MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 9, 2000

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SUBJECT: OPDRA Postmarketing Safety Review for Advisory Committee, July 12, 2000
Drug: Today® Sponge (Nonoxynol-9, NDA 18-683)
Reaction: Toxic Shock Syndrome and Other Safety Concerns

EXECUTIVE SUMMARY

Our objective was to evaluate cases of Toxic Shock Syndrome (TSS) and provide an overview of other adverse events such as sponge removal difficulty potentially associated with the use of the Today® Sponge.

Cases of TSS associated with the sponge were retrieved from the FDA Adverse Event Reporting System (AERS) and Spontaneous Reporting System (SRS). Prior to November 1997, all reports were entered into the FDA Spontaneous Reporting System (SRS) and coded using COSTART terminology. Using the SRS data to enumerate cases of TSS and sponge removal difficulty is complicated because of coding limitations of the SRS system. No specific COSTART terms exist for these outcomes, the criteria for flagging serious events varied over the time period, and each case has only four searchable COSTART terms. Searching strategies to overcome these difficulties may result in under representation of the actual number of events in the database, and may lead to difference between individuals using different searching criteria. As a result, the findings in this report likely represent a minimum level of concern, since there may be additional unidentified cases that could not be retrieved.

Local reactions such as cervical disorder, vaginitis, migration of implant, vaginal discharge, and application site reaction were the most frequent adverse events reported in association with the sponge. Of the infection-related cases reviewed (those with a reported serious outcome), the majority of the cases were TSS or TSS-like cases. The remaining infection-related cases in which a serious outcome was reported were either very small in number or provided insufficient information to assess causality or determine why it was considered serious.

One hundred fifty-six unique cases had a reported diagnosis of TSS or at least three symptoms of TSS. All of these were temporally associated with the use of the Sponge. Eighty-nine of the 156 cases met three or more of the CDC criteria for TSS diagnosis. Sixteen of the 89 had other possible contributing factors to include menstruation and/or possible tampon use (13) within seven days of onset of TSS symptoms; four patients reportedly were postpartum. Approximately 85% of all cases reported a vaginal insertion time of less than the recommended maximum time of 30 hours. In many cases, the patients had difficulty removing the sponge. Thirteen reported requiring medical assistance to remove it. The outcomes include 120 patients that required hospitalization. At least 10 of the cases reported ICU admission and two reported the event to be life threatening. Twenty-six patients required some type of medical intervention such as emergency room treatment, clinic visit, and/or antibiotic therapy.

A cursory review of a sample of migration of device reports suggest that these were reports of sponge "removal requiring assistance" from either the sponsor's talkline advisor or a health care provider.

OVERVIEW OF THE AERS REPORTS

As of June 2000, there were 5930 adverse event reports with the Today Sponge in the AERS database. Of these, 267 reports had a serious outcome. There were no deaths reported.

Individual safety report characteristics

Distribution by age:	< 12 (2), 12-16 (23), 17-20 (312), 21-30 (1651), 31-40 (1350) 41-50 (206), 51-60 (17), > 60 (2), null age values (2367)
Outcome:	Hospitalization (176), Life-threatening (10), Disability (2), Required Intervention (16)
Distribution by year:	1983 (23), 1984 (215), 1985 (561), 1986 (686), 1987 (252), 1988 (230), 1989 (198), 1990 (513), 1991 (285), 1992 (285), 1993 (250), 1994 (3), 1995 (2321), 1996 (94), 1997 (14)
Report type:	Direct (117), 15-day (184), Periodic (5629)
Report source:	Consumer (5049), Health Care Provider (117), Foreign (13), Null values (765)

Most of the reports in AERS were submitted by the manufacturer as a periodic report. Report distribution by year was notable for a large number of reports received in 1995. During that year, there were 2321 reports with 1009 and 1319 submitted the first and fourth quarter, respectively. Although there were a large number of reports with a reported serious outcome, report distribution by report type indicate that many of the events were either not serious or they were labeled events. Consumers reported approximately 83% of the adverse event reports.

The table below provides a list of the 10 most frequently reported adverse event terms of all reports (5930) and the count by event with a serious outcome. Of note, a report may contain more than one adverse event term.

