP

Dear Dr. Fein:

You asked me to provide some more documentation about the use of intravenous injections of secretin preparations during ERCP examinations.

For at least 20 years I have used secretin routinely in selected cases (perhaps 5% of all cases) for several indications. The commonest initially was for the collection of pure pancreatic juice secretions after cannulating the pancreatic duct, for biochemical analyses. Nowadays we do not do that very often, but it is still useful in very specific cases. The second indication is to collect pancreatic juice for cytological examination; this remains useful, although often we replace that examination (or compliment it) with brushing cytology during ERCP.

Our biggest current usage is to help identify the orifice of the pancreatic duct when this is not obvious endoscopically. Almost always this occurs in patients with the congenital anomaly of pancreas divisum, which occurs in 5-8% of the population, at least in western countries. Attached A you will find a series of color photographs, illustrating this phenomenon. Image 6 shows the catheter in the main papilla of Vater (actually in the bile duct). Frame 1 shows the area of the accessory papilla; the papilla itself is not visible. Frames 2, 3, and 4 show the open accessory papilla 2, 3, and 4 minutes after an intravenous injection of secretin (50 units). This injection allowed us to place a catheter deep into the accessory orifice for diagnosis and therapy.

I do not believe that anyone has done a very specific scientific study demonstrating the value of secretin in this context; however, it is in routine use in many centers. I enclose some comments about its use from standard textbooks, including my own.

Please let me know if further information would be helpful.

Best personal wishes.

000484

APPEARS THIS WAY
ON ORIGINAL

Appendix 2

Review of sponsor provided meta-analysis of published literature on the diagnostic value of the secretin stimulation test for the diagnosis of pancreatic exocrine insufficiency in the setting of chronic pancreatitis.

At the request of the division the sponsor requested that an expert in the field of pancreatic diseases, Dr. Philip Toskes, review the published literature and provide a meta-analysis of the various parameters of diagnostic accuracy of the SST. The search terms used were secretin, chronic pancreatitis and pancreatic insufficiency. The total number of articles retrieved and the basis for inclusion and exclusion was not prespecified or fully explained.
The ultimate meta-analysis contained seven articles. There were no consistent reference diagnostic criteria used among the studies. The approved Ferring BPS was not the only form of BPS used and in some cases the actual test was not the SST but rather the secretin-pancreazymin or cholecystokinin test. In some circumstances slow intravenous infusion rather than bolus was used. The diagnostic test parameter and cutoff value was not always listed. The reference standards are not always listed and are not consistent in the articles that specify them.. Each study was reviewed and a statistical meta-analysis was performed.

Study 1: This study was published in abstract form only at the American Gastroenterological Association Meeting in 1993 and was not subsequently published in full form. It is therefore unclear whether this study should have been included. The author of the abstract is the author of the meta-analysis, Philip Toskes. Unfortunately Dr. Toskes did not specify any criteria for inclusion and exclusion from the met-analysis.

Study 2: This study included pancreazymin as well as KABI secretin. The dose is assumed to be 1CU although not stated in the article. The pancreazymin is not anticipated to affect the results of bicarbonate concentration.

Study 3: This study used 0.5 CU rather than the 1CU used in the current NDA and most published articles. Infusion was 0.25CU/kg/hr. The test was performed as a secretin-CCK test.

Study 4: This study used 0.5 CU rather than the 1CU used in the current NDA and most published articles. Infusion was 0.25CU/kg/hr. The test was performed as a secretin-CCK test.

Study 5: This study used the secretin –CCK test

Study 6: This study used the secretin-CCK test. The secretin used was biologic porcine secretin produced by Esai of Japan.
Study 7: This study used the secretin-CCK test. The secretin used was biologic porcine secretin produced by Esai of Japan.

The summary tables appear below.

