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Dockets Management Branch (HFA-305)
 Food and Drug Administration
 5630 Fisher Lane, Room 1061
 Rockville, MD 20852

March 13 2000

Dear Sir/Madam

Docket No. 99D-5199: FDA Guidance Document on Adhesion Barriers

Please accept the following comments to the above document.

By way of introduction and as a declaration of financial and related interests, I have been involved in the science and business of adhesion prevention for nearly 13 years. For the past four years I have operated Synechion, Inc., which provides consulting, research and business services to companies engaged in the development of anti-adhesion products.

Synechion has consulted with and/or conducted research on behalf of a number of companies in this field. I also have financial interests in some of these companies. In addition, Synechion has participated in the Ad hoc Industry Task Force which has provided its own comments to you in this matter.

Lastly, I am the founder of the International Adhesions Society on behalf of whom I have submitted separate comments.

I share the enthusiasm of others in the industry for FDA's initiative in drafting this document. This is an important step in ensuring a consistent and scientifically sound rationale for the regulatory approval of anti-adhesion products.

I will address my comments to various matters in the draft guidance document in the order that they appear.

1.0 Comments relating to Section: "Preclinical III C" and also "Clinical Investigation Plan - IV - Pivotal Studies - H - Special Considerations"

The draft document states:

"Performance studies should be conducted in the appropriate animal model(s) to provide "proof of concept," that is, these studies should suggest that there is reasonable premise for efficacy in the human. Animal studies may also suggest better designs for the clinical studies to follow. These studies should represent, insofar as

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possible, the surgical approach (laparotomy versus laparoscopy), the specific surgical site(s) (e.g., between viscera and body wall, around loops of bowel), the types of adhesions (e.g., de novo adhesion formation versus reformation of existing adhesions), the method of adhesion evaluation (e.g., score, incidence, extent, severity, etc.), and the method of application that will be used in human studies”

also:

H. Special Considerations Laparotomy versus laparoscopy

Products should, in general, be evaluated separately for laparotomy and laparoscopic surgical indications. Sponsors are encouraged to develop laparoscopic animal models to estimate efficacy of laparoscopic use prior to initiation of human laparoscopic trials

The underlined passages are worthy of comment:

1.1 “the appropriate animal model(s)”

Until recently, there was no scientific basis for the selection of an animal model of adhesions. Recently correlations between animal and clinical outcomes have been established for some models (Wiseman, 2000). These correlations are stronger, and/or more robust for some models than others. Nonetheless, there are many limitations in the way that these correlations can be used.

We of course endorse the use of well conducted studies, in well established models. We also endorse the exploitation of new knowledge concerning the performance of animal models, as it becomes available. However we believe, given the state of the art, that the term “the appropriate animal model(s)” implies, erroneously, the availability of models which have been shown conclusively to correlate with the clinical situation.

We therefore propose that the word “the” be deleted from this passage.

1.2 laparotomy versus laparoscopy

We believe that the inclusion of this term may imply differences between laparotomy and laparoscopy in terms of:

- a) the rates of adhesion development
- b) the pathobiology of adhesion formation
- c) the ability to reduce adhesions

We assert that there is not only no evidence to suggest that this is true, but there are data which suggests it is not true (discussed more fully under section 3.0 below).

Currently efficacy studies in animals are intended to establish that there is a “*reasonable premise for efficacy in the human*”¹. To require these studies be done laparoscopically increases the threshold of reasonableness in a way that is practically difficult to obtain and unrealistic. Despite recent advances in animal modeling (Wiseman, 2000), no animal models have been shown to predict with certainty the results of clinical outcomes. The tremendous biological variability in animal models is another factor. A

¹ Draft Guidance Document, Special Considerations for adhesion barriers:Section 5C

laparoscopic model would have no more relevance than some animal models already accepted by FDA, and used by FDA as the basis for suggestions to small manufacturers.

