# Trends-in-Medicine

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# Quick Pulse



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## FDA Panel Recommends Approval of Two New Cosmetic Fillers: Restylane and Hylaform

The FDA's General and Plastic Surgery Devices Panel recommended on November 21, 2003, that the FDA approve two new cosmetic fillers – Medicis/Q-Med's Restylane and Genzyme's Hylaform (to be marketed by Inamed). Both clear gel products were found to be comparable, not superior, to Inamed's Zyplast, which has been considered the gold standard of fillers for many years. Zyplast is composed of highly purified bovine dermal collagen that is dispersed in a phosphate-buffered saline solution containing 0.3% lidocaine, and it is approved for the correction of contour deformities of the dermis. Dermatologists and plastic surgeons have been anxious for a non-bovine fillers like Restylane and Hylaform, though neither contains lidocaine or another pain killer.

### Restylane

Restylane is a clear, transparent, viscous and sterile gel, supplied in a syringe. It consists of non-animal, stabilized, hyaluronic acid (NASHA), which is generated by streptococcus bacteria and suspended in the buffer EDDB.

**The panel voted six to three to recommend approval of Restylane – without skin tests – with four conditions, but the panel did not support the company's request for a superiority label.** The conditions are:

1. A post-marketing study of persons of color as proposed by the sponsor is conducted.
   **(Passed: 6 yes, 1 no, 2 abstentions)**
2. The sponsor educate physicians prior to use of the device.
   **(Passed: 6 yes, 1 no, 2 abstentions)**
3. The superiority language be removed from the label.
   **(Passed: 5 yes, 4 no, 1 abstention. There was initially a tie vote, broken by the vote of the chairperson.)**
4. The label specify: "There is limited clinical study data are available in patients with skin types V and VI on the Fitzpatrick scale and people of color."
   **(Passed: 5 yes, 1 no, 3 abstentions)**

After the voting, panel members discussed the reasons for their vote. A doctor voting in favor of approval of the product said, "There is a need for this product, and it certainly is safer than what is on the market." Another doctor who voted for approval said, "There are loose ends…However, the large world-wide experience is valid to consider." A doctor voting against the product explained, "This is not a great study…There are a lot of loose ends here that cause me concern…When this product moves forward, I think there will be issues...that should be clarified now

…If we don't do it now…it may never get done…I hope my words don't echo three or four years from now and that the manufacturer will do what is promised."

## THE COMPANY PERSPECTIVE

Medicis was able to get new data introduced at the panel meeting that may have helped influence the final decision. During the open public session at the beginning of the meeting, dermatologist Dr. Nicholas Lowe, a professor at UCLA and at University College in London, said it was his paper, published in 2001, that found 0.42% of Restylane patients had delayed nodular reactions. However, he noted that this was with the older formulation of Restylane. He then presented a recently-completed review of 558 of his U.K. patients who got a total of 1,537 injections of the newer formulation of Restylane since 2000. Among these patients, there were zero instances of hypersensitivity or allergic reactions.

Dr. Lowe estimated that 70% of his patients experienced some immediate erythema which was clinically not significant and usually resolved in one to two days. Edema was common with Restylane patients for two to five days, and there were transient lumps in five patients. All reactions, he claimed, were less severe than with Zyplast, its sister product Zyderm, or with Inamed's other collagen fillers, CosmoDerm or Cosmoplast.

The formal case for Restylane was made by a professor of dermatology from the University of Pennsylvania, who reviewed the pivotal trial data on 138 patients. The speaker said, "I agree with (the FDA) reviewer that after six months, there is not enough information to say anything (about efficacy), but up until then Restylane is superior to Zyplast." This investigator admitted there is a significantly greater incidence of events in patient diaries of "severe+bruising," redness, swelling, pain, tenderness and itching in the first 14 days. However, he insisted, "This is not a sign of something going wrong. It is true there are more of these minor reactions in the first few days, but there are…no allergic reactions, no hypersensitivity reactions in either the Zyplast or Restylane group."

**Comparison of Efficacy of Restylane vs. Zyplast**

| Restylane vs. Zyplast | Patients (by physician evaluation) | Patients (by patient evaluation |
|---|---|---|
| Superior to Zyplast | 56.9% | 52.6% |
| Equivalent to Zyplast | 33.6% | 41.6% |
| Inferior to Zyplast | 9.5% | 5.8% |

A plastic surgeon who has worked with Restylane in U.S. trials and who has used it clinically at his other office in Jamaica reviewed a Swedish study from 1995/1996. He insisted reactions are minimal, even with the higher protein level of the older formulation.

An expert from Johns Hopkins discussed the hypersensitivity issue. He made a good case that Restylane is not associated with hypersensitivity reactions. He noted:

- All reported hypersensitivity reactions were local at the injection site only, which "would be unexpected if true hypersensitivity were manifested."
- Almost all reactions required days or weeks to manifest.
- All reactions observed in CTs resolved without treatment.
- >50% of local reactions occurred at some but not all injection sites.
- Observed local reactions were fewer after re-treatment.

Medicis was criticized by several public witnesses – and some panel members – for not studying Restylane in African-American and Asian patients, but a company official pointed out that there is extensive experience in other populations outside the US, and Medicis has committed to doing a 100-patient U.S. post-marketing study in African-Americans. The company also proposed adding the following wording to the label: *Limited controlled clinical study data are available regarding the use of Restylane in patients with skin types V and VI on the Fitzpatrick scale.*

Medicis officials outlined what appears to be a solid training approach. The CEO said, "We have one of the strongest CME commitments in the field…Our largest expenditure is supporting education grant symposiums…We understand there are subtle differences in technique with this…We hired a medical education firm to provide live training in 50 cities to dermatologists and plastic surgeons, using doctors trained outside the U.S. (Canada, etc.) to do that…And we have a video tutorial to educate physicians when they purchase syringes of Restylane."

## THE FDA PERSPECTIVE

The FDA presented a rather negative view of the Restylane data. An FDA reviewer concluded:

- Optimal correction is achievable with both Restylane and control by a mean 1.5 unit SRS increase in a comparable number of sessions.
- Wrinkle SRS assessment that 1 unit is a clinically significant change was ***not*** confirmed on study photos.
- SRS at 6 months was 1 unit higher for Restylane than control in 59.7% of patients, but less than 1 unit higher on average for the overall cohort,

- SRS interpretation at months 9 and 12 post-treatment is limited as most patients were re-treated as six months,

**Questions raised by the FDA included:**

1. Problems with masking occurred.
2. Absolute difference compared to control was small.
3. Optimal cosmesis required 1-3 treatments.
4. Higher bruising, swelling, etc. occurred with Restylane than control. The reviewer pointed out that during the U.S. pivotal study:
   a. "Symptoms of inflammation with 14 days post-treatment were of statistically significantly higher intensity after initial treatment with Restylane compared to control.
   b. Two papule/nodule lesions were reported with onset at more than 40 days post-treatment.
   c. Antibody titers were not evaluated, and symptom profiles were not correlated to immunologic status."
5. Hypersensitivity reactions. The FDA reviewer said, "Hypersensitivity reactions may have been under-estimated as injection reaction and early hypersensitivity symptom profiles overlap, and this may have confounded diagnosis for hypersensitivity reaction to a new product."
6. Evaluations are subjective.
7. Missing data. A missing value was handled according to LOCF (last observation carried forward), and an FDA reviewer said this "is problematic because effects tend to get worse with time."

**FDA Interpretation of Restylane Pivotal Trial Results**

| Time | Number of patients | Restylane | Control | Absolute Difference |
|---|---|---|---|---|
| **SRS Scores by Evaluator Assessment** | | | | |
| Pre-treatment | 138 | 3.29 | 3.31 | 0.02 |
| Baseline | 138 | 1.80 | 1.79 | 0.01 |
| 6 months | 134 | 2.36 | 2.94 | 0.58 |
| **SRS Scores by Patient Assessment** | | | | |
| Pre-treatment | 138 | 3.33 | 3.37 | 0.04 |
| Baseline | 138 | 1.96 | 1.97 | 0.01 |
| 6 months | 134 | 2.44 | 3.01 | 0.57 |
| **Optimal Cosmesis** | | | | |
| Initial treatment alone | 89 Restylane 85 Control | 65.0% | 62.0% | Nss |
| 3 treatments required | 7 Restylane 3 Control | 5.1% | 2.2% | Nss |
| **Patients Re-treated in Open Label Extension** | | | | |
| Re-treated at 6 months | 100 | 72.5% | --- | --- |
| Re-treated at 9 months | 34 | 24.6% | --- | --- |
| Re-treated at 12 months | 7 | 5.0% | --- | --- |

8. With respect to superiority: 43.1% of patients were not superior to control.
9. There were insufficient non-retreated patients.
10. Neither Restylane or control lasted more than six months for 75% of patients.
11. The sample size was small and biased.

## THE PANEL PERSPECTIVE

The FDA posed several questions to the panel members for their discussion before the final Restylane vote. *(The FDA questions are in bold black, and the panel response follows in red.)*

**1. Based on the data in the PMA (pre-market application), please discuss the potential of Restylane to induce hypersensitivity reactions. There is not a likelihood of hypersensitivity reactions.**

**2. 21 CFR 860.7(d)(1) states that there is a reasonable assurance that the device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses, when accompanied by adequate instructions for use and warnings against unsafe use, outweigh any probable risks. Considering the data in the PMA, please comment on whether there is a reasonable assurance that the device is safe. YES**

A panel member said, "The carcinogenicity issue has been (adequately) addressed." Another said, "Every filler that was or will be injected will have its own potential safety issues...When compared to the safety of collagen, this appears to be a much safer product…The hypersensitivity reactions are much less than with Zyderm/Zyplast grouping, even after they've had the one-month hypersensitivity test…so even with nodule concern, it appears to have fulfilled their requirements of safety."

**3. 21 CFR 860.7(e)(1) states that there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will produce clinically significant results.**

**a. Considering the data in the PMA, is there reasonable assurance that the device is effective? YES**

**b. If you believe that there is a reasonable assurance of effectiveness, please comment on whether the data demonstrate that Restylane is superior to the control device (Zyplast) for the proposed intended use. NO**

The chairperson said, "Due to the unmasking failure -- and that this is a subjective rating of the endpoint – the sponsor has not demonstrated superiority to control." Another panel member said, "In the comparative part of the study, there are serious issues…The SRS score is not highly reliable despite the sponsor's claim that it is…And the integrity of the masking is not good. There is masking failure, so you can't assume there is a lack of bias. We just can't do that. And the analysis of the primary outcome is not complete as a result...so I have to answer that my own feeling is that no (it is not superior to control)." A third panel member said, "I agree the device appears to have an effect similar to other injectables, but superiority based on this study has not been demonstrated…To really make a claim of superiority you need something more objective." A fourth panel member said, "I agree with the rest of panel that the sponsor has not demonstrated clear superiority." However, a fifth panel member noted, "They have shown it is safer."

**4. Only two African-American patients were enrolled in the Restylane clinical study (i.e., patient #s 410 and 618). Ten patients listed as "other" were enrolled and the remaining patients were Caucasian.**

**a. If the device is approved, should the sponsor be required to conduct a post-approval study to collect safety data on specific minorities? YES, and should be considered a condition of approval.**

**b. Is specific labeling needed to address potential use in minorities that may be at a higher risk for adverse clinical outcome, e.g., African Americans? MIXED as to how strong the warning should be but the panel agreed there should be some warning.**

**5. Investigators treated 138 nasolabial folds in the study. The sponsor proposes the following indications for use: "Restylane is intended for temporary correction of moderate to severe facial wrinkles and folds, such as nasolabial folds." Please discuss the adequacy of these indications based on the fact that only nasolabial folds were treated in the PMA. MIXED**

Company officials noted that Zyplast doesn't have the word "temporary" in its label and argued that, in fairness, neither should Restylane. A panel member said, "I think it is reasonable to give them comparable language." Another panel member said, "The nature of this filler is a little different and longer-lived, according to some of the reports sent along with the PMA, so I am concerned it would be used in areas where there is not adequate dermal thickness to mask the characteristics of the gel, so I think it certainly temporarily corrects nasolabial folds, but I don't have data on the other sites…I am comfortable with nasolabial fold but not necessarily in the other areas yet -- but I look forward to it."

## HYLAFORM

While the panel spent the morning reviewing Restylane, the afternoon was devoted to a consideration of Hylaform. The two presentations were quite different. Genzyme did a much more professional, organized job than Medicis/Q-Med. In addition, the Genzyme trial, while also small, was much better done, and panel members were impressed that photographs were taken of all patients at all visits. The biggest problem turned out to be a concern by some panel members that the comparator – Zyplast – was not shown in the company's trials to be effective, skewing the interpretation of the efficacy of Hylaform.

After first defeating a motion ***not*** to approve Genzyme's Hylaform, **the panel voted 6 to 3 to recommend approval, based on non-inferiority, with the following six conditions:**

**1. Assessment of hypersensitivity to avian products. (Passed: 4 yes, 5 abstentions)**

The panel left to the FDA the decision about what this will entail. This condition appeared to be mostly the result of concerns by one member who wanted blood or skin tests recommended, if not required. He said, "The directions for use should be limited to those who pass an assessment of avian allergy…I asked for some assessment of avian protein allergy in patients before they are treated, without specifying what that needs to be." Three other panel members went along with the proposal, but they indicated they would be satisfied with a recommendation to doctors to check for avian allergies, stopping short of demanding skin tests. In addition, there were more abstentions than there were votes in favor of this condition, so it is likely the FDA will not ***require*** skin tests but will make some recommendation with respect to avian sensitivity.

**2. Physician education be incorporated as a condition for approval. (Passed: 5 yes, 4 abstentions)**

**3. Require the label to specify:** *"There is limited clinical study data available in patients with skin types V and VI on the Fitzpatrick scale and people of color."* **(Passed: 6 yes, 3 abstentions)**

**4. Require the sponsor to conduct post-approval study of efficacy and safety in persons of color. (Passed: 6 yes, 3 abstentions)**

**5. Require a statement in the label that there is limited controlled clinical data regarding the safety and efficacy of repeated injections. (Passed: 6 yes, 3 abstentions)**

**6. Require a statement in the label that the safety and efficacy of the device for lip augmentation has not been demonstrated. (Passed: 6 yes, 3 abstentions)** The panel member who proposed this condition explained, "Many of my patients want augmentation of the lips…It's one of the most frequently requested areas of augmentation…And there is nothing to indicate this is effective for lips…I would like to see in the guidelines that it has not been officially tested for safety or efficacy for lip augmentation."

**Panel members discussed the reasons for their votes.**

*In favor of approval:*

- "The sponsor did an excellent job designing a study to try to objectively measure an aesthetic outcome, which is very difficult to do – with photographs, digitizing, and morphing. That was very creative, and I appreciate their rigorousness…If you suggest Zyplast is not efficacious, you raise questions about all tissue fillers…The study, as designed, is unique and maybe didn't capture the effect of Zyplast…but it demonstrated the comparability of Zyplast and Hylaform."
- "My vote reflects my frustration with the process. This was a well-done study...but coming away from it and trying to be scientific, you don't get the bang for the buck you probably want. I think it probably is safe, but my cry is for a better way to do these things (filler trials)."
- "I feel comfortable with the panel decision on safety…I do have reservations about efficacy, but the weight of the evidence and the conditions we imposed reassure me that we met our mandate."
- "On efficacy, I cannot discount my own personal experience with Zyplast. I recognize that there is a definite improvement that is efficacy with Zyplast...and because this product has at least comparable efficacy, I felt comfortable with that part of my decision…On safety, there is no question it is as safe or safer than Zyplast short-term…I am not as concerned about long-term safety as other panel members because I am comforted by the worldwide data."

***Against approval:***

- "The sponsor did an excellent job of presentation...but I was terribly confused by the data."
- "It is all about the data…What we are doing here today is stunning to me…We are saying the sponsor, just because they do a good study -- even if it doesn't show efficacy – gets approval. That is not the way I understand the panel's job, and I'm surprised."

Genzyme was not seeking a superiority label for Hylaform, only non-inferiority to Zyplast – the same comparator Restylane used. The panel did not appear to have much trouble with the non-inferiority claim. The problem was that several panel members were not convinced that Zyplast was shown to have any efficacy. *(See FDA Question #2 on page 6.)* The panel member most opposed to Restylane approval commented early in the session, "I'm convinced you showed non-inferiority to Zyplast, but I'm not sure Zyplast is effective…You are not superior."

## THE FDA PERSPECTIVE

The FDA had very few problems with the Genzyme data on Hylaform. A reviewer said the company successfully passed preclinical tests for:

- Irritation
- Sensitization and immunogenicity
- Cytotoxicity
- acute systemic toxicity
- hemocompatability
- mutagenicity
- subchronic toxicity

The FDA statistician praised the design of the pivotal study design, saying:

- This was a strong study design.
- The randomization and masking (were) effective.
- Accountability was good – 255 of 261 patients completed the initial phase.
- It was not a true intent-to-treat analysis, but it was close.
- There is no reason to suspect any bias was introduced by the excluded patients
- There was no missing data
- Hylaform met the non-inferiority criteria (of <.5 inferior with -0.38) – on both ITT and per-protocol basis)
- The superiority criteria was not met.
  - The 1 point improvement in both folds at two weeks was 9.5% for Zyplast and 4.1% for Hylaform, though that was not statistically significant.
  - The investigator live severity scores were very close between the two products and not statistically significantly different
  - The results at two, four and eight weeks showed the same consistent pattern as any of the 12 week endpoints.

The pivotal study was designed as both a non-inferiority and a superiority study, with separate criteria for each. A special six-point "Genzyme grading scale" was created and validated

**Analysis of Trial Masking**

| Patients believed they got: | Hylaform Group | Zyplast Group |
|---|---|---|
| Hylaform | 27.1% | 19.2% |
| Zyplast | 13.5% | 24.2% |
| Didn't know | 57.1% | 53.9% |

for this study, utilizing photographs. FDA reviewers concluded that the trial was well-masked.

On safety, an FDA official said, "Adverse events were similar in both groups. Improvement in wrinkle severity at 12 weeks was comparable." FDA reviewers concluded:

- Most adverse events were mild.
- The study was not powered to detect subtle differences between treatments.

Some panel members wondered about the safety of the formaldehyde in Hylaform, but the FDA's toxicology expert said there is no concern with the formaldehyde in the product. He said, "It contains <2.3 ppm in a 1 cc injection, so it would add a negative amount of formaldehyde…Formaldehyde in the body would seep into the product rather than the other way around...so formaldehyde is not an issue."

The FDA was concerned about:

1. The preponderance of women in the trial (94%)
2. The lack of ethnic groups (80% Caucasian)
3. Duration of effect

Patients were entered into the pivotal study based on a "live" wrinkle score of 3 or 4, but the analysis was based on the IPR blinded assessments, which showed more variability. Of the 261 patients randomized and treated, 255 completed the 12 weeks of the initial study phase (130/133 Hylaform and 125/128 Zyplast). Three patients in each treatment group withdrew from the study. The primary efficacy and all safety analyses were done on the ITT population.

**Pivotal trial of Hylaform**

| Measurement | Hylaform n=115 | Zyplast n=109 | Confidence interval |
|---|---|---|---|
| ***Primary endpoint:*** Mean of the median IPR scores at 12 weeks by ITT | 2.3 | 2.2 | -0.38 * |
| % of patients experiencing ≥1 point improvement in both nasolabial folds at 12 weeks | 4.1% | 9.5% | Nss |
| **% of Folds Returned to Baseline** | | | |
| 2 Weeks | 38.2% | 21.9% | --- |
| 4 Weeks | 56.1% | 26.3% | --- |
| 8 Weeks | 68.9% | 46.7% | --- |
| 12 Weeks | 73.3% | 65.1% | --- |
| **Folds Rated <3 at Baseline by IPR Assessment**** | | | |
| With rounding | 57.4% | 49.2% | --- |
| Without rounding | 73.4% | 67.0% | --- |

*** Satisfied criteria for non-inferiority.**

****All folds rated at least a 3 on the "live" assessment for study entry**

## THE PANEL PERSPECTIVE

The FDA posed several questions to the panel members for their discussion before the final vote. *(The FDA questions are in bold black, and the panel response follows in red.)*

**1. 21 CFR 860.7(d)(1) states that there is a reasonable assurance that the device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses, when accompanied by adequate instructions for use and warnings against unsafe use, outweigh any probable risks. Considering the data in the PMA, please comment on whether there is a reasonable assurance that the device is safe. Please comment on whether there is a reasonable assurance that the device is safe. (Safe, but mixed opinions about whether there should be skin testing suggested or required for avian protein sensitivity)**

A panel member who was pushing for skin/blood testing for avian products said, "A skin test for avian sensitivity should be a requirement here…Do we want to leave it to primary care doctors to assess this or require a test that allergists use?" Another doctor said, "There doesn't seem to be any significant immune response...but it is a select population, selected to exclude those with a history of reacting to foreign proteins...so this raises questions in my mind…(but) This is similar to (company's) arthritis product (Synvisc)." A third panel member said, "The full battery of protocols required by the agency (FDA) were carried out, and no toxicity alerts occurred that raise serious concerns about safety."

**2. 21 CFR 860.7(e)(1) states that there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will produce clinically significant results. Considering the data in the PMA, is there reasonable assurance that the device is effective? (Divided panel. In terms of the data presented, there is a question about the efficacy of the control. The sponsor has shown no difference between the two, so some members of the panel feel very strongly the data has not shown efficacy for the control, and by extension Hylaform. However, panel members feel experience has shown, if not the data, that Zyplast is effective.)**

A panel member said, "Touchup appears not to be effective from baseline…and there is no data to assess efficacy in African-Americans." Another member said, "It has shown non-inferiority to Zyplast, but Zyplast has not been shown to be effective in this study, based on the data shown to us here…unless there is some reason to believe Zyplast is effective, then the sponsor has shown non-inferiority to something that is not effective, and therefore this product is not effective." Another panel member said, "I agree that is logically correct, but I'm not sure how to factor in years of experience of using Zyplast to correct these problems, with an effectiveness to warrant its continued use, even if it was not demonstrated in as rigorous a fashion as we would like. I came into this (meeting) assuming Zyplast is effective because of experience with it over many years…To question the

validity of Zyplast is a sudden question to raise that I am having trouble with…But, on the data, you are correct." A third panel member said, "I cannot fault the statistical analysis of the data…However…having used the products (Zyplast and Zyderm), there is efficacy associated with them." The industry representative on the panel added, "The sponsor has worked with the FDA to determine what is an appropriate control, and the sponsor was told Zyplast is an appropriate control...The sponsor followed FDA directions on control...so I think we need to take that into consideration."

**3. Only three African-American patients were enrolled in the Hylaform clinical study. There were 16 Hispanic, 5 Asian and 5 "Others".**

a. **If the device is approved, should the sponsor be required to conduct a post-approval study to collect safety data on specific minorities? YES**

b. **Is specific labeling needed to address potential use in minorities that may be at a higher risk for adverse clinical outcome, e.g., African Americans? YES**

**Panel members agreed there were the same concerns over this issue as with Restylane, and they recommended a parallel approach.**

**4. The sponsor proposes the following indications for use: "Hylaform is intended for the correction of soft tissