VOLUME 3, NO. 5 • MAY 1996

FDA Review

HUMAN & ANIMAL DRUGS • BIOLOGICS • MEDICAL DEVICES

Incorporating DICKINSON's FDA and DICKINSON's FDA INSPECTION
A monthly newsletter focusing on early drug/device/biologic regulatory policy, compliance and field enforcement, and personnel developments inside the Food and Drug Administration.
Published by Ferdic, Inc., P.O. Box 367, Las Cruces, NM, 88004-0367. James G. Dickinson, Editor, (505) 527-8634 • Fax: (505) 527-8858. INTERNET: ferdic@lascruces.com
David McFarland, Washington Editor, (717) 731-1426. John Scharmann, Consulting Editor, (303) 277-9531. Annual subscription: U.S. $735. Overseas Airmail $795.

MD TO FDA: RESCIND IT!

In a 4/20 letter to FDA Commissioner David Kessler, ophthalmologist William Ellis urges that Summit Technology's PMA for a photorefractive keratectomy (PRK) 6 mm excimer laser, approved 10/20/95, be rescinded because of data irregularities in the PMA.

Ellis alleges that the data included studies on young naval recruits whom the Summit device made far-sighted, producing "good visual acuities but will cause disabling side effects to these young men as they enter their 40s," and other studies that used software different from Summit's approved model. ***See story below ...***

Getting too close to FDA: the eye laser scandal

"That's crazy!" the seasoned Washington FDA lawyer exclaimed. "How can your relations with FDA possibly be *too* good?" Yet it seems that high-flying Summit Technology's excellent connections in CDRH's Division of Ophthalmic Devices not only helped give it dominance of the fledgling U.S. excimer laser eye surgery market even before its devices were approved for that, but might ironically have also been just what brought to Summit CEO **David F. Muller**'s home a malignant FDA envelope containing confidential agency documents about rival Visx Inc.'s excimer laser marketing application last November.

The previous month, Summit's own corneal surgery laser had been approved, so the package on Visx's still-pending application, including a draft approval letter, engineering data, another competitor's data and internal CDRH memoranda, wasn't valuable in an approval sense.

Whether it was of other potential value, Muller isn't saying, although others speculate that the data would have been *(continues on p. 20)*

Highlights:

Temple: PhRMA's FDA reform ideas are 'silly ... absurd'

"I find the PhRMA position completely incomprehensible," CDER director of drug evaluation I **Robert J. Temple** told ***FDA Review*** 5/3, commenting on FDA reform arguments presented that day by Pharmaceutical Research and Manufacturers of America (PhRMA) president **Gerald J. Mossinghoff** in a *Washington Post* letter to the editor. "What they're setting up is a situation where the first time they hear about the new data we want is in a non-approvable letter," Temple went on. "It's really silly of them. The right test is whether we're doing our work on time." Temple was addressing Mossinghoff's support of reform legislation that would abolish raw data filing

within the 15-day time frame as stated earlier to Ms. Aveta of the NY District Office.

OAI further stated that it had already initiated a review of SOPs dealing with complaints and MDRs and its intention to provide training to employees in these areas. The firm continued that it was "puzzled, based on the above as to the reasons for the issuance of this Warning Letter.

> *OAI feels strongly, based on our two previous responses to you and the additional specific clarifications provided, that the issues cited in both 483 observations and the Warning Letter are very minor in nature and have been satisfactorily addressed.*

Furthermore, we feel that the 510(k) moratorium cited in your Warning Letter should be lifted immediately." OAI asked for a meeting with New York District to discuss these concerns and to seek assurance that FDA was satisfied that OAI had fully addressed the issues in the Warning Letter.

In a telephone conversation with Dr. **Amiram Daniel** of Olympus America 4/17, he stated that the firm had received a letter from New York District to the effect that its reply to the Warning Letter was adequate and that follow-up would be in the District's normal inspection schedule.

—John Scharmann

LASER SCANDAL (from p. 1)

very useful in Summit's ongoing patent litigation with Visx, as well as with a possible PMA supplement to upgrade its approved product.

Whatever its value to Summit, the packet's arrival launched both FDA and FBI investigations into all those extremely effective connections Summit has enjoyed at CDRH for at least two years. Close company and FDA observers of some of those connections say they seemed so friendly as to cross the conventional — if not the legal — boundary separating official business from personal relations. For example, Summit vice president for regulatory affairs **Kim Doney** was known to regularly (some say even routinely) engage in lengthy telephone conversations two or three times a day with **Emma Knight**, CDRH lead reviewer on Summit's pending PMA.

