SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Injectable Bulking Agent
Device Trade Name:	Deflux® Injectable Gel (referred herein as "Deflux")
Applicant:	Q-Med AB Seminariegatan 21 SE-752 28 Uppsala Sweden
Official U.S. Correspondent:	Buchanan Ingersoll, P.C. 1776 K Street, N.W., Suite 800 Washington, DC 20006
Premarket Approval (PMA) Number:	P000029
Date of Notice of Approval to Applicant:	September 24, 2001

II. INDICATIONS FOR USE

Deflux is indicated for treatment of children with vesicoureteral reflux (VUR) grades II-IV.

III. CONTRAINDICATIONS

Deflux is contraindicated in patients with any of the following conditions:

- Non-functioning kidney(s)
- Hutch diverticuli
- Duplicated ureters
- Active voiding dysfunction
- Ongoing urinary tract infection

IV. WARNINGS AND PRECAUTIONS

Warning:

- Do not inject Deflux intravascularly. Injection of Deflux into blood vessels may cause vascular occlusion.

Precautions:

- Deflux should only be administered by qualified physicians experienced in the use of a cystoscope and trained in subureteral injection procedures.
- The risks of infection and bleeding are associated with the cystoscopic procedure used to inject Deflux. The usual precautions associated with cystoscopy (e.g., sterile technique, proper dilation, etc.) should be followed.
- The safety and effectiveness of the use of more than 6 ml of Deflux (3 ml at each ureteral orifice) at the same treatment session have not been established.
- The safety and effectiveness of Deflux in the treatment of children under 1 year of age have not been established.
- Deflux is supplied prefilled in a 1 ml syringe with a luer lock fitting, and is intended for single use only. Carefully examine the unit to verify that neither the contents nor the package has been damaged in shipment. **DO NOT USE** if damaged. Immediately return damaged product to Q-Med AB.
- Deflux is supplied sterile. Do not re-sterilize, as this may damage or alter the product.
- Deflux is supplied in a syringe ready for use. Never mix Deflux with other products.
- Deflux must be stored at 2°C – 8°C, and used prior to the expiration date printed on its label. Do not expose Deflux to either sunlight or freezing, as this may damage or alter the product. Do not use Deflux after its expiration date.

V. DEVICE DESCRIPTION

Deflux is a sterile, injectable bulking agent composed of microspheres of cross-linked dextran ("dextranomer," 50 mg/ml) suspended in a carrier gel of non-animal, stabilized hyaluronic acid (17 mg/ml). The dextranomer microspheres range in diameter from 80 to 250 microns (average diameter approximately 130 microns). Deflux is sold pre-filled in a single use, 1 ml syringe. Sterile syringe needles (23 gauge tip; 35 cm in length) for use during the Deflux injection procedure are packaged separately

Deflux is injected submucosally in the urinary bladder in close proximity to the ureteral orifice. The injection of Deflux creates increased tissue bulk, thereby providing coaptation of the distal ureter during filling and contraction of the bladder. The dextranomer microspheres are gradually surrounded by body's own connective tissue, which provides the final bulking effect.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder into the ureter and kidney. VUR occurs in patients who have an anatomical abnormality of the vesicoureteral junction, and is most common in children.[1] If left untreated, the risks of urinary tract infection and subsequent pyelonephritis are significantly enhanced, which can lead to renal damage and loss of renal function.

Conventional procedures used in the treatment of VUR are:

- antibiotic prophylaxis to prevent infection until the patient's VUR spontaneously resolves, and
- open surgery to reimplant the refluxing ureter(s) into the urinary bladder.

VII. MARKETING HISTORY

Deflux has been marketed for the treatment of VUR since December 1998 in the following countries: Australia, Austria, Belgium, Finland, France, Germany, Great Britain, Iceland, Italy, The Netherlands, Spain, Sweden, and Switzerland. Approximately 1000 patients have been treated with Deflux for VUR. Deflux has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Deflux in the treatment of VUR is based on a randomized study in which 39 subjects were treated with Deflux and 21 subjects were treated with antibiotic prophylaxis, and two nonrandomized studies in which a total of 170 subjects were treated with Deflux. The follow-up duration for all three studies was 12 months. See Table 7 for a complete listing of the adverse events observed in this study.

