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May 24<sup>th</sup> 2012

The IAS is a volunteer organization for the promotion of awareness and research into Adhesion Related Disorder, as well as the support of patients and families afflicted with ARD.

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SprayShield: Approval status, clinical trials, reasons for delay, patient posts  
*Maker not seeking FDA approval. European clinical study planned. Patient Action*

By David M. Wiseman

A request was made to post the following message on our web site from our old friend Annie Hayashi who raises a number of important issues. We took this opportunity to address these issues by providing an update on the status of SprayShield, its FDA approval, a new clinical trial, background information about SprayShield's development and the rumors that have been circulating about these matters. Our summary analysis and further discussion follows Annie's message.

1. Finally an answer- Annie's message about SprayShield

Had adhesiolysis done with Dr. Jens Pagels in 2010. There was an initial adhesiolysis done with Sprayshield, and Covidien the pharmaceutical maker was present. Four weeks later a second look was done and there was no indication of any adhesions, Covidien was also present. Prior to this adhesiolysis, I had an operation done in the U.S. with no barriers, and an unnecessary resection also done, because the sigmoid was kinked with adhesions, and I had difficulty defecating.

Had I gone to Germany originally, none of this would have happened. The adhesions would have been removed and Sprayshield applied. It would appear that two years later I still have no internal adhesions, because after a colonoscopy, the GI MD. stated that the colon behaved as a normal colon, not one that was adhered in any way.

Surgery is cheaper in Germany, but your insurance may not pay. I can substantiate that Dr. Jens Pagels is the ONLY surgeon I would use. Sprayshield is not available here. Covidien has chosen to market it only in Europe. It is very easy to have surgery done by Dr. Pagels. St. Joseph Moers, where he is chief of gynecology is not far from Dusseldorf, and I am quite sure he would even arrange for transportation to and from the airport. I had a ruptured teratoma (dermoid cyst) in 1965, but was unable to get the colon freed up totally. If you want more information these are the ways you can reach Dr. Pagels, of course, email is the most easiest way:

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My email address is: [Mhaya0902@gmail.com](mailto:Mhaya0902@gmail.com) if you need more information I believe he also has a website on the internet.  
Anne Hayashi

Suggested citation for this work:

Wiseman DM (2012). SprayShield: Approval status, clinical trials, reasons for delay, patient posts. Maker not seeking FDA approval. European clinical study planned. Patient Action. International Adhesions Society [www.adhesions.org/WisemanSprayshieldUpdate052412.pdf](http://www.adhesions.org/WisemanSprayshieldUpdate052412.pdf), [date of access].

<u>Contents</u>	<u>Page</u>
1. Finally an answer- Annie’s message about SprayShield	1
2. Editorial: SprayShield Update: maker not seeking FDA approval. New European clinical study	2
2.1 Background	2
2.2 Summary of SprayShield’s approval status, clinical trials, reasons for delay, patient posts	2
3. Detailed Discussion	4
3.1 SprayShield History	4
3.2 Is SprayShield safe and effective?	5
3.3 How does a product receive FDA approval?	5
3.4 If I want to have SprayShield used in me what do I do?	6
3.5 Posting your experience with doctors	6
3.6 Did the withdrawals of Intergel and Adcon affect SprayShield’s approval?	6
4. References	8

## **2. SprayShield Update: maker not seeking FDA approval. New European clinical study**

### 2.1 Background

It is nice to hear this good news from Annie Hayashi who has certainly suffered many years. Annie was one of the first members of the IAS. If memory serves me correctly she organized our first IAS meeting in San Francisco around 1998.

We have been asked about Sprayshield many times and because of the voluminous and confusing chatter it is appropriate for us to clarify the situation. Patients have told us they have heard from “reliable sources” the “reasons” why Sprayshield is not approved in the US. These "reasons" include:

- a. The FDA is making hurdles impossible for Covidien, the makers of SprayShield, to pay for the clinical data needed to get it approved here and holding up the approval of Sprayshield.
- b. The makers of Sprayshield tried to get the product approved right after some barrier that caused infections and had been approved by FDA had been removed from the market and FDA were making things harder for that to happen again.
- c. There is a conspiracy to destroy Covidien and the doctors who use its products (according to this version it seems that in various ways FDA, the Big Pharmaceutical Companies and even the IAS are involved !!)