DIAGNOSTIC EFFICACY OF SECRETIN FOR CP

Study #	Secretin		Best Reference Standards		
	Sensitivity	Specificity	Test	Sensitivity	Specificity
1 (%)	49/50 (98)	2/2 (100)	ERCP+	50/50 (100)	0/2 (0)
2 (%)	95/100 (95)	102/102 (100)	ERCP+	100/100 (100)	84/102 (82.4)
3 (%)	22/25 (88)	NA	H	25/25 (100)	NA
4 (%)	30/36 (83.3)	20/24 (83.3)	ERCP+	36/36 (100)	24/24 (100)
5 (%)	21/23 (91.1)	16/17 (94.1)	H, ERCP, CL	23/23 (100)	17/17 (100)
6 (%)	24/25 (96)	74/83 (89.2)	H	25/25 (100)	83/83 (100)
7 (%)	97/98 (98.9)	44/44 (100)	H, ERCP, CL	98/98 (100)	73/73 (100)
Totals (%)	338/357 (94.7)	258/272 (94.9)		357/357 (100)	281/301 (93.4)
Avg. of %s	92.9	94.4		100	80.6
Range of %s	83.3 – 98.9	83.3 – 100		100	0 - 100

ERCP = Endoscopic retrograde cholangiopancreatography
H = Histology
CL = Clinical follow-up

DIAGNOSTIC EFFICACY OF SECRETIN FOR CP
SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE
AND NEGATIVE PREDICTIVE VALUE

Measure	Secretin		Best Reference Standards		*Likelihood* Ratio Chi-Square P-Value
	Estimate	95% Exact Confidence Interval	Estimate	95% Exact Confidence Interval	
Sensitivity	94.7	91.8 – 96.8	100	99.0 – 100	0.001
Specificity	94.9	91.5 – 97.2	93.4	89.9 – 95.9	0.45
Positive Predictive Value	96.0	93.4 – 97.8	94.7	91.9 – 96.7	0.39
Negative Predictive Value	93.1	89.5 – 95.8	100	98.7 - 100	0.001

The lack of criteria for study inclusion in this meta-analysis and unknown total universe of articles from which these seven studies were chosen is of concern. This reviewer found two other estimations of sensitivity and specificity in the literature that are worth noting at this juncture. In an article by Kankisch [11] a German language article [Otto M. Pancreasfunktiondiagnostic. Internist 1979;20: 331-340] is referenced:

" The secretin- pancreazymin test is considered to be the gold standard in pancreatic function testing. Otto, in a study involving 403 patients, found false-abnormal results in 8% of the subjects and false normal results in 6% of the patients. It is unlikely that these percentages will be improved because of the wide variation in normal pancreatic function."

Chris Forsmark M.D. states in a major textbook of Gastroenterology that:

"The sensitivity of these tests depends on the severity of the disease (sensitivities are 74-90%, and specificities 80-90%). A number of studies have compared these tests of pancreatic function with other diagnostic tests, especially ERP documentation of changes in the pancreatic duct. All of these studies have reached the same conclusion: that these hormonal stimulation tests are more sensitive, more accurate, and more able to diagnose chronic pancreatitis in its less severe stages, compared with other tests."

The meta-analysis results were very similar compared to one large published study and a summary statement within a major textbook of gastroenterology. The meta-analysis is flawed and the available literature has inherent limitations. However, it is unlikely that any future study by this or any other sponsor would produce better quality data due to difficulties in establishing an independent gold standard, the biologic variability in severity of disease and the limitations of the test methodology.
This reviewer would recommend a statement in the label stating that the sensitivity, specificity, positive and negative predictive values for the SST for the BPS in the medical literature are all in the range of 90%. The SPS should have the same performance characteristics based on results of the sponsors comparative studies.

FEB 11 2000

Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Review

NDA # 21-209

Submission Date: August 19, 1999

Review Completion date: February 10, 2000

Generic name: Synthetic porcine secretin (SPS)

Proposed trade name: —

Sponsor: ChiRhoClin

Pharmacologic category: GI hormone/ pancreatic polypeptide secretagogue

Proposed indications: Diagnosis of — (gastrinoma)

Dosage forms and route of administration: Intravenous 0.4 micrograms/kg over one minute

Related reviews: 18-290 approved 1981, 21-136 under review

Background:

The sponsor submitted the original NDA for this product on May 14, 1999. Four indications were listed: For diagnosis of pancreatic exocrine function, — , diagnosis of gastrinoma — and facilitation of — during ERCP. There were no controlled data on the last two indications and no subjects with — had received SPS. Thus, these two indications were not filed in view of the lack of clinical data to review. The sponsor was informed of the decision to file only the first two indications at a meeting with the division on September 14, 1999. The lack of controlled data was discussed and the sponsor was informed that independent diagnostic accuracy data or pharmacodynamic comparability to the approved Ferring secretin in the setting of gastrinoma diagnosis would be needed to adequately label SPS. The sponsor was informed that the impurities in the Ferring product might well constitute bioactive peptides in the secretin stimulation test. Any such bioactivity may affect the dynamic range of the secretin stimulation test using the SPS and the associated diagnostic range to be used in interpreting the SST. Literature review on the diagnostic range of the post-SST serum gastrin levels was the basis of approval for the Ferring secretin. The literature referenced for approval used the Ferring secretin and was therefore adequate to derive a

dynamic range and diagnostic range for the test. In fact differences between the Ferring secretin and Boots secretin, another biologically derived product, have been addressed in the medical literature.[1] The particular issues related to Boot's secretin were different than the issues related to the use of a synthetic product. The generic issues of diagnostic comparability, diagnostic ranges, sensitivity, specificity and dose of secretin however, are applicable to the current submission.

The proposed SPS has no published literature upon which to draw such support. The clinical relevance of this point was highlighted in an article by McGuigan and Wolfe published in Gastroenterology [79:1324-1331 (1980)].

"At the present time there is insufficient information in the literature to compare secretin provocation results using the several available forms of synthetic secretin with the results using the purified naturally occurring porcine secretins."[1]

During the September 14, 1999 meeting the sponsor agreed to conduct a controlled study of patients clinically presenting for diagnosis. The size of the study was not agreed upon. It was understood that the small number of patients available for study with gastrinoma would preclude a study with the power to assess specificity, sensitivity, accuracy, and predictive value in a statistical fashion. Thus the division agreed to assess the results of a small study of 6-12 patients initially. As of the date of this review, the sponsor has not submitted a study report for such a study.

The information in the September 14th, 1999 meeting supplemented advice given by the division to the sponsor at a pre-NDA meeting on November 18, 1998. A reproduced section from the meeting minutes appears below.

The clinical program for synthetic porcine secretin consists of the volunteer subject study (CRC97-1), the chronic pancreatitis patient study (CRC98-1), and the ERCP study (CRC97-3) for additional safety data.

ChiRhoClin believes these studies establish the diagnostic efficacy, safety and dosing guidelines for synthetic porcine secretin for the diagnostic indications and with the published literature on porcine secretin, which provided the basis for approval of the biologically derived drug, fully satisfy the requirements for NDA approval. Does the FDA concur with this assessment?

Any decision regarding the approvability of an application is based on the data for your product submitted in the NDA. It is premature at this time to make any conclusions regarding approvability. Since efficacy for the proposed NDA is to be supported by a small database consisting of only 24 patients in two studies, it is possible that more support may be needed. It may be necessary to submit clinical data, including data regarding the sensitivity and specificity, in support of the efficacy of your product for each requested indication. If literature is provided in support of efficacy, it must be from studies using your product or bioequivalence between the product used and your product must be demonstrated. Source documents from the referenced studies must be provided as well.

Literature for studies utilizing the porcine derived product may be submitted as background information, but cannot serve as the basis for approval.

Despite the previous communications with the division, the sponsor chose to file over protest and the current NDA was filed separate from NDA 21,136. This administrative separation of the gastrinoma indication from the other indications was due to the priority status required for a review of an NDA for a product that was proposed to be superior to available diagnostic modalities. Furthermore the proposed diagnostic use is for a life threatening condition.

Scientific background and review of NDA 18,290 (Ferring secretin) can be found in the review of NDA 21,136.

Description of clinical data sources:

The clinical experience with the SST using SPS is limited to a small study in 12 healthy subjects (study 99-10) and an open label study of secretin for the various proposed indications (study 97-2). To date 17 subjects have undergone the SST for the diagnosis of gastrinoma in study 97-2.

Clinical Studies

Study 97-2

Objective:
To obtain supplemental pharmacological efficacy and safety data in standard clinical use for the diagnostic indications approved for the extracted product.

Design:
Multicenter, open-label, non-comparative clinical use study of SPS as a diagnostic agent for chronic pancreatitis, pancreatic cancer, gastrinoma and to facilitate pancreatic duct cannulation during ERCP.