The following potential risks of subureteral injection procedures were not reported in any of the studies: vascular occlusion, urinary retention, dysuria, bleeding/hematuria, urgency, and urinary frequency.

IX. SUMMARY OF PRECLINICAL STUDIES

Bench Performance Testing:

The following bench performance tests were conducted on final, sterilized samples of Deflux-filled syringes to evaluate the performance characteristics of the device:

- Injection time/force testing: Using a syringe plunger rod equipped with a finger grip, the Deflux-filled syringe could be emptied in 2 minutes with a force of 37 to 38 N. These results verified compliance with the injection force specifications.
- Syringe leak testing: Syringe leak testing was performed to measure the maximum injection force that can be applied to Deflux-filled syringes without leaking. The results of this test demonstrated leakage at the luer lock fitting at a mean injection force of 85 N was applied, confirming that the syringe will not leak under normal use conditions.
- Drying resistance testing: This testing was performed to assess the tendency of the syringe contents to begin drying out when prepared for use and left to stand at room temperature for 15 minutes (to simulate the anticipated conditions of use immediately prior to injection). No increases in injection time or force were observed, indicating that Deflux is sufficiently resistant to drying.
- Environmental/transportation testing: Environmental and transportation testing (according to ASTM 4169) verified that the packaged product can withstand the expected conditions of shipping.

Sterilization, Endotoxin, and Shelf Life Testing:

Steam sterilization of Deflux-filled syringes was validated to provide a sterility assurance level (SAL) of 10^{-6}. Testing performed on finished product verified that Deflux has endotoxin levels

≤ 0.1 EU/ml. Accelerated aging testing on sterilized, Deflux-filled syringes supports a shelf life claim of 12 months.

Biocompatibility Testing:

Deflux and its component materials were evaluated for biocompatibility in accordance with the provisions of the Good Laboratory Practice (GLP) regulations, and FDA Blue Book Memorandum #G95-1. Testing performed on the final formulation of Deflux included cytotoxicity, sensitization, hemolysis, intracutaneous toxicity, muscle implantation (90 days), and mutagenicity testing. The results of these tests demonstrate that Deflux is non-toxic, non-hemolytic, and biocompatible.

Additional testing was conducted in rabbits to evaluate the potential for distant migration of the dextranomer microspheres. In this test, ^{125}Iodine-labeled dextranomer microspheres were submucosally injected into the bladders of six rabbits. Samples of blood and various tissues were examined for radioactivity at 1 day, 1 week, and 4 weeks post-injection. Whole body radiographic scans were also performed at these intervals. No distant migration of dextranomer microspheres was detected after submucosal injection of Deflux in the rabbit bladder wall.

Bladder Submucosa Implantation Testing in Rabbits:

A 2-year implant study of Deflux was conducted using 22 rabbits. In each rabbit, 1 gram of test article was injected submucosally into each of the following bladder sites: right and left bladder neck, and right and left bladder wall. The objectives of this study were to determine the biocompatibility and migration potential of Deflux when implanted into the rabbit bladder submucosa. Follow-up evaluations were conducted at 1 week, and 1, 3, 6, 12, and 24 months. In each animal, the bladder, pancreas, kidney, liver, lung, draining lymph nodes, and brain were removed and examined histologically for inflammation, infection, irritation, foreign body responses, tissue necrosis, and scarring. Additionally, other organs were examined for gross abnormalities.

A total of five rabbits died or were euthanized for reasons unrelated to Deflux implantation. This study reported the following significant findings:

- The dextranomer microspheres contained within Deflux remained in the tissue in all injection sites for at least 2 years without causing any adverse foreign body reaction.
- The dextranomer microspheres induced a fibrous tissue reaction around each microsphere without any adverse inflammatory reaction.
- The dextranomer microspheres do not appear to migrate to other tissues during the 2-year post-implantation period.
- Deflux appears to be safe when injected into the bladder submucosa of rabbits.

Bladder Submucosa Implantation Testing in Dogs:

A 2-year implant study of Deflux was conducted using 12 dogs. In each dog, 2.5 grams of test article was injected submucosally into each of the following bladder sites: right and left bladder neck, and right and left bladder wall. The objectives of this study were to determine the biocompatibility and migration potential of Deflux when implanted into the canine bladder submucosa. Follow-up evaluations were conducted at 2 weeks, and 3, 6, 12, and 24 months.