### 2.2 Summary of SprayShield’s approval status, clinical trials, reasons for delay, patient posts

So let’s try to straighten this out and summarize what we know to the best of our knowledge. Following this summary is a more comprehensive discussion that includes SprayShield’s history, available information on SprayShield, how to be treated with SprayShield, FDA approval of adhesions products and the how the Intergel and Adcon stories have affected SprayShield and other adhesions products.

- a) Covidien has made a business decision not to seek FDA approval. Covidien has told us that it is neither seeking FDA approval nor conducting further clinical studies with SprayShield. This is a business decision as it views SprayShield, even in Europe, as a low business priority. Covidien has indicated that it would not be able to assist in obtaining “Compassionate Use” exemptions for severe cases in the USA. I personally wish this situation were otherwise, but it is Covidien’s decision to

make. And so for the moment do not “wait” for any FDA approval. The company, as it has told us, has decided not to pursue it.

- b) SprayShield’s safety and effectiveness The little information available would likely not be sufficient for FDA to draw any conclusions (one way or the other) about SprayShield’s safety and effectiveness. In response to our request, Covidien has undertaken to provide additional information that we can post, which we will do when we receive it. Countries in Europe and elsewhere do not require testing as extensive as that required in the USA, but according to the standards of the countries in which SprayShield is marketed, the product is regarded as safe and effective.
- c) A number of factors contributed to the delay until now of SprayShield in the USA likely related to business decisions made by Confluent to focus its efforts in other areas, the need to reformulate SprayGel, the acquisition of original company by Tyco, poor clinical trial recruitment and reluctance of investors to invest in adhesions research because of misperceptions about the adhesions market (estimated currently at about \$250 million) stemming from the market withdrawals of Intergel and Adcon.
- d) FDA’s treatment of SprayShield appears to be no different from that of other products. There is no evidence of any diabolical conspiracy on the part of FDA, Big Drug Companies or the IAS to harm SprayShield or anyone associated with it.
- e) Rumors Harm Patients. Perpetuating unsubstantiated rumors about the “reasons” for SprayShield’s delay is harmful to patients as it fuels the flames of a fire that says “don’t invest in adhesions”. We have seen companies (with products with excellent prospects) fail to obtain investment in adhesions research because of similar kinds of rumors that reach the ears of would-be investors. No investment in adhesions (in any company) means no new products. No new products means very little hope to an end in patient suffering. If you see others doing this, ask them to stop and get the facts for everyone’s sake.
- f) Medical Treatment Abroad is one of many options patients are encouraged to explore for treatment, but only after thoroughly weighing all the available data (or lack thereof), benefits and risks with their doctor and checking the training and experience of the foreign providers. We are happy to post information about doctors and treatments around the work to the extent that they provide patients more options to explore, but in a way that tries to allow patients to make informed and objective decisions about those treatments.
- g) Doctors are encouraged to collect and publish their data in the peer-reviewed medical literature so that patients and other doctors can evaluate it objectively. With good data a new treatment will be adopted by doctors so that hundreds of thousands of patients can receive the help that they need.
- h) You may be able to join a clinical trial that will study the effect of SprayShield and adhesiolysis on pain. Depending on the data, all patients will eventually be offered treatment with SprayShield. To proceed, more study centers and patients will be needed. The IAS is assisting the planners by publicizing information about the study to other possible study centers in Europe as well as potential patients. If you are interested in traveling to Finland or another European country to participate in the study, please let me know by email: [david.wiseman@adhesions.org](mailto:david.wiseman@adhesions.org).