Protocol: Patients with suspected gastrinoma received a dose of 0.4 micrograms/kg SPS and had blood samples obtained at (pre-dose SPS) and 1, 2, 5, 10 and 30 minutes post – dose for serum gastrin concentration.

Reviewer comment:
The sponsor did not specify clincial criteria for suspected gastrinoma. Thus, careful review of the clinical presentation of each subject will be necessary.
The Ferring secretin label states that the patient should have fasted for 12 hours. The sponsor does not state in protocol 97-2 whether subjects had fasted for 12 hours.

Efficacy endpoint:

Diagnosis of gastrinoma based on elevation of serum gastrin from baseline.

Reviewer Comment:
The sponsor did not define diagnostic serum gastrin blood level parameters for the test. The approved Ferring secretin label states:

" Gastrinoma is strongly indicated in patients with elevated fasting serum gastrin concentrations in the 120-500 pg/ml range (determined by RIA using the antibody to gastrin similar to that prepared by Rehfeld) and in patients who show an increase in serum gastrin concentration of more than 110 pg/ml over basal level."

This may be assumed to be the sponsor's diagnostic criteria. It is not clear however in the submission what diagnostic gold standard would be used to define the diagnosis of gastrinoma distinct from the SST.

Statistical considerations:

No statistical plan is proposed for this uncontrolled study.

Results:

17 subjects underwent SST using SPS. As noted above no specific clinical entry criteria were prespecified. The sponsor did not submit any clinical data to indicate the appropriateness of the SST. 5/17 subjects had a baseline gastrin level under 100 (subjects # 3, 32, 39, 48 and 60). Normal levels of baseline serum gastrin are compatible with the diagnosis of gastrinoma, however it is important for the review process to have prespecified criteria and/or complete clinical data presented in the submission.
Using the Ferring label definition of a positive test suggestive of gastrinoma (a rise of 110 pg/ml or more) six subjects had a positive SST. The study report summary states that all six positive tests had histologically confirmed gastrinoma. However, the case report forms submitted only documented three such cases (41, 43 and 46. One subject had been diagnosed 5 years earlier and a second had known metastatic disease to the liver. Therefore, these subjects represented advanced cases and may not represent recent or "clinically suspected" cases that may yield some information on the value of the SST in the initial diagnosis of gastrinoma. This issue is not as critical as with many other diagnostic products because of the great variability in clinical course, and lack of tight correlation between extent of disease and gastrin levels as well as response to secretin stimulation testing. There may however, be enough correlation to bias the choice of diagnostic criteria for the SST if all subjects used for comparative study have advanced disease. Therefore, for labeling purposes, data generated only from patients with known extensive longstanding disease may not be adequate.

No clinical information was given on the third histologically confirmed case.
Two subjects with positive SSTs were defined as "consistent with gastrinoma" but no supportive documentation was presented. One subject had a positive SST but the clinical diagnosis was G cell hyperplasia. No explanatory information was provided. This would appear to contradict the claim that all six positive tests occurred in subjects with histologically confirmed gastrinoma.
One subject had a high baseline gastrin level of 413 (subject #81)but the SST was negative with a peak post-stimulation level of 450. The final diagnosis was not provided. It is unknown whether this case represents a false negative or a true negative.

Reviewer's Comment:
This open label study did not list inclusion criteria or adequate data to provide adequate quantitative or qualitative information on the value of the SST using the proposed SPS. This study does not allow for any bridging between the approved Ferring biologic product and the proposed SPS. Such bridging may allow for approval of the proposed SPS if the bioactivity of the two forms of secretin were adequately close to extrapolate diagnostic value associated with the approved biologic secretin.

Study 99-10

"A single center study evaluating the pharmacokinetic profile of a single intravenous dose of synthetic porcine secretin and synthetic human secretin in normal subjects."