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In each animal, the bladder, pancreas, kidney, liver, lung, draining lymph nodes, and brain were removed and examined histologically for inflammation, infection, irritation, foreign body responses, tissue necrosis, and scarring. Additionally, other organs were examined for gross abnormalities.

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- The dextranomer microspheres induced a fibrous tissue reaction around each microsphere without any adverse inflammatory reaction.
- The dextranomer microspheres do not appear to migrate to other tissues during the 2-year post-implantation period.
- Deflux appears to be safe when injected into the bladder submucosa of dogs.

X. SUMMARY OF CLINICAL STUDIES

Objectives

Three single-center, European clinical studies were performed to assess the safety and effectiveness of Deflux in the treatment of VUR in children. The objectives of these studies were as follows:

- A randomized study was performed to compare the safety and effectiveness of Deflux to antibiotic prophylaxis at 12 months. This study was performed at the Ospedale Bambino Gesú (Rome, Italy).
- A non-randomized study ("Study 1") was performed to investigate the safety and effectiveness of Deflux at 12 months. This study was performed at the University Children's Hospital (Uppsala, Sweden).
- An non-randomized study ("Study 2") was performed to investigate the safety and effectiveness of Deflux at 12 months. This study was performed at the Ospedale Bambino Gesú (Rome, Italy).

Study Designs

Randomized Study

A prospective, single-center, randomized controlled clinical trial was performed to compare the safety and effectiveness of Deflux to standard treatment (i.e., antibiotic prophylaxis). Patients were randomized (2:1) to either Deflux or standard, long-term, antibiotic prophylaxis. Although blinding of the patients and treating physicians was not possible in this study, the evaluation of the primary effectiveness endpoint (i.e., reflux grade, observed on voiding cystourethrogram, "VCUG") was performed by independent radiologists who did not know the treatment received by any individual patient.

Effectiveness (i.e., reflux grade on VCUG) was evaluated prior to treatment and at 12 months following initial treatment. Additionally, reflux grade beyond 12 months was reported for Deflux-treated patients.

Non-Randomized Studies

The two non-randomized studies were prospective, single-center clinical studies, in which all patients received Deflux treatment. For these studies, the baseline status of patients served as the comparison for the assessment of device outcome.

Effectiveness (i.e., reflux grade on VCUG) was evaluated prior to treatment and at 12 months following last treatment. Additionally, reflux grade beyond 12 months was reported for Study 1 patients.

Effectiveness Endpoints

The primary effectiveness endpoint for each study was change in the severity of VUR at 12 months, as observed on VCUG. As indicated below in Table 1, VUR severity is classified separately for each ureter into one of six reflux grades (Grades 0 – V) according to the International Classification System[1]. Treatment success was defined as improvement to reflux grade 0.

Table 1: International Classification System for VUR

Grade 0	No reflux.
Grade I	Reflux into the nondilated ureter.
Grade II	Reflux into the pelvis and calyces without dilation.
Grade III	Mild to moderate dilation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices.
Grade IV	Moderate ureteral tortuosity and dilation of the pelvis and calyces.
Grade V	Gross dilation of the ureter, pelvis, and calyces, loss of papillary impressions, and ureteral tortuosity.

The secondary effectiveness endpoint was reflux grade beyond 12 months, which was assessed to evaluate the durability of Deflux treatment.

Safety Endpoints

The safety endpoints for these three studies were: assessment of the severity and frequency of adverse events, urinalysis, serum blood chemistry measurements, renal ultrasound examination, intravenous pyelogram (IVP), and scintigraphy.

Patient Selection

The patient population in the clinical studies consisted of children (both boys and girls) who were diagnosed with VUR. The inclusion criteria were: patients with grade II-IV reflux in at least one ureter (further restricted to grade III-IV reflux in Study 1); duration of VUR $\geq$ 6 months; age $\geq$ 1 year; normal serum creatinine levels; and patients/parents sign the informed consent form. Exclusion criteria for the studies were: serious concomitant illness; prior endoscopic treatment of VUR; active UTI; Hutch diverticulum; duplicated ureters; and neurogenic bladder.

Patient Assessments

Prior to enrollment, patients underwent the following screening tests: clinical exam/history, VCUG, renal ultrasound examination, IVP (*randomized study only*), scintigraphy, serum blood chemistry measurements, and urinalysis. Immediately prior to treatment, all patients underwent cystoscopy to rule out Hutch diverticuli and duplicated ureters. Only those children satisfying the inclusion and exclusion criteria were enrolled.

Follow-up for Deflux-treated patients was scheduled for 1 day, 1 week, 3 months, and 12 months post-treatment. Three months following the initial treatment, patients with persistent reflux were eligible for a second Deflux treatment, after which the 1-day, 1-week, and 3-month exams were repeated. The 12-month exam was scheduled from the time of the initial Deflux treatment in the randomized study, while in Studies 1 and 2 it was scheduled from the time of the last Deflux treatment. Patients treated with antibiotic prophylaxis in the randomized study were only followed at 12 months post-treatment.

The following data were collected post-treatment: clinical examination (all time points), assessment of adverse events (all time points); VCUG (3 and 12 months), renal ultrasound examination (1 and 12 months), IVP (12 months, *randomized study only*), scintigraphy (12 months, *randomized study only*), serum blood chemistry measurements (12 months, *randomized study only*), and urinalysis (3 and 12 months).

Demographic Data/Baseline Characteristics

A total of 231 patients were screened and enrolled into the three studies. Of these 231 patients, 209 were treated with Deflux (randomized study = 39, Study 1 = 50, and Study 2 = 120), 21 were treated with antibiotic prophylaxis, and 1 patient assigned to Deflux treatment in the randomized study withdrew from the study for personal reasons prior to receiving treatment. Of the 230 patients treated with either Deflux of antibiotic prophylaxis in these studies, 210 are available for analysis at 12 months: 189 Deflux-treated patients (randomized study = 39, Study 1 = 43, and Study 2 = 107) and 21 antibiotic prophylaxis patients.

Table 2 summarizes the number of patients enrolled, treated, and included in the statistical analyses for each study. This table also summarizes the reasons for missing data.

Table 2: Study Participants

	Patients enrolled	Patients treated	Patients available for analysis @ 12 months[1]	Enrollment period
Randomized Study (Rome, Italy)	Deflux: 40 AP[2]: 21	Deflux: 39[3] AP: 21	Deflux: 39 AP: 21	Oct. 1997 – Sept. 1998
Study 1 (Uppsala, Sweden)	50	50	43[4]	May 1993 – Aug. 1994
Study 2 (Rome, Italy)	120	120	107[5]	Jan. 1995 – June 1996

[1] This includes patients who attended the 12-month exam and those who dropped out of the study at an earlier time due to persistent reflux (i.e., failures).
[2] AP = Antibiotic Prophylaxis
[3] 1 patient randomized to Deflux withdrew prior to treatment.
[4] 6 patients who were successfully treated at early follow-up missed their 12-month exams, and 1 patient was not evaluated due to protocol deviations.
[5] 12 patients who were successfully treated at early follow-up missed their 12-month exams, and 1 patient was not evaluated due to missing baseline reflux grade.

Although the majority of treated patients are included in the 12-month effectiveness analysis, there are additional missing data for various parameters (e.g., renal ultrasound exam, scintigraphy, etc.) at all follow-up visits.

Table 3 summarizes the relevant demographic and baseline characteristics of study patients:

Table 3: Demographic and Baseline Characteristics

	Gender distribution (% females)	Mean age (range) in years	Racial distribution (% Caucasian)	% bilateral reflux	Baseline grade[1]
Randomized Study					
Deflux arm (*n=40 pts.*)	60.0%	4.1 (1.0-13.4)	100%	32.5%	II: 37.5% III: 47.5% IV: 15.0%
AP arm (*n=21 pts.*)	61.9%	3.9 (1.0-10.0)	100%	42.9%	II: 61.9% III: 28.6% IV: 9.5%
Study 1 (*n=50 pts.*)	66.0%	4.9 (1.0-18.3)	100%	28.0%	III: 70.0% IV: 28.0% V: 2.0%[2]
Study 2 (*n=119 pts.*)[3]	74.2%	4.4 (0.9-15.6)	91.8%	40.3%	II: 30.3% III: 47.9% IV: 21.8%

[1] "Baseline grade" refers to the highest reflux grade of the patient's two ureters at enrollment.
[2] 1 patient with bilateral grade V reflux was enrolled; this patient is a protocol deviation, and is not included in the effectiveness analyses.
[3] 1 patient enrolled into Study 2 had missing demographic and baseline information.