### 3. Detailed Discussion

#### 3.1 SprayShield History

- a) An earlier version of SprayShield called SprayGel was developed by a company called Confluent in the early 2000's. The product then, as now, consists of two liquids sprayed through a nozzle where they mix and then gel on the surface of an organ forming a barrier to adhesions. Preclinical studies (including some performed by my company Synechion) as well as some clinical studies were conducted with SprayGel in the early 2000's with generally positive results. A number of IAS members/visitors traveled to Germany to one of at least two surgeons who were using it, with mostly, but not always, good results.
- b) Although Confluent certainly planned to obtain FDA approval of SprayGel, it made a business decision to focus its efforts on what was a more lucrative market for DuraSeal, a related product used in spine surgery. This decision no doubt slowed the progress of SprayGel. In 2006 Confluent was acquired by Tyco who placed the SprayGel assets in a division called Covidien. As is common after an acquisition and restructuring of this sort there is a period during which the new company reviews of all its projects in order to determine which ones should be prioritized. This process itself would almost certainly slow the progress of SprayGel/SprayShield.
- c) Because of the carbon dioxide used in conventional laparoscopy, SprayGel did not gel properly. This problem was solved (at least partly as far as we know) by altering the composition of the product and its method of application to make the SprayShield version. This work no doubt consumed company resources and contributed to the delay in over product development. There was also a suggestion that SprayGel could cause some sort of reaction. My company also found a reaction to SprayGel in [one particular animal model](#) which was surprising given the fact that we had not found any reaction in [earlier studies](#) (conducted then for Confluent) using other models.
- d) Covidien did start one, possibly two clinical studies in the US for SprayShield and sponsored some other studies (see below) for which only incomplete information is available.
- e) In response to our direct questions, Covidien has told us that they have no plans to conduct clinical studies in the US or Europe, nor does it have any plans to seek FDA approval of SprayShield in the USA.
- f) SprayShield is marketed in Europe and elsewhere, but Covidien has informed us that marketing support for the product is a low priority for the company.
- g) Enshrined in the US Constitution is the inalienable and self evident right of every American to criticize the Government in general and the FDA in particular, a right that even this writer has exercised on occasion. But I have not seen any evidence to suggest that SprayShield has been treated any differently from other products. Not even Covidien has claimed this. Covidien is a publicly traded company with annual sales of over \$11 billion. It certainly has the financial and legal resources to pursue such claims if there were any substance to them.

### 3.2 Is SprayShield safe and effective?

The little information we have about SprayShield would likely not be sufficient for FDA to draw any conclusions (one way or the other) about its safety and effectiveness. In response to our request, Covidien has undertaken to provide additional information that we will post. Products are often approved first in the countries that do not require testing as extensive as that required in the USA, but according to the standards of the countries in which SprayShield is approved, the product is regarded as safe and effective. Here's what we know.

1. *Preclinical (animal) studies*: Positive results were reported in one small study with eight pigs treated with SprayShield and three without ([Ferland and Campbell, 2009](#)). However encouraging, it is essential to have human clinical data.
2. *Clinical Studies*: There appear to be four or possibly five small clinical studies conducted with Sprayshield. Only for the first two of these, some data are available:
  - a. A study described in the [SprayShield brochure](#) had 12 treated and 4 untreated patients. Although positive, this is an extremely small study by anyone's standards upon which to make decisions about treatment.
  - b. A company-sponsored study conducted in the USA with 14 treated and 7 control patients undergoing adhesiolysis for pain or infertility found a reduction in adhesion scores using SprayShield, and no adverse events attributed to the product (Luciano et al., 2010).
  - c. A company-sponsored study in the USA was terminated after about 50 patients. It is possible that this is the same as the previous study. We did hear that the effectiveness was insufficient to justify further work. The company told us that the study was terminated because patient enrollment was too slow (although this is something that can be fixed many times). We have not seen any data for this study.
  - d. A now [terminated company-sponsored study in 30 ulcerative colitis patients and polyposis patients](#) was conducted in eastern Europe.
  - e. A [company-sponsored study with 15 myomectomy patients](#) was completed in Oldenburg, Germany.

In general the larger the study (or number of studies), the more reliable are the conclusions drawn from them.

3. *Adverse Events*: Five (5) [adverse events have been reported to FDA](#) for SprayShield as of May 20 2012. A report of an event does not necessarily mean that the device actually caused the event. These events most likely occurred during the US clinical trial(s).

### 3.3 How does a product receive FDA approval?

To receive approval in the USA to market a medical device for adhesion prevention a company must show that the product is safe and effective. It must also show that it can manufacture the product consistently to defined specifications of quality.

Certain studies must be conducted including:

1. *Non-animal tests*: These determine whether the product might cause cancer or genetic mutations. Other tests may examine the physical or chemical properties of the product.
2. *Pre-clinical (animal) studies*: Some studies detect if the product increases the risk of birth defects or cancer, birth or if it impairs the healing of wounds or the body's ability to fight infection. Other studies (usually with rats, rabbits, dogs or pigs) will mimic a surgical operation to predict whether the product will reduce adhesions in human patients. As encouraging as any animal study may be, it is essential that we have clinical data to know just how effective and safe something is in people.
3. *Clinical (human patients) studies*: The "Gold Standard" of evidence that a product is working is a well-conducted Randomized Clinical Trial (RCT) of which at least one is required. In a typical study, the ability of a product to reduce adhesions after surgery in about 150 patients will be compared with the effect of surgery alone in another 150 otherwise similar patients.
4. *Post-Marketing Surveillance*: Companies must track of adverse events and report them to FDA. Companies often conduct specific studies after approval to track the safety of the product once it is used in the larger population and/or to monitor its effectiveness in special cases.

The requirements for approving an adhesion barrier are described in the [2002 Guidance Document](#) finalised after FDA sought the input of a panel of external medical experts and the public. I was one of two speakers chosen to represent the group of companies developing anti-adhesion products at a public hearing (see [transcript](#)) and was intimately involved in submitting written comments to FDA on behalf of the group. I also provided oral and [written comments](#) in my capacity as Founder of the IAS.

The cost of obtaining approval by FDA or other countries runs into the millions of dollars. Since companies are ultimately accountable to their shareholders, they must determine whether the money they spend on developing any product could be more effectively used to increase shareholder value by investing a different product.

<p><u>3.4 If I want to have SprayShield used in me what do I do?</u> With the little data on the safety and effectiveness of SprayShield in mind and after consulting with your doctor, there are three options if you are still wish to use it:</p> <ol style="list-style-type: none"><li>1. <i>Compassionate Use:</i> FDA regulations provide for special “<i>Compassionate Use</i>” or “<i>Humanitarian Use</i>” approvals for specified patients to be treated in the USA with a product not yet approved. This almost always requires the cooperation of the company involved. In the past we have asked Confluent (for SprayGel), and Covidien (5/17/12) to assist US doctors in obtaining SprayShield under these circumstances. Both Confluent and Covidien declined, as is its right to do.</li><li>2. <i>Travel Abroad:</i> A patient could certainly benefit from a treatment only available abroad that turns out to be effective years (if ever) before introduction into the USA. Although it should not be the first consideration, the cost (including travel etc.) is often less than the cost for the same procedure in the USA. In addition to considering treatment’s safety, a patient should evaluate the qualifications and experience of the doctor and account for differences between training and standards of doctors in those other countries and those in the USA.</li><li>3. <i>Participate in a clinical trial:</i> Doctors in Finland are planning a study entitled “Adhesiolysis in Chronic Abdominal Pain.” in which patients will be randomly and blindly assigned to receive either:<ol style="list-style-type: none"><li>a. Laparoscopic adhesiolysis and Sprayshield, or</li><li>b. Anaesthesia and skin incisions without laparoscopy or related procedures.</li></ol>If once the code is broken, a benefit is found in the first group, then patients in the second group will be invited to undergo adhesiolysis with Sprayshield.</li></ol>	<p><u>3.5 Posting your experience with doctors.</u> The biggest complaint we hear is that patients cannot find a doctor who will treat them. We therefore encourage patients to post their experiences with individual doctors for others to consider. We welcome Dr. Pagels to the names that you will find elsewhere in our message board. Please investigate any doctor thoroughly before embarking on treatment with him/her.</p> <p>We try to balance the benefit of encouraging these posts against the problems ensuing from excessive postings about one doctor. Suppose that a new treatment really benefits 50 of every 100 patients. Most (let’s say 40 of 50) adhesions patients after suffering for years will have the understandable desire to broadcast the good news of a successful treatment. Fewer (say 20 of 50) of those not so fortunate will be motivated to make postings about yet another failure. So now because we will see twice as many (40) positive posts as negative (20) ones, instead of seeing 50 on either side, patients are left with an inaccurate picture of how good the treatment really is, impairing their ability to make an informed decision about their health. This gets much worse if the tone in the positive postings is more exuberant than in the negative postings, and even worse if it appears that postings are being manipulated.</p> <p>This ultimately harms both doctors and patients. By exaggerating expectations about a treatment, patients will be all the more disappointed if even the tiniest thing goes wrong. The real tragedy is that because of a misperception about what might be an excellent new treatment, medical practice is even less likely to change. A few patients may benefit, but until medical practice changes because doctors act on what they read in their journals, the many thousands of needy patients will never receive a perfectly good treatment. Doctors must publish the results of their work in established medical journals where it will be subjected to the scrutiny of their peers. We can help by encouraging them to do so.</p>
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We have contacted the organizers, who have told us that the study is on hold due to the withdrawal of some of the collaborating hospitals in Finland. With his permission, we have contacted some of our medical colleagues in Europe to determine their interest in participating in this important study. We have also offered to assist patient recruitment by posting details of the study on our web site. There are many administrative details to work out, and we will post more information when we have it. If you think you would be interested in traveling to Finland or another European country to participate in the study, please let me know by email: [david.wiseman@adhesions.org](mailto:david.wiseman@adhesions.org).