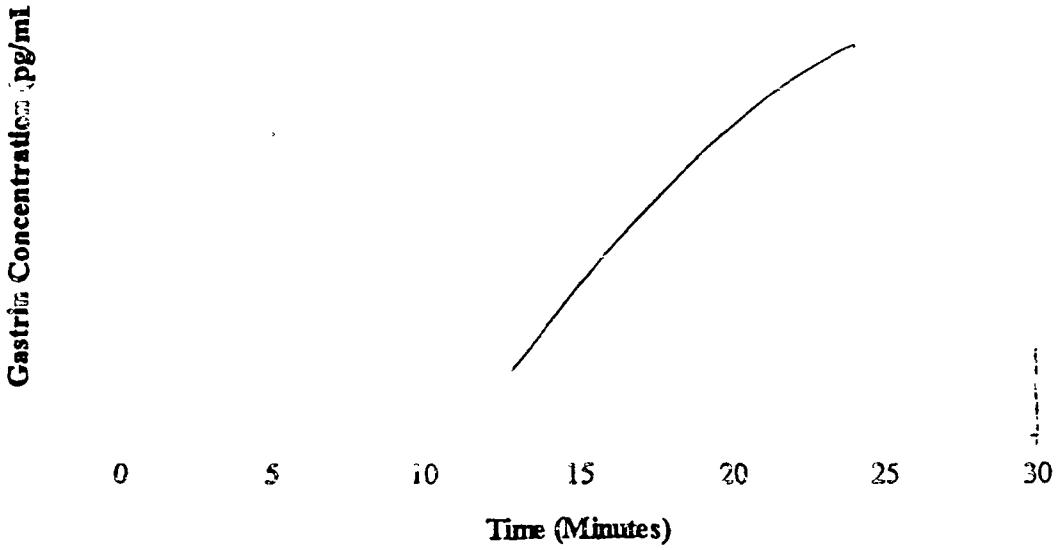
This title suggests that the primary goal of this study was to assess pharmacokinetics. A secondary objective was the evaluation of the effects of SPS and SHS on serum gastrin levels in normal subjects. The sponsor did not indicate which assay was used to measure serum gastrin levels in this study.

Only an interim synopsis of the gastrin data has been provided and is reproduced below. Each subject received 0.4 micrograms/kg SPS intravenously over 1 minute.
The data are consistent with the medical literature, which suggests that normal subjects do have a small rise in serum gastrin levels in response to SST, using the Ferring product. This rise is early (within the first 2-4 minutes) and much more modest than that seen with gastrinoma patients. Thus, this small study is reasonably convincing that in healthy subjects SPS produces a response similar to that seen with the approved and historically studied biologic porcine secretin.

GASTRIN CONCENTRATION (pg/mL) FOR SPS

Subject No.	0 Minutes	2 minutes	4 Minutes	10 minutes	15 minutes	30 Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	39.58	50.5	50.18	44.55	43.09	38.64
Std.	13.69	12.38	13.3	16.4	11.12	8.418
Min.						
Max.						
%CV	34.58	24.51	26.51	36.81	25.81	21.79

Gastrin Results - sPS



Reviewer's Comments:

The interim synopsis provided by the sponsor suggests that healthy subjects respond to the SST using SPS in a manner similar to the biologic approved product. One may extrapolate this finding to non-gastrinoma clinical settings where the SST is used to differentiate between gastrinoma and other conditions where basal gastrin level is elevated (chronic renal failure, achlorhydria, gastric cancer, vagotomy, gastric outlet obstruction, antral G cell hyperplasia or hyperfunction, retained gastric antrum, short bowel syndrome). This extrapolation would not be necessary if the approved biologic secretin, which was used in the published studies to document the accuracy of using the SST to differentiate these conditions from gastrinoma, was shown to produce similar results to SPS in a small group of patients with these conditions. Extrapolation to these groups without any supportive data requires an assumption that the impurities present in the biologically derived secretin will not significantly affect the gastrin response in these conditions. This reviewer is willing to accept this assumption. The lack of an exaggerated or paradoxical response to the SST using the Ferring product in these conditions suggests biologic similarity to the "normal or healthy volunteer" subjects used in the current study. Likewise, in patients with a clinical presentation that suggests gastrinoma but have normal gastrin levels (aggressive duodenal ulcer disease or diarrhea) there is no reason to suspect an abnormal response to a synthetic more pure form of secretin compared to the biologic product.

The final report is not available. The protocol will need to be evaluated before a review of this study can be finalized.