Frequently, observers say, those conversations got into after-hours subjects. Doney declined to comment to ***FDA Review*** on her FDA relationships, but her boss, Muller, pulled no punches about the company's familiarity with CDRH people, boasting that he has made himself well known to "everyone" in the ophthalmic devices division and others, both during numerous personal visits and over the telephone.

too close?

When does such obvious rapport become too close, and run the risk of unleashing a potential backlash against the very company that culti-

KNIGHT: RUMORS 'NOT TRUE'

Emma Knight, who voluntarily transferred full-time to CBER's human tissue program 8/95, told *FDA Review* that the allegation that she leaked the documents to Summit was "specifically not true." She worked only on the Summit PMA, not the Visx PMA, and then only on a half-time basis on parts of the submission that could be brought to conclusion. She had no role with newly submitted data after she left CDRH.

"I am aware that there are efforts to point fingers by people who probably don't know a lot," Knight told us, making it clear she was talking only "very reluctantly."

"I had very, very limited involvement" in the Summit PMA, Knight said. Another reviewer, however, told us she had total control of the PMA and he was not allowed access to it even after she left the Center and Knight continued to work it from CBER.

In her last four months at CDRH before she left, Knight said, she purposely limited her involvement in excimer lasers. "I was only there to clean up what I had," she said. "There was probably a time when documents weren't being looked at and people thought they should have been, but the idea that I did everything is obviously impossible."

She knew "very minimal" about the package sent to Summit in November. "I don't have the full involvement of everything that went on, and I kind of don't want to know." Furthermore, she has no suspicions about who might have sent the package.

vated it in the first place? That point may not have yet been reached in Summit's case, but some in the medical practitioner community who have been using Summit's earlier-model but basically identical lasers for years say the company has a way of getting FDA to do just what it wants, even to the point of helping it build market domination. The ways Summit has done this, they allege, include:

- *Causing FDA to issue a 2/23 import alert on all previously exported Summit lasers so that ophthalmic surgeons can't buy them more cheaply overseas, as they have been doing for years; clinically, most of the re-imported devices are identical to the recently approved model, except that they lack a built-in procedure-counter and a Summit-devised lock-out device that would prevent them from being used in a newer procedure known as photorefractive keratectomy (PRK). Both these non-clinical add-ons are necessary to ensure that Summit collects $250 royalties on each PRK procedure performed in the U.S.*
- *Causing FDA to conduct inspections of practitioners who have bought reimported lasers that don't carry royalty mechanisms and to cite them for investigational device exemption (IDE) and/or nominal misbranding/adulteration violations.*
- *Persuading FDA to limit, in the terms of its approval of Summit's new laser, PRK surgeries to devices approved for oblating corneal tissue in a 6 mm optical zone, when all predecessor devices had approval only to 5 mm or less; until last month when Visx's excimer laser was approved, only Summit's newest model had approval for 6 mm, giving the company effectively six months of competition-free marketing time.*
- *Using its influence with FDA staffers to slow down the review of its main rival's (Visx) PRK laser.*

preapproval lock ...

According to former Summit western sales manager **James C. Fallon**, who is suing Summit for wrongful dismissal, this was all part of a broader plan to gain a pre-FDA approval lock on the U.S. eye surgery laser market. Summit's strategy, developed in 1990, included preselling upgradable "holmium" lasers (limited glaucoma indications) to ophthalmologists in anticipation of eventual FDA approval of the Summit device for more advanced phototherapeutic keratectomy (PTK) and PRK procedures some one to two years down the road. These 510(k)-covered holmium lasers were sold as "workstations" at six times the price of competitive holmium lasers, Fallon says, because they could be easily and quickly upgraded after FDA approval, thus saving purchasers expected post-approval delays of 12-18 months facing ophthalmologists who did not buy early. Fallon says he was fired for not accepting verbal orders to participate in this preselling scheme while the company was issu-

LASER's SAFETY QUESTIONED

Are Summit Technology's excimer lasers as safe as FDA thought when it approved them last October? San Francisco ophthalmologist William Ellis has drawn FDA's attention to recent overseas reports that implicate the company's devices in an increased incidence of retinal detachments.

Rockford, IL ophthalmolgist Edward Yavitz informally reported to FDA and to Ellis four retinal detachments in Malta, 12 others noted by two ophthalmologists in the UK, and a report by Israel's Isaac Lipshitz of a 0.7% incidence of retinal detachments and post-operative hemorrhage with the Summit laser in that country. Ellis says he relayed these to CDRH device evaluation director Susan Alpert in February with the recommendation that the agency alert practitioners to the possible risk.

Increasing the beam area from 5 mm to 6 mm as Summit has done, Ellis says, directs 44% more energy onto the retina, and others have reported pressures of 20 to 40 atmospheres in the eye from Summit's device, which Yavitz says "should not be allowed for surface PRK."

Asked about this 4/3, Alpert told *FDA Review* she believes any problem in these "isolated" reports probably derives from poor patient selection, not the device.

Ellis also cites one of Summit's own pivotal domestic 6 mm studies used to gain approval, in which none of the 89 subjects (unrepresentative, young, predominantly male naval recruits) were followed for more than a year and thus produced positive results that he charges will be undone when the young men reach their 40s and need corrective lenses to overcome the eyestrain caused by the PRK treatment's over-correction of their myopia.

To justify its final approval last year, Summit submitted 1,610 cases which Ellis criticizes as mostly unaudited and foreign. "It is surprising that not one case of retinal detachment occurred in Summit's data, while other investigators in the Common Market countries where the machines have been in use for six years report multiple instances," Ellis says.

ing phony written directives (for FDA's benefit) to its sales team warning them not to presell the unapproved lasers.

"Summit management practiced a web of deceit by instructing the sales force in writing not to promote, market or sell the excimer laser," Fallon says in a 3/3 declaration. "Factually, Summit management including but not limited to **J. Frantzis, Peter Litman** and David Muller himself put tremendous pressure to secure sales of the Summit laser, prior to its FDA approval. The sales force were told that Summit needed the cash flow to stay alive as it was hemorrhaging red ink, because of the delay in securing FDA approval." Fallon told us that according to (John) Frantzis, Summit's national sales manager and close Muller confidant, Muller planned a $1 million contribution to Senator **Edward Kennedy**'s re-election campaign and $500,000 to the Democratic National Committee with the intent of expediting FDA approval of Summit's new laser. Fallon did not know how or if these campaign contributions were ever consummated.

a power guy ...

Another who was fired, former vice president of sales and marketing **William Kelley**, told ***FDA Review*** he was miserable the whole 10 months he was at Summit, mainly because Muller dominated everything and used questionable tactics, including the preselling of the excimer laser disguised as a holmium workstation. "He's a power guy. He thinks he can get away with murder, and he pushes things to the limit. During the time I was there, he used the expression 'pushing the envelope,' and I remember one time, regarding the FDA, he said we were going to go until we were nose-to-nose with them, and they would have to say 'Stop doing this' before we would stop doing some of the things we were doing and saying in terms of getting sales."

Kelley said Summit sold 80 to 100 holmium systems using the excimer sales carrot. "There were lots of commitments by sales reps and even the sales manager that 'You'll have the excimer head within six months of approval,' or 'You'll be the first one in line,' that sort of thing."

Amid a barrage of ophthalmologist and trade complaints extending over three years, FDA finally received something in the summer of 1994 that it couldn't ignore: a four-page purported 7/11/90 internal Summit memo to Muller describing the scheme. This moved CDRH compliance director **Lillian J. Gill** to send Summit its only FDA protest: a 10/27/94 Warning Letter that was subsequently followed by a 1/18-26/95 inspection. During the inspection, Kim Doney and other executives were apparently able to convince Boston District Investigators **Michael J. Leal** and **George T. Allen** that the incriminating memo was a forgery and that Summit had done all it could by

THE CALENDAR ....

MEETINGS	SPONSOR	DATE	LOCATION	PHONE
MDMA Annual Meeting	MDMA	May 16-18	Vista, Washington, D.C.	(202)898-5700
US & European Reg Submissions	ASQC	May 17-19	Copley Plaza, Boston, MA	(303)239-6961
115th Annual NDMA Meeting	NDMA	May 18-21	Broadmoor, Colorado Springs	(202)429-9260
92nd Annual Meeting	NABP	May 18-22	Marriott Copley, Boston, MA	(847)698-0124
ASCP Midyear Conference & Exhibition	ASCP	May 19-22	Marriott, Marco Island, FL	(703)739-1300
Intro. Workshop: Medical Device Law	FDLI	May 20-21	Crowne Plaza, Seattle, WA	(202)371-1420
Pharmacokinetic Concepts in Drug Development	PERI	May 20-23	Merck Conference Ctr., NJ	(703)276-0178
Baltimore Courses III	PDA	May 20-24	Sheraton Int.,Baltimore,MD	(301)986-0293
The Inspection Process:Interacting with FDA	FDLI	May 22	Crowne Plaza, Seattle, WA	(202)371-1420
FDA Inspectin & Enforcement Issues	RAPS	May 29-30	DoubleTree, Rockville, MD	(301)468-1100
Clinical Trials:New EU Directive	DIA	May 30	Berkley Court Dublin, Ireland	(215)628-2288
New Variations Regulations & Procedures: EU	DIA	May 31	Berkley Court Dublin, Ireland	(215)641-1229
31st Annual Meeting & Exposition	AAMI	June 1-5	Marriott, Philadelphia, PA	(703)525-4890
Medical Design & Manufacturing	Canon	June 4-6	Jabits Ctr, New York, NY	(310)392-5509
Current Situation Self-Medication	DIA	June 6-7	Corwne Plaza, Mexico City	(215)628-2288
DIA Annual Meeting	DIA	June 9-13	Convention Ctr.,San Diego,CA	(215)628-2288
Biotechnology Industry Organization '96	BIO	June 9-13	Marriott, Philadelphia, PA	(202)857-0244
Pharmaceutical & Biotechnology Management	MIT	June 10-14	MIT,Cambridge, MA	(617)253-2101
Managed Pharm Care:Theory & Application	AMCP	June 23	Westin Crown, Kansas City,MO	(703)683-8416
Medical Device Update '96	FDLI	June 24-25	Renaissance,Washington, D.C.	(202)371-1420

way of written directives to stop any preselling of the unapproved excimer laser.

Their FDA-483 merely cited Summit for inadequate rework documentation, use of an obsolete test data sheet and failure to calibrate a digital thermometer, observations that Summit readily consented to. Interestingly, during a 12/18/95 deposition in a civil suit in Boston, Doney swore that Summit never received Gill's Warning Letter.

actual excimers, too ...

Not all the sales during this preapproval period were of the holmium workstation, according to Fallon. In a 12/15/95 memo to pioneering laser surgery ophthalmologist **William Ellis**, MD, he named four such purchases, with the handwritten notation to Ellis: "The physicians above bought excimer lasers before approval! I'm not talking about the workstation but actual lasers." One downside of preselling excimers in this manner was that Summit could hardly pay patent royalties due to IBM, since officially no sales were occurring. Eventually IBM found out about this and is seeking $1 million in a settlement now being negotiated.

Some ophthalmologists balked at paying up to $380,000 for a $60,000 holmium laser with upgrade commitments from Summit.

An estimated 30 to 40 of these practitioners bought exported and foreign-built Summit lasers overseas and in Canada for a fraction of the U.S. price, and began importing them for use as "investigational" or "custom" devices exempt from FDA interference, often waiting until after Summit's first approval for PTK 3/10/95. Eventually, however, FDA began interfering, allegedly at Summit's behest, sending "adulteration/misbranding" Warning Letters to Ellis and several others even though these devices were clinically identical to the lasers Summit used in its U.S. clinical trials to gain approval for the PTK and PRK indications last year. According to Ellis and others, the only difference between the various models is that Summit's post-approval models have counters and card-reading lock-out attachments for assessing per-procedure royalties due.

There is another difference, however — Summit refused to service the reimported devices, or to provide operating manuals. Field Service Engineering, of Fitchburg, MA, composed of ex-Summit personnel, stepped into the void and is now providing service.

When ***FDA Review*** asked Summit's David Muller what it was about the previously reimported Summit devices that was clinically different, he seemed unsure:

Q: Do the reimported, older devices that lack approved new labeling, a counter and a PRK lock-out have a clinical difference from your approved device?

Muller: Well, the counter has no clinical effect, but there's a whole variety of things that could have a clinical effect, and in fact, the FDA asked the Customs Department to seize all devices being imported into the U.S. that don't comport to ours. So they're seizing devices. Obviously somebody else besides us decided they shouldn't be reimported either.

Q: But is it clinically significant, or just a legal technicality?

Muller: No, there certainly — We've been shipping lasers outside the U.S. for eight or nine years. Yes there are — That's the deal with the approval process. You have a certain set of parameters which you study, and based on that, they're approved. Most of the devices outside the U.S. aren't within the bounds of those parameters.