Furthermore laparoscopic application of products into laboratory animals would require the development of special instruments as well as special skills even on the part of skilled laparoscopic surgeons. There is no guarantee that these instruments and techniques can mimic their human equivalents. Any gain that would be made by developing these techniques would be more than offset by the unreliability of animal models in general.

The insistence on laparoscopic models of adhesion formation is not scientifically justified, may conflict with the Animal Welfare Act. As a past chairman of two Institutional Animal Care and Use Committees, I would not vote to approve the conduct of any study that was done merely for the reason of satisfying a requirement that is based on an unproved or even disproved premise.

1.3 method of application

We agree with FDA that animal studies should demonstrate efficacy of the method of application of a product, including its application through a laparoscope. Such a demonstration may be performed using separate studies, designed specifically to test that aspect of product use.

1.4 reformation

Although there are some data which suggest differences in the pathobiology of reformed versus de novo adhesiogenesis, it has been shown empirically that the performance of materials in some animal models of de novo (1b) adhesion development correlate with their performance in human models of adhesion reformation (Wiseman, 2000). This is perhaps not surprising given the physical method of action of these materials.

It is interesting to note that had the developers of one product relied on an animal reformation study rather than on a de novo type study, many patients would have been deprived of its benefit.

The performance of animal reformation studies requires at least two surgical procedures to be performed on one animal. This raises legitimate concerns for an Institutional Animal Care and Use Committee, who is charged, by Federal Law, to approve the use of animals in scientific studies.

In considering our comments stated in 1.1 above, we believe that to require the performance of reformation animal studies before the conduct of a reformation human study, is unnecessarily burdensome, or from the perspective of the Animal Welfare Act, not justifiable.

1.5 method of adhesion evaluation

We believe that it is important to note for the record that anatomic differences between animal and human species may preclude the duplication of scoring systems.

1.6 insofar as possible

We agree with FDA with the sentiment expressed by this passage and wish to emphasize the limitations of animal studies described by the above comments. To do this we propose that the Guidance Document includes a statement to the effect that while animal studies are extremely valuable, an overreliance on them effectively usurps the raison d'être for the performance of a human study.

2.0 Comments Relating to Section II Intended Use and VI: Labeling: A: Indications for Use

The draft document states:

Labeling should accurately reflect the data that has been collected on the device. A device's labeled indication for use should be based on the studies conducted to support the indication.

The document further recognizes that:

"One of the most difficult issues with respect to adhesion barrier devices is how broad or narrow the indications should be, i.e., how much can the data from the clinical trials be extrapolated to broader or related uses?"

Given:

- a) the many practical problems in conducting studies based on clinical endpoints such as pain, infertility or bowel obstruction
- b) the absence of any reliable method of non-invasive evaluation of adhesions
- c) the limitation in the range of surgical procedures (and hence anatomic sites) that can be studied using a second look observation

The draft documents articulates the problem of how to extrapolate data gathered from a clinical study involving one set of abdominal tissues, to abdominal tissues not accessible to clinical study.

The essentially similar nature of healing in most abdomino-pelvic tissues implies that not only should adhesion development be similar throughout the abdomen/pelvis, but the ability to reduce this development be similar. Where differences between tissues do occur, they may be due not only to subtleties in the healing process, but also differences in the extent and type of injury inflicted on different organs.

Other than obvious anatomic and physiologic differences that raise specific functional (the ability of a membrane barrier to remain in place on a constantly moving structure such as the bowel) or safety (e.g. infection related or wound healing issues for a bowel anastomosis) issues, we believe that there should be no general impediment to permit a product to be used in a manner that is more widespread than the clinical trial was able to study. Indeed at the GYN FDA Panel meeting of January 25 2000, the panel heard from its two invited experts, that this should indeed be the case.

As safeguards, we propose that specific safety issues be addressed by studies in which products are tested in more generalized procedures. Although not lending themselves to efficacy evaluation, these procedures do permit safety evaluation. For example, a certain product can be tested in patients undergoing small bowel surgery. while it is not possible to conduct second look evaluations of adhesions in these patients, it is possible to monitor the incidence of any complications such as infections or wound dehiscence.