Safety review:

Nine adverse events occurred in 4 of the 12 subjects in this study. Two subjects experienced headache and two subjects experienced nausea. One subject experienced hypotension with associated diaphoresis and lightheadedness. These adverse events are similar to those seen in studies discussed in NDA-21,136. In trials submitted under NDA-21, 136, flushing, diaphoresis, decreased blood pressure, abdominal cramps and headache were seen. The label for SPS should include the adverse events seen in studies from trials submitted under both NDAs.

Recommendation for regulatory action:

1. **SPS should not be approved for the diagnosis of gastrinoma.**
2. **The sponsor should be informed of the following deficiencies.**

a. **Adequate and well designed studies comparing the gastrin response to the SST using the SPS and the approved Ferring product is required to confirm the biologic similarity between the two agents when administered to patients with gastrinoma. Accurate labeling requires data on how to interpret results of any proposed diagnostic test. Diagnostic accuracy must be addressed in the label. The sponsor has not provided adequate data upon which to label their product. The sponsor is referred to meeting minutes from the November 18, 1998 and September 14, 1999 Agency meetings for further clarification.**
b. **In addition, the final report on study 99-10 must submitted.**

/S/

Lawrence Goldkind M.D.

Concur. Feb 10/00
D., PhD.

cc:
NDA 21-209
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/LGoldkind
HFD-181/BStrongin
HFD-180/JChoudary
HFD-180/LZhou
f/t 2/10/00 jgw
N/21209002.0LG

References:

1. McGuigan JE, Wolfe MM, Secretin injection test in the diagnosis of gastrinoma. Gastroenterology 1980, 79: 1324-31

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

CHEMISTRY REVIEW(S)

NDA 21-209

SecreFlo

Arthur B. Shaw, Ph.D.

Division of Gastrointestinal and
Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-209
2. REVIEW #: 2
3. REVIEW DATE:
4. REVIEWER Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

ORIGINAL	17-May-99
REVIEW #1	31-Jan-00
AE Letter	16-May-00
AE Letter	28-Nov-00
Meeting	06-Dec-00
AMENDMENT BZ	17-Sep-01
AMENDMENT AC	05-Oct-01
Meeting Request	02-Nov-01
Meeting Request	21-Dec-01
IR Letter	17-Dec-01
Meeting Minutes	12-Feb-02

6. SUBMISSION(S) BEING REVIEWED:

Amendment BL	13-Feb-02
Amendment BC	01-Mar-02
C	13-Mar-02
Telecon	02-Apr-02
Amendment BC	02-Apr-02
Telecon (labeling)	03-Apr-02

7. NAME & ADDRESS OF APPLICANT:

Name:	ChiRhoClin, Inc.
Address:	15500 Gallaudet Avenue Silver Spring MD 20905
Representative:	Edward Purich, Ph.D.

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: SecreFlo
   b) Non-Proprietary Name (USAN): Secretin
   c) Code Name/# : N/A
   d) Chem. Type/Submission Priority
      - Chem. Type 3
      - Submission Priority: P
9. LEGAL BASIS FOR SUBMISSION: New drug
10. PHARMACOL. CATEGORY: Secretory hormone

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Proposed expiration date not acceptable See review notes	13-Feb-2002	Milton Fan
EES	AC	04-Mar-2002	
Pharm/Tox	N/A		Independent review
Biopharm	N/A		Independent review
LNC	Secretin		Per USAN see below
Methods Validation	Not submitted See review notes		
DMETS	Secreflo Acceptable	07-Mar-2002	Alina R. Mahmud,
EA	N/A		Categorical Exclusion
Microbiology	Acceptable	16-Oct-2000	Carol Vincent

The Chemistry Review for NDA 21-209

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Phase IV Commitment:
   Develop an assay to measure impurities in the drug product.
2. Additional Post-Approval Commitments:
   The applicant has made a number of commitments to clarify procedures, identify impurities in the drug substance, submit a complete Methods Validation Package, and submit stability protocols and data.

II. Summary of Chemistry Assessments

A. Description of Drug Product and Drug Substance:

- Drug Product Description: Sterile lyophilized powder for injection at 16 µg per vial, to be reconstituted with 8 mL of 0.9% NaCl
- Drug Substance Description: Synthetic 27 amino acid peptide, whose sequence is the same as naturally occurring porcine secretin. The synthetic peptide has the same biological activity in a cat bioassay as the biological peptide.