Top 10 Terms of all AERS Reports		
	Total count	Total count with serious outcome reported
Cervical disorder	1072	2
Vaginitis	968	54
Unintended pregnancy	868	10
Migration of implant	809	18
Vaginal discharge	600	23
Application site reaction	552	1
Pruritus	341	16
Infection	278	121
Menometrorrhagia	262	12
Unevaluable reaction	261	2

Based on information in the table above, local reactions such as cervical disorder, vaginitis, migration of implant, vaginal discharge, and application site reaction were the most frequent adverse events reported in association with the sponge. In contrast to those reactions, the infection reports show a larger proportion with a serious outcome.

OVERVIEW OF INFECTIOUS CASES

We searched the AERS database utilizing the system organ class term "infections and infestations" to get a broad overview of the types of infectious events that have been reported with the use of the Today Sponge and to determine if any of these resulted in a serious outcome. As of June 2000, there are 1551 infectious adverse event reports in the AERS database. The reported outcomes include 174 reported as serious, 141 requiring hospitalization, nine considered life threatening, and two reported as disabling. The table below lists all of the adverse infectious events reported with the Today Sponge. The number of events exceeds the number of reports (1551) because one report may contain more than one event.

Term	**Total count**
Vaginitis, vulvovagnitis	993
Bacterial infection, infection (including TSS), sepsis	286
Vaginal candidasis, candida, skin fungal infection	171
Cystitis, urinary tract infection, urethritis	124
Salpingitis	36
Cervicitis	28
Pharyngitis	12

Other than general infection reports, this data indicates that local inflammation and infection, namely vaginitis and vaginal candidasis constitute a large number of the total adverse infectious reports.

Excluding the TSS cases reviewed below, there were 52 reports under the SOC term "infections and infestations" with a serious outcome reported. The reported diagnoses of these cases include pelvic inflammatory infection, cystitis or urinary tract infection, balanitis, uterine infection, vaginitis, peritonitis, and nonspecific infections. Of note, these cases were retrieved only if they reported a serious outcome (died, hospitalization, required treatment, permanent disability, and

congenital anomaly). The previous Adverse Reaction Report (Form FDA 1639) also had the category "none of the above". If this box was marked, it is possible that some of these were retrieved by our AERS search. The table below provides the diagnosis and outcomes reported with each of these events.

Reported Diagnosis	Hosp	Treated RX drug	Treatment not specified	Other
Unspecified infection (22)	7	8	6	DS (1)
PID (11)	8	---	3	---
Vaginitis (10)	2	8	---	
Cystitis, bladder or urinary tract infection (9)	4	4	1	---
Balanitis (1)	---	1	---	---
Uterine infection (1)	---	1	---	---
Peritonitis (1)	---	---	---	Surgery (1)

Twenty-two cases reported in the above table were unspecified infections. The reporter generally listed a number of symptoms to include fever, elevated WBC, muscle aches, dizziness, or GI symptoms that occurred in association with the use of the sponge. None of the reports provided enough symptoms to suggest TSS and are therefore categorized as unspecified or miscellaneous infections. The ages ranged from 17 to 45 years old. Seven patients required hospitalization; eight were treated as an outpatient with antibiotics, and the remaining received unspecified treatment. One patient did report disability secondary to what appeared to be mild trauma from removing the sponge. She claimed that it resulted in recurrent infection.

There were 36 reports of salpingitis or PID reported with the Today Sponge, 11 of which reported a serious outcome. There were three cases of TSS with a possible co-diagnosis of PID. The patient's ages ranged from 19 to 37 years old. The time to onset ranged from less than 1 day to 6 days after use of the sponge (unknown-2). One patient required medical assistance to remove the sponge. Seven patients required hospitalization and IV antibiotic treatment and all patients appeared to recover with no major sequelae.

There were nine cases involving infections of the urinary tract (female-8, male-1). The reported diagnosis includes urinary tract infection (4), cystitis (3), nephritis (1), and pyleonephritis (1). The time to onset was reported to have occurred within 1 to 4 days of the sponge use (not reported in four cases). Three patients reported that they had used the sponge in the past (for one year or greater) without any adverse event. The reported outcomes include four hospitalizations, three requiring prescription medication treatments, one reported a permanent disability in addition to prescription medication treatment, and one that did not require any medical treatment. The case involving a permanent disability was not well described.