3.6 Did the withdrawals of Intergel and Adcon affect SprayShield’s approval?

One “reason” why SprayShield’s approval was delayed makes a connection between SprayShield and Intergel:

*“The makers of Sprayshield tried to get the product approved right after some barrier that caused infections and had been approved by FDA had been removed from the market and FDA were making things harder for that to happen again.”*

Whatever the connection, I believe it has nothing to do with FDA. It is true that there was a different product (Intergel), made by one company (Lifecore), and sold by another (J&J) that reached the US market (in 2002) and was withdrawn (in 2003) after reports of tissue reactions, infection, unexplained fever and some deaths. But the circumstances of the Intergel story have no bearing on the approval of other products as evidenced by the approval of Baxter’s ADEPT in 2006 by FDA.

The Intergel story did apparently hamper other companies trying to develop adhesion barriers, but for other reasons. Intergel’s initial effort to obtain approval was rejected after FDA upheld the unfavorable recommendations of its Advisory Panel in January 2000. Cries of “foul” and months of argument resulted in a successful appeal hearing in September 2001 and Intergel was finally approved in 2002.

After the rejection in 2000, questions about FDA’s ability to fairly consider the approval of Intergel (and any other any anti-adhesion product for that matter) circulated within the medical device industry and the investment community that followed it, taking one of four main forms:

- a) Possibly as “spin” on the part of Lifecore, its investors or advisors in an effort to maintain investor confidence in the company;
- b) As part of well founded industry opposition to elements of FDA’s proposed “Guidance Document on Adhesion Barriers” discussed only a month after Intergel’s original rejection (these proposals were later removed after arguments made by an industry group, one of whose representatives was this writer);
- c) As small aftershocks tracing back to about 1991 to FDA’s handling of INTERCEED (approved in 1989) based on what turned out to be untenable extrapolations made by one particular surgeon from studies he had conducted in mice;
- d) As ridiculous and sometimes offensive drivel - one particular gem related to me by a top industry executive was that the panel’s decision had been entirely due to the depression of mood occasioned by the coincident menstrual period of a prominent female member!!

All of this served to obscure the fact that, in the opinion of this writer, the real reasons for the panel’s and FDA’s rejection were:

- a) The company made a poor presentation to the panel. There were parts of the data that showed nicely that Intergel was effective. Instead of focusing on these data, the company presented a more difficult to comprehend metric to which it applied an inappropriate statistical test and which failed to convince the panel of the product’s effectiveness.
- b) The company attempted to change the method of accounting for patients that did not complete the study that they had declared in its agreed-upon protocol with FDA. Knowing that this is generally frowned upon, the company failed to prepare arguments why in this case it was justified in making the switch. These arguments were available, and the company used them to good effect in its 2001 appeal.
- c) Knowing what was contained in the proposed Guidance on Adhesion Barriers, as well as questions that FDA had raised about an issue called “surrogate outcomes” in earlier public hearings relating to the approval other adhesions products, the company again did not come prepared to argue that point.
- d) There was a concern that Intergel may increase the possibility of infection, based on an increased infection rate in humans and an animal study whose data the company failed to analyse properly as pointed out by one of the panels who was concerned that this was the “smoking gun”. This

possibility was later supported by some of the clinical observations that led to Intergel's withdrawal in 2003.

The real reasons obscured, would-be investors were now dissuaded from funding anti-adhesion development in other companies (including Confluent) because of the dismal prospects painted for an FDA approval.

The tremors from Intergel's rejection-appeal-approval in 2002 proved to be only foreshocks of what occurred when Intergel was withdrawn in 2003. Investors as a group (or should I say "herd") had been emboldened in their view of FDA after FDA's public humiliation by Intergel's unprecedented 2001 dispute hearing that led finally to its 2002 approval. Investors would never now appreciate the scientific reasons for Intergel's demise, and when Intergel was withdrawn in 2003, became even more entrenched with their bleak outlook of the adhesions business, once again limiting investment and progress. This was compounded further when another company in the adhesions business, Gliatech, was forced into bankruptcy in 2002 after FDA actions against it connected with Gliatech's guilty plea to Federal charges that included submitting a false or misleading report to FDA and failure to report adverse events.

I have personal knowledge of companies who had difficulty in obtaining venture funding or who have halted development of adhesions products based on this outlook which still exists in some quarters. Resurrecting the charge of FDA's unfair treatment of [*add the name of your favorite barrier here*] serves only to fuel the fire that is killing investment in products for the prevention of adhesions. Ultimately this hurts patients.

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