Q: But what's the clinical significance?

Muller: Well, the clinical significance is that the devices haven't been shown by the FDA to be safe and effective in the bounds of those clinical parameters that those devices have. That's the significance.

Q: The assertion is that the devices are essentially identical.

Muller: Well, they're welcome to —

Q: They're mechanically and engineering-wise identical.

Muller: It's not true.

Q: What are the differences?

Muller: I'm not going to go into it here. It's simply not true. We've been shipping them outside the U.S. for eight years. There's some that are very close, there's some that are very different. There's still probably Serial No. 5 out there somewhere. To assert that that's mechanically or electrically equivalent to the device we have in the U.S. is false. They're different. The agency has made their statement on it, I don't have to make any more of a statement on it than that. There's Warning Let-

WHAT VALUE FDA's SELF-INVESTIGATIONS?

FDA can be breathtakingly diligent in investigating errant companies, but when its own internal police unit, the Office of Internal Affairs (OIA), investigates FDA employee misconduct, don't hold your breath waiting for outcomes.

Set up two years ago by Commissioner David A. Kessler out of the wreckage of the dysfunctional and discredited Division of Ethics and Program Integrity, OIA has yet to produce any public results.

Asked by Rep. Tom Coburn (R-OK) during the FDA reform hearing 5/1 for such results, Deputy Commissioner and Senior Advisor Mary K. Pendergast promised to provide them promptly. Her office, however, acknowledged to *FDA Review* the next day that the "results" did not exist and would have to be created for the congressman.

"OIA is a black hole from which nothing ever emerges," a former FDA reviewer told us. Industry informants who have dealt with it say they have no confidence in the unit.

CDRH Office of Device Evaluation director Susan Alpert acknowledged to *FDA Review* 5/2 that a 14-month-old OIA investigation into alleged corruption of a dental advisory panel hearing still has not emerged.

This is the office that is now investigating the leaking of proprietary ophthalmic documents to Summit Technology.

ters to a whole variety of doctors saying they're different and they violate the act, and there's a whole variety of reasons behind that. The agency is simply doing its job on that issue.

Q: But whether there's a clinical difference or merely a legal deficiency remains unanswered.

Muller: No, I answered it. I told you that there are some of those devices that are absolutely clinically different.

Q: Some are?

Muller: Yes. And there are some that are very close.

Q: Would the ones that are very close have a significant clinical difference?

Muller: Yup. The devices that are used outside the U.S., for instance, are able to treat patients over a much larger range of treatment parameters that the U.S. ones can't, and that has major significance.

Q: And that is a mechanical limitation?

Muller: It's both hardware and software, and were those devices to be imported and used in the mode that they're used in the U.S., then they would be clinically operating well outside the bounds of what the FDA has deemed to approve.

When we asked CDRH director of device evaluation **Susan Alpert** about the clinical differences and the justification for the import alert, she said the imported devices did not bear current approved labeling, and the PRK lock-out feature could have some clinical significance, although she could not discuss that. Informed that Ellis and others claimed they could not obtain copies of the approved labeling in order to bring their machines into compliance, Alpert said: "The labeling is FOI-able." (Laser ophthalmologist Ellis, however, told ***FDA Review*** an FOI request he filed in December for the final labeling still has not been complied with.)

On other aspects of the controversy, Alpert declined to comment in view of the current Office of Internal Affairs investigation into the leakage of confidential documents from FDA to Summit. She did say, however, that her office has increased document security since the leak, through intensified employee training, and the addition of locks to offices and desks that contain sensitive documents.

In a separate conversation, again constrained by the ongoing internal investigation, CDRH director **Bruce Burlington** admitted that the new security measures might result in slower reviews by impeding the previous "flexibility" that reviewers enjoyed. ODE would try to avoid this, he emphasized. As for the import alert, Burlington said the reimported devices had no assurance of compliance with GMPs. However, ophthalmologist Ellis told ***FDA Review*** that FDA does not retain GMP jurisdiction over devices once they are sold and in private hands; further, the reimported Summit lasers had been continuously maintained by Summit overseas.

Neither Alpert nor Burlington would acknowledge that Summit may have had "too much" familiarity with their employees. That, after all, is what the investigation is all about. And if FDA's internal investigation isn't enough, Rep. **Joe Barton**'s oversight and investigations subcommittee indicated 4/29 in a letter to Commissioner **David A. Kessler** that it is intensely interested.