There were 54 cases of vaginitis with a reported serious outcome. Forty-four of these had another diagnosis that resulted in the serious outcome. The remaining 10 cases were generally not well documented. The following symptoms were reported: vaginal discharge, itching, bleeding, odor, burning, redness, irritation, and cramps. Eight reported being treated with prescription antibiotics. Most of the vaginitis cases did not appear to be serious. There were two patients that required hospitalization. The reason for their hospitalization was not clearly specified in these reports.

There was one case of balanitis with a reported serious outcome in a male (age unknown). He developed irritation on his penis for one week after contacting the sponge. He was treated with tetracycline. No sequalae were reported. There was one case of uterine infection with a reported serious outcome in a female who noted blood on removal of the sponge. This was her first use of the product. The following day, she experienced abdominal pains, which was diagnosed by her physician as a uterine infection. She was prescribed antibiotics. There was one poorly documented case of a 45-year-old female who was admitted one day after use of the sponge for peritonitis. On admission her WBC was elevated to 16,300. She underwent exploratory laparotomy for an acute abdomen. The peritoneal fluid was positive for Streptococcus viridans.

TOXIC SHOCK SYNDROME

Case Definition

The CDC criteria for TSS include fever, hypotension, rash, desquamation, and abnormalities in three or more organs. A definite case fulfills all of the five clinical criteria. A probable case fulfills four of the five criteria.[1,2]

Selection of Cases

Prior to November 1997, there was no COSTART term in SRS for TSS. We searched the AERS database utilizing the preferred terms "infection", "bacterial infection", "sepsis", and "acute circulatory failure" to identify all reports of Toxic Shock Syndrome (TSS) associated with the Today Sponge. Additional cases of TSS (not coded as infection) were identified by combining various terms such as fever, hypotension, myalgia, influenza like illness, and pharyngitis. There is no guarantee that we were able to identify all cases of TSS reported to the FDA without a manual review of all 5930 reports. Because AERS summary results do not include specific case information (e.g. narrative summary or laboratory data), we printed the images of original reports and manually abstracted the relevant information from each form. The data were then entered into an Excel spreadsheet, which was used for subsequent analysis.

A total of 305 reports were reviewed. One hundred, twenty-seven reports were not included for the following reasons:

- Not TSS cases - These reports were not felt to be reports of TSS because there was no diagnosis of TSS or there wasn't sufficient information to determine whether it was a TSS case.
- Unable to read direct report (2)
- Probably not related (3) - one patient developed an infection 6 weeks after use of sponge, one was diagnosed with endometritis and another with gonorrhea.
- Product (Tagamet and Mevacor) inadvertently linked in SRS to Today sponge (2)
- No patient identified in report (1)

Summary of Cases

We reviewed all reports with a diagnosis of TSS. We also reviewed cases that did not have a diagnosis of TSS but met at least three CDC criteria for TSS. A total of 178 reports representing 156 cases of TSS or reporting at least three symptoms of TSS were reviewed. Demographic data for all of the cases are provided below.

Age:	Range 16 to 42 years old, median 25, mean 26 (unknown-21)
Outcome:	Hospitalization (120), Required Intervention (26), Not reported (10)
Total insertion time:	Ranged from 1.5 hours to 3 days (not reported-49)
Event year:	1983 (15), 1984 (27), 1985 (11), 1986 (11), 1987 (8), 1988 (16), 1989 (13), 1990 (7), 1991 (15), 1992 (14), 1993 (7), 1994 (11), 1995 (1)
CDC Criteria:	Met all 5 (24), met 4 (24), met 3 (41), and met less than 3 (67)

All 156 cases were temporally related to the use of the Today Sponge. The ages ranged from 16 to 42 years old with a mean and median of 26 and 25, respectively. The time to onset of symptoms appeared to occur in most cases within four days of use of the sponge product, however this information was not always provided. The total vaginal insertion time of the sponge ranged from 1.5 hours to 3 days but was not reported in 1/3 of the cases. The case reported to occur at 1.5 hours was questionable because the patient had a history of PID and only met two CDC criteria. Approximately 85% of the cases, that reported a vaginal insertion time, specified that it was less than the recommended maximum time of 30 hours. In many cases, the patients had difficulty removing the sponge. Thirteen reported requiring medical assistance to remove it.