Such studies would be conducted after appropriate studies in animals.

There is already a precedent for this type of arrangement. The labeling for Seprafilm™ Bioresorbable Membrane (Genzyme Corp.) limits the use of the product to structures studied in the clinical trials, but permits its use in procedures other than the ones studied in the clinical trials, where these procedures include the clinically studied structures.

As an additional solution to the problem, it is noted that procedures performed in one surgical specialty may have direct bearing on those performed in another. For example in myomectomy, a significant number of patients form adhesions to the small bowel. The effect of an agent on the small bowel in this GYN procedure could be used to support an indication for clean, small bowel adhesiolysis in general surgery. FDA representatives at a scientific symposium on adhesions in October 1999 have indicated their willingness to consider this proposal.

3.0 Comments relating to: “Clinical Investigational Plan - IV - Pivotal Studies - H - Special Considerations”
H. Special Considerations *Laparotomy versus laparoscopy*

The draft guidance document states:

“Products should, in general, be evaluated separately for laparotomy and laparoscopic surgical indications (Refs 8, 12). Due to significant differences, both quantitative and qualitative, in adhesion formation following laparoscopic procedures as opposed to similar procedures performed via laparotomy, data derived from laparotomy studies may not be fully extrapolated to predict efficacy in the laparoscopic model.”

3.1 Differences in adhesion development: Guidance Document “evidence”

In asserting that there are “significant differences, both quantitative and qualitative, in adhesion formation following laparoscopic procedures as opposed to similar procedures performed via laparotomy”, the draft document cites two papers as support (Lundorff et al., 1991; Operative Laparoscopy Study Group, 1991).

Neither of these references do indeed supports this assertion!!

The first of these reports involved a prospective trial by Lundorff et al. Patients undergoing surgery for ectopic pregnancy by laparotomy apparently developed more adhesions than those undergoing similar procedures by laparoscopy. Unfortunately, 32/105 of the patients randomized to treatment did not undergo second look laparoscopy. The reasons given were no desire for pregnancy (18), became pregnant (9), recommended for IVF after the initial surgery due to extensive adhesions (5). Since the group assignment of these patients was not stated, and no “Intent to Treat” analysis was performed, the results of the study are difficult to interpret.

The second of these reports (Operative Laparoscopy Study Group, 1991) does not involve a comparison of adhesion formation between laparoscopy and laparotomy, thus is irrelevant to the argument. Furthermore this report includes some patients treated with Dextran 70, a fact reported in a later publication (Wiseman et al., 1998).

3.2 Differences in adhesion development: published data

Before continuing this discussion it is important to note that there are two main types of adhesions (Diamond and Nezhat, 1993), each with two subtypes. It did appear from the panel discussion of Jan 25 2000, that there was some confusion about these adhesion types, particularly the two subtypes of de novo adhesion where an important distinction regarding laparoscopy is to be made:

Type 1: De novo adhesions: Adhesions occurring at sites with no previous adhesion

- 1a: de novo adhesions at sites where no surgical procedure was performed e.g. adhesions due to indirect trauma
- 1b: de novo adhesions at sites of a surgical procedure other than adhesiolysis, due to direct trauma.

Type 2: Reformed Adhesions: Adhesions reforming at sites of previous adhesiolysis

- 2a: Adhesions occurring at sites of adhesiolysis only
- 2b: Adhesions occurring at sites of adhesiolysis plus another procedure e.g. treatment of endometriosis

Only in the case of the de novo type 1a (indirect trauma) adhesions is there evidence that the rate of adhesions is different in laparoscopy and laparotomy (Nezhat et al., 1990). Since there is less tissue manipulation and desiccation in laparoscopy, de novo (type 1a) adhesions are less likely to form.