The majority of subjects in each study was female, consistent with published reports stating that up to 85% the general VUR population occurs in females.[1] Patients were children, typically between 1 and 5 years of age at enrollment. Nearly all study subjects were Caucasian. Although these patient populations do not reflect the racial diversity of the general U.S. population, the literature suggests that VUR is much more prevalent among Caucasian children (particularly Caucasian girls).[1]

The study populations are similar with respect to (1) the proportion of unilateral versus bilateral reflux and (2) baseline reflux grade, with the exception of Study 1 did not enroll any patients with grade II reflux (its protocol restricted enrollment to grades III and IV reflux). The demographic and baseline characteristics between the Deflux and antibiotic prophylaxis arms of the randomized study were found to be sufficiently similar to permit statistical comparison of these groups.

Treatment

Deflux

In each of the studies, Deflux treatment was performed on an outpatient basis. All patients were treated under general anesthesia, consistent with other pediatric cystoscopic procedures. The injection procedure was performed similarly across the three studies. Using a cystoscope, Deflux was injected submucosally into the urinary bladder in close proximity to the orifice of each refluxing ureter (at the 6 o'clock position). Deflux was injected until a prominent bulge appeared and the ureteral orifice had assumed a crescent-like shape. Each refluxing ureter was injected with a mean volume of 0.8 to 1.1 ml per treatment session (range 0.2 to 3.0 ml).

In each study, patients were eligible for a single retreatment if they had persistent reflux (i.e., meeting the study inclusion criteria) in either ureter on the 3-month VCUG. These patients repeated the same 1-day and 1 and 3-month follow-up exams that were required following the initial treatment (12-month exams were scheduled from the date of initial treatment in the randomized study, and from the date of retreatment in Studies 1 and 2). The retreatment rates for the randomized study, Study 1, and Study 2 were 28.2%, 20.0%, and 11.8%, respectively. Retreatment was performed in an identical fashion as the initial treatment. In addition to the single retreatment permitted during the 12-month study period, Study 1 patients were allowed to receive a third and final injection after the 12-month exam if they had persistent reflux (as demonstrated on VCUG).

The only reported problem related to the injection procedure was one case of disconnection of the needle from the syringe (reported in the randomized study). However, this procedure was successfully completed.

All patients were prescribed prophylactic antibiotics following the injection procedure in the event the patient's reflux is not immediately corrected. In the randomized study, Deflux patients received prophylactic antibiotics until the 1-month exam, after which no antibiotics were administered unless a UTI was observed or suspected. In Studies 1 and 2, patients received prophylactic antibiotics until the 3-month follow-up exam. After that, only those Study 1 and 2 patients with persistent reflux received further antibiotic prophylaxis.

Antibiotic Prophylaxis

In the randomized study, patients randomized to antibiotic prophylaxis were prescribed legally marketed antibiotics for the entire 12-month follow-up period.

Data Analysis and Results

Effectiveness Endpoints

Due to the design of the randomized study, its results are used for the primary assessment of the effectiveness of Deflux treatment. The effectiveness results of the two non-randomized studies are reported separately as supporting information.

Although each refluxing ureter was separately graded and treated with Deflux, the outcomes of ureters within a patient are likely correlated (i.e., they are not independent observations). Therefore, all statistical analyses of device effectiveness were performed on a per-patient basis.

In the randomized study, the evaluation of device effectiveness is based on the results of 39 patients who were treated with Deflux and 21 patients who underwent antibiotic prophylaxis. The primary study endpoint was change in reflux grade from baseline to 12-months post-initial treatment. A patient was classified as a treatment success if all refluxing ureters (eligible for treatment under the protocol) improved to grade 0. Continued patient follow-up beyond 12 months was performed to evaluate the durability of the treatment.

VCUG was obtained at 12 months for 31/39 patients in the Deflux arm and 21/21 patients in the antibiotic prophylaxis arm. The remaining 8/39 Deflux patients dropped out of the study prior to 12 months due to persisting reflux and are categorized as failures. For these Deflux and antibiotic prophylaxis cohorts, the percentages of patients improved to grade 0 at 12 months are 69.2% (27/39) and 33.3% (7/21), respectively. A logistic regression was performed to analyze these results, adjusting for the following covariates: baseline grade, number of refluxing ureters eligible for treatment, and baseline age. This analysis demonstrated that this difference is success rates is statistically significant ($p=0.0041$). Patient gender was initially included as an additional covariate in the statistical model. However, this variable did not contribute any more information or explanation of the variance, and, as a result, was not included in the final model. Based on this result, it can be concluded that there was no gender effect associated with Deflux treatment.

The 12-month success rates reported in Studies 1 and 2 are similar to those reported in the Deflux arm of the randomized study: 23/43 (53.5%) and 64/107 (59.8%) for Studies 1 and 2, respectively. As with the analysis of the randomized study, all Study 1 and 2 patients who dropped out prior to the 12-month exam due to persistent reflux are categorized as device failures.

Table 4 summarizes the 12-month effectiveness results of each of these studies:

Table 4: 12-Month Effectiveness Results

	Number (%) Patients Improved to Grade 0 @ 12 months	Statistical significance between groups
Randomized Study Deflux arm AP arm	 27/39 (69.2%) 7/21 (33.3%)	p = 0.0041
Study 1	23/43 (53.5%)	N/A[1]
Study 2	64/107 (59.8%)	N/A

[1] N/A = Not applicable.

For all three studies, the percentage of patients improved to grade 0 at 3-month results is similar to the rates reported above for 12 months.

As indicated by the logistic regression analysis performed on the results of the randomized study, the success of Deflux treatment is influenced by the following covariates: baseline reflux grade, and number of refluxing ureters eligible for treatment. As expected, the success rate increases with decreasing baseline grade and for unilateral vs. bilateral reflux. For the randomized study, the Deflux success rate is higher than the antibiotic prophylaxis rate for each of these stratifications. Tables 5 and 6 summarize the effectiveness results for each of these stratifications.

Table 5: 12-Month Effectiveness Results vs. Baseline Reflux Grade

	% Pts. Improved to Grade 0 @ 12 Months		
Baseline Reflux Grade	**Randomized Study**	**Study 1**	**Study 2**
Grade II	Deflux: 93.3% AP: 46.2%	N/A	73.5%
Grade III	Deflux: 61.1% AP: 16.7%	60.0%	58.0%
Grade IV	Deflux: 33.3% AP: 0%	38.5%	43.5%

Table 6: 12-Month Effectiveness Results vs. Number of Refluxing Ureters

	% Pts. Improved to Grade 0 @ 12 Months		
Number of Refluxing Ureters	**Randomized Study**	**Study 1**	**Study 2**
Unilateral	Deflux: 76.9% AP: 50.0%	64.5%	67.2%
Bilateral	Deflux: 53.8% AP: 11.1%	25.0%	48.8%

The secondary effectiveness endpoint was change in reflux grade at time points greater than 12 months. The objective of this long-term assessment was to evaluate the durability of Deflux treatment. Although the three clinical studies were not designed to assess the safety and effectiveness of Deflux beyond 12 months post-implantation, the applicant was able to report the results of additional follow-up examinations which were conducted by the investigators of the randomized study and Study 1. For the 27 Deflux-treated patients in the randomized study who were improved to grade 0 at 12 months, reflux grade was assessed via VCUG at a mean follow-up time of 35 months post-treatment (range 28 to 39 months). Among this subgroup, all but one were still free of reflux. It should be noted that none of these patients were retreated following the 12-month exam. Assuming that all of the Deflux

patients who were study failures at 12 months continue to have reflux (worst case scenario), the 35-month success rate is 26/39 (66.7%).

Similarly, for the 23 Deflux-treated patients in Study 1 who were improved to grade 0 at 12 months, all but one were still free of reflux on their most recent VCUG (performed 9 to 67 months post-treatment; median = 18 months). Six of these 23 patients received a single retreatment following the 12-month exam. Using a time-to-event analysis for the entire 50-patient cohort of Study 1, the estimated cure rate at 36 months is 49.4% (standard deviation = 10.3%).

Safety Endpoints

The safety of Deflux was evaluated using the following endpoints: assessment of the severity and frequency of adverse events, urinalysis, serum blood chemistry measurements, renal ultrasound examination, intravenous pyelogram (IVP), and scintigraphy.

A total of 209 Deflux-treated patients were evaluated for adverse events in the three clinical studies. Additionally adverse events were evaluated in all 21 patients randomized to antibiotic prophylaxis. In all, 28 (13.4%) Deflux-treated patients and 1 (4.8%) antibiotic prophylaxis patient reported adverse events at some time during the 12-month study periods. There were no serious unanticipated adverse events or patient deaths reported in any of the studies. Table 7 provides a description of the observed adverse events.

Table 7: Adverse Events

Adverse Event Category	**Randomized Study**		**Studies 1 & 2 (n=170 pts)**
	Deflux (n=39 pts)	**AP (n=21 pts)**	
UTI	6 (15.4%)	0[1] (0%)	13 (7.6%)
Ureteral dilation	1 (2.6%)	0[2] (0%)	6 (3.5%)
Nausea/vomiting/ abdominal pain	0 (0%)	0 (0%)	2 (1.2%)
Stomatitis	0 (0%)	1 (4.8%)	0 (0%)

[1] Patients randomized to antibiotic prophylaxis were assumed to be free of UTI. However, since these patients were not examined as frequently as Deflux-treated patients, this value may underestimate the true UTI rate.

[2] Since patients randomized to antibiotic prophylaxis were not examined as frequently as Deflux-treated patients for the occurrence of de novo ureteral dilation, this value may underestimate the true rate of this complication.

UTI: Urinalysis was performed at all follow-up examinations to assess the frequency of UTI. In the randomized study, six Deflux-treated patients reported a total of nine UTIs. These nine cases were categorized as asymptomatic bacteriuria (n=4), cystitis (n=4), and pyelonephritis (n=1). In Studies 1 and 2, 13 patients reported a total of 14 UTIs. In all three studies, the UTIs typically occurred in patients with persistent reflux, and were successfully treated with standard antibiotic therapy. In interpreting these results, it is important to note that patients treated with Deflux in the randomized study received antibiotic prophylaxis for 1-month following each injection procedure, whereas Study 1 and 2 patients received antibiotic prophylaxis until the 3-month follow-up exam (with additional antibiotic prophylaxis prescribed for those patients with persistent reflux).

Ureteral dilation: Patients were assessed for the presence of ureteral dilation pre- and post-treatment by renal ultrasound examinations. The overall rate of de novo ureteral dilation following Deflux treatment was low. None of the observed cases of de novo ureteral dilation required intervention, and most cases resolved spontaneously prior to the 12-month exam. It should be noted that, in Studies 1 and 2, a total of 18 patients with baseline ureteral dilation had no signs of dilation at 12 months.

Nausea/vomiting/abdominal pain: In Study 1, nausea, vomiting, and abdominal pain were reported in two patients immediately following the injection procedure. This complication resolved in both cases.

Stomatitis: In the randomized study, one antibiotic prophylaxis patient was hospitalized for stomatitis toward the end of the 12-month follow-up period. This complication was successfully resolved.

The following potential risks of subureteral injection procedures were not reported in any of the studies: vascular occlusion, urinary retention, dysuria, bleeding/hematuria, urgency, and urinary frequency.

IVP, scintigraphy, and serum blood chemistry measurements were performed at baseline and 12-months post-treatment on all patients in the randomized study. These studies revealed no clinically significant differences between Deflux-treated patients and patients receiving antibiotic prophylaxis with regard to the onset of renal scarring, parenchymal damage, and changes in kidney size and function.

Device Malfunctions/Replacements

No device malfunctions or replacements occurred during the three studies.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The bench, animal, and clinical data provide reasonable assurance that the benefits of use of Deflux in children with VUR grades II-IV outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

The clinical data from patients treated with Deflux demonstrate that the treatment cured grade II-IV reflux in the majority of patients with low morbidity. The 12-month effectiveness results for the Deflux-treated patients demonstrate that the treatment response is superior to that of standard antibiotic prophylaxis treatment. The long-term (i.e., > 12 months) effectiveness results demonstrate that the results of Deflux treatment are durable.

Adverse effects were generally transitory and minor, and consisted mainly of UTI and mild ureteral dilation. There were no reports of unanticipated adverse events, severe reactions to either the Deflux material or the injection procedure, or patient deaths. There was no urinary retention or significant decrease in kidney function reported among study subjects.

XII. PANEL RECOMMENDATIONS

At an advisory meeting held on October 19, 2000, the Gastroenterology and Urology Devices Panel recommended that Q-Med's PMA for Deflux be approved subject to, and approval by the Center for Devices and Radiological Health (CDRH) of, the following conditions:

1. revised physician labeling (a) indicating the device for use in children with grades II-IV reflux, (b) contraindicating patients with nonfunctioning kidneys, active voiding dysfunction, duplicated ureters, and Hutch diverticuli, (c) summarizing the adverse events and other clinical study results, and (d) including sufficient patient counseling information on the risks, benefits, and limitations of Deflux treatment and alternate therapies for VUR;

2. collection and analysis of the available, long-term (i.e., > 12 months) safety and effectiveness data from existing study subjects; and

3. a postapproval study designed to collect long-term (i.e., 5-year) data on the safety and effectiveness of Deflux at multiple U.S. sites.

XIII. CDRH DECISION

CDRH concurred with the Panel's October 19, 2000, recommendation, and issued a letter to Q-Med, on November 20, 2000, advising the applicant that review of its PMA could not be completed until the following major deficiencies were adequately addressed: (1) collection and analysis of the available, long-term (i.e., > 12 months) safety and effectiveness data from existing study subjects; (2) statistical analysis of device effectiveness by relevant stratifications; and (3) submission of a postapproval study protocol proposing a 5-year, multi-center, U.S. study to investigate the long-term effects of treatment. Additionally, the November 20, 2000, letter requested that the applicant address the following minor deficiencies: (1) revision of the physician labeling to address the concerns raised by the Panel; (2) revision of the proposed promotional brochure to be consistent with the revised physician labeling; (3) submission of patient labeling; (4) statistical analysis of the 12-month effectiveness results between the Deflux and control arms of the randomized study using logistic regression; (5) clarification of the randomized study's patient-level data previously submitted to CDRH in electronic format; (6) additional chemistry information regarding the particle size and degree of crosslinking of the dextranomer microspheres, the viscosity of the carrier gel, and the accuracy of the hyaluronic acid content in Deflux; (7) clarification of the stability/shelf life testing, including information on the number of samples tested, description of how the product will be shipped, and request to limit the labeled shelf-life to 12 months; and (8) clarification of the order of the packaging and sterilization processes to confirm that the device is terminally sterilized.

In amendments received by FDA on May 1 and 15, August 21, and September 12 and 18, 2001, Q-Med submitted the required information. Specifically, these amendments demonstrate the following: (1) the effect of Deflux treatment continues out to at least 2-4 years post-treatment, with no serious long-term adverse events; (2) the effectiveness of Deflux is superior to that of antibiotic prophylaxis for all relevant stratifications; (3) Q-Med will perform the requested 5-year post-approval study in the U.S. to assess the long-term safety and effectiveness of Deflux; (4) the physician and patient labeling have been revised as requested by FDA; (5) the overall effectiveness of Deflux is superior (p=0.0041) to that of antibiotic prophylaxis when adjusting

for all relevant covariates; (6) the electronic files for the randomized study have been sufficiently described; (7) the chemistry of Deflux and its components have been sufficiently described; (8) the stability testing has been sufficiently described to justify a 12-month shelf-life; and (9) the sterilization process has been changed to permit terminal sterilization of the product.

Q-Med's PMA for Deflux was granted expedited review status on August 22, 2000 because FDA believes that an injectable bulking agent for the treatment of VUR is a breakthrough technology since it may present a clear, clinically meaningful advantage of existing technology (i.e., safer than open surgery and more effective than observation with antibiotic prophylaxis).

Inspection of the applicant's manufacturing facility was completed on June 14, 2001, and was found to be in compliance with the device Quality Systems regulations.

FDA issued an approval order on September 24, 2001.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Walsh, P. C., A. B. Retik, E. D. Vaughan, and A. J. Wein, eds. Campbell's Urology (7th Ed.), Vol. 2, pp. 1859-1916, W.B. Saunders Co., Philadelphia, 1998.