Approximately 30% of the TSS cases were reported within the first two years of product marketing. The reporting of this event appeared to decrease after 1984. The rates however increased somewhat in 1988 and 1991 in comparison to the prior year. Many of the earlier cases (1983 to 1985) were submitted along with a CDC TSS report form, which made identification of CDC criteria much easier. It is not clear if CDC TSS reports were submitted directly to the FDA from the CDC and if so, why these CDC reports did not continue to be submitted to the FDA after that time. The outcomes include 120 patients that required hospitalization. At least 10 of the cases reported ICU admission and two reported the event to be life threatening. Twenty-six patients required some type of medical intervention such as emergency room treatment, clinic visit, and/or antibiotic therapy.

There was interest by the division to identify those cases that met certain CDC criteria. Those that met all five of the CDC criteria were considered definitive cases of TSS. Those that met four of the five CDC criteria were considered probable cases of TSS, while those that met three of the CDC criteria were considered possible. For those cases that met less than three CDC criteria, TSS cannot be ruled out, however most did not provide sufficient clinical information to determine if it truly was a case of TSS. Based on the information provided in the reports, 89 cases met three or more of the five CDC criteria. Of these 89, 48 could be considered definite (24) or probable (24) TSS cases. The table below breaks down the number of cases by year and number of criteria met. Worth mentioning, the largest numbers of definite cases were reported to have occurred in 1984.

CDC Criteria	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995
Met < 3	4	3	8	6	1	8	6	5	6	8	6	5	1
Met 3 or more	11	24	3	5	7	8	7	2	9	6	1	6	0
3 criteria	5	4	0	2	5	2	6	2	8	4	0	3	0
4 criteria	3	4	2	3	1	3	1	0	1	2	1	3	0
5 criteria	3	16	1	0	1	3	0	0	0	0	0	0	0

Of those cases that met three or more CDC criteria, 13 were possibly menstruating or had used a tampon within one week of the onset of TSS symptoms. Four patients (one that was also menstruating) were postpartum from 4 weeks to 3 months. One patient discovered she was also pregnant at the time she was hospitalized. It is not known how these factors may have contributed to the development of TSS.

We did not look at reporting rates of TSS with the Sponge relative to tampons. Because the Today Sponge and tampons are available only as OTC products, there is no reliable usage data available that would allow us to estimate incidence rates for TSS based on exposure to these products.

SPONGE REMOVAL DIFFICULTIES

Given the fact that in many of the TSS cases, there was reported difficulty in removing the sponge and 13 reported requiring medical assistance to remove the sponge, we felt this issue may pose a safety risk. There is no reliable way to ascertain the total number of reports of "sponge removal difficulty" and "removal with medical assistance" in AERS or SRS. This is because there was a limit of four coded terms in SRS and there were no specific COSTART terms for either of these two events. There are 809 reports in AERS that are coded as "migration of implant". A cursory review of a sample of these reports suggest that these were reports of sponge "removal requiring assistance" from either a Whitehall Laboratories advisor or a health care professional. The severity of the event was not always adequately addressed in the report and follow up of potential cases requiring medical assistance to remove the device was not always provided.

CONCLUSIONS

Local reactions such as cervical disorder, vaginitis, migration of implant, vaginal discharge, and application site reaction were the most frequent adverse events reported in association with the sponge. Of the infection-related cases reviewed (those with a reported serious outcome), the majority of the cases were TSS or TSS-like cases. The remaining infection-related cases in which a serious outcome was reported were either very small in number or provided insufficient information to assess causality or determine why it was considered serious.

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85% of all cases reported a vaginal insertion time of less than the recommended maximum time of 30 hours. In many cases, the patients had difficulty removing the sponge. Thirteen reported requiring medical assistance to remove it. The outcomes include 120 patients that required hospitalization. At least 10 of the cases reported ICU admission and two reported the event to be life threatening. Twenty-six patients required some type of medical intervention such as emergency room treatment, clinic visit, and/or antibiotic therapy.

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1. Reingold, AL, et al. Toxic shock syndrome surveillance in the United States, 1980 to 1981. Ann Intern Med 1982; 96 (part 2): 875-80.
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cc:

HFD-560	Division File Archival NDA 18-683
	GanleyC/ChinL/Keravich
HFD-430	Beitz/Trontell/Karwoski/ Guinn/Division