The rate of de novo (type 1a) adhesion formation in laparotomy is already relatively low (30%) compared with the rate of development of de novo type 1b (direct trauma) or reformed (type 2a and 2b) adhesions. It is these adhesions that most efforts have been and will be directed by manufacturers. The rates of development of these (1b, 2a, 2b) adhesions do not appear to differ substantially in laparotomy or laparoscopy.

In a meta-analysis (Wiseman et al., 1998; see Appendix 1) we found a very slight, but non-statistically significant, increase in the rate of adhesion development in laparoscopy compared with laparotomy (for type 1b - direct and reformed adhesions). If correct, this may be a reflection of a reduced ability to handle tissues atraumatically at direct sites of surgery. Additionally there is a suggestion that the flow of cold, arid gases during laparoscopy may damage mesothelium (Ott, 1998a,b) as may the products of combustion from laparoscopic cautery (Ott, 1997a,b).

We believe therefore that there is no clinical evidence to suggest that the rate of adhesion development (at de novo 1b or reformed sites) is substantially different in laparoscopy or laparotomy. This assertion is not based on a lack of evidence, but the presence of evidence from our meta-analysis (Wiseman et al., 1998). There are certainly no data to suggest that the pathobiology is any different. These points were confirmed at the FDA GYN Panel meeting of Jan 25 2000, both by the panel's invited experts, as well as a number of experts present.

At the aforementioned panel meeting, FDA representatives stated that there were other published studies which supported their contention. Via email, I requested that a list of these studies be supplied and received no response.

3.3 Other differences between laparotomy and laparoscopy

Even if differences in the rates of adhesion development do exist, there is no reason to believe, and there are no data available, which suggest that such differences could be due to differences in pathobiology.

At the OBGYN Advisory Panel meeting of Jan 25 2000 statements were made regarding other theoretical differences between laparoscopy and laparotomy:

3.3.1 "The amounts of tissue drying and the types of damage (laser, electrocautery etc.) distinguish the two types of surgery."

There are no data, and there is no theoretical basis to believe that any of these things may alter the way that adhesions form. Even if they did, since we are dealing with physical barriers whose action does not depend on a biological mechanism, we have no reason to believe that these factors make a difference.

If laser or electrocautery damage is indeed greater in laparoscopy than in laparotomy, then this itself should have by now caused sufficient concern to move FDA into regulating the use of these power sources in laparoscopy, in regard to this matter. Since this is not the case, we do not believe that this argument merits any serious consideration.

3.3.2 *“The use of carbon dioxide gas may alter the response of the body to the barrier”*

Even if true there are no data to support this highly theoretical contention that such an alteration may even be harmful. If CO₂ gas does alter the body’s response to adhesion barriers, then it should alter the response to a wide range of other implants (degradable or non-degradable), including sutures, staples, meshes, vascular grafts etc. We would then expect to see more adverse events associated with these devices after laparoscopic implantation than after the equivalent implantation via laparotomy.

If CO₂ gas reduced the rate of degradation, we would expect to see reports of granuloma formation or infection potentiation with laparoscopic application of implantables. If CO₂ gas increased the rate of degradation then we would expect to see premature loss of strength for absorbable sutures and possible wound dehiscence.

Since FDA has not, to our knowledge raised these concerns with other products, the entirely theoretical argument that CO₂ gas affects adhesions adversely, cannot merit serious consideration.

Certainly, we have information that in the case of one adhesion barrier (INTERCEED), in nearly 10 years of laparoscopic use in the USA and other countries, these adverse events have not occurred.

3.4 *“the same barrier might not work well in the laparoscopic surgical environment”*

3.4.1 *Published Data*

In its questions to the panel, FDA has stated that *“some studies have shown that the same barrier might not work well in the laparoscopic surgical environment”* INTERCEED is the only product to which this statement might be applied. Published data clearly shows that the statement is incorrect. By way of comparison, this product has been shown conclusively to be efficacious in gynecologic laparotomy (Wiseman et al., 1999). There are four (independent) published studies which attest to its efficacy in laparoscopically equivalent procedures (Mais et al., 1995a,b; Keckstein et al. 1996; Wallwiener et al., 1998). The levels of efficacy observed in these studies (over 78 patients) is equivalent to that seen in laparotomy. An non-randomised study involving laparoscopic myomectomy (Korrell, 1995) shows a level of adhesion development with INTERCEED similar to that seen in laparotomy controls and INTERCEED treated patients respectively.

In contrast, only two studies (Greenblatt and Casper², 1993; Saravelos et al., 1996) failed to show a benefit of INTERCEED in laparoscopy. Both of these studies involved patients with polycystic ovary disease (PCOD), a condition not studied in laparotomy. Since data for INTERCEED’s performance is equivalent in laparoscopy and laparotomy for procedures other than PCOD, the lack of performance in the Greenblatt and Saravelos reports is most likely due to some intrinsic difference in PCOD rather than laparoscopy itself.

In all of these reports, as well as in a number of experiential reports (Azziz et al. 1991; Dlugi et al. 1992; Liu 1992; Marchino et al. 1993; Pados et al., 1992; Wood et al., 1992) and over 10 years of clinical use in laparoscopy, there is no suggestion that the safety of INTERCEED is compromised in laparoscopy.

² The Greenblatt study involved only seven evaluable patients, limiting its interpretative value.

3.4.2 Unpublished Data

At the OBGYN FDA panel meeting of January 25 2000, some details of an unpublished study involving INTERCEED in laparoscopy were disclosed by panel members and FDA. This study, it was claimed, supported the contention that *“some studies have shown that the same barrier might not work well in the laparoscopic surgical environment”*

This study it seems was the subject of a letter written by the makers of INTERCEED to doctors in the winter of 1998-9. That letter states that *“postoperative adhesions may be caused by application of INTERCEED Barrier, if adjacent structures (e.g. ovary and tube) are coapted of conjoined by the device”*. Any failure of INTERCEED in this study therefore appeared to be have been due to the inappropriate application of the product causing coaptation rather than its use in laparoscopy. Such coaptation in laparotomy would have been just as likely to yield similar results.³ Thus the citing of this study to support the contention that *“some studies have shown that the same barrier might not work well in the laparoscopic surgical environment”* is entirely without merit.

Consequently, there is no reason to believe that the ability to reduce adhesions will be any different in laparoscopy or laparotomy.

We therefore believe that there is no justification to require that “products should, in general, be evaluated separately for laparotomy and laparoscopic surgical indications”.

Such a requirement is not only burdensome, but having conducted one study in laparotomy and shown that an agent is effective, there may be ethical concerns regarding the initiation of a second study.

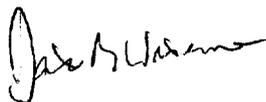
3.5 Safeguards in Laparoscopy

We do agree that appropriate studies be performed to demonstrate the safe and effective deployment of any device laparoscopically, and that where there are concerns that a product may be compromised in the presence of bleeding, the labeling should indicate that the surgeon checks hemostasis by partial desufflation prior to deployment of the device. Safety concerns may be addressed by safety studies and/or post marketing surveillance.

I shall be pleased to answer any further questions you may have and to assist you in the preparation of this important document.

Thank you for the opportunity of allowing me to furnish you with my comments.

Sincerely



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³ This product “failure” is therefore the result of poor instructions being given to physicians rather than to any intrinsic property of the material itself.

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Appendix 1

In a recent meta-analysis (Wiseman et al., 1998), adhesion-free outcome of surgical sites undergoing abdomino-pelvic surgery was documented for a number of clinical studies, with either laparoscopy or laparotomy.

In both comparisons adhesion-free outcome was slightly higher for laparotomy than for laparoscopy, but this difference was not statistically significant.

Adhesion-free outcome

	Laparoscopy		Laparotomy		p
	%	N	%	N	
de novo 1b (-)	37	19/51	45	98/217	NS
Reform (-)	14	3/21	27	105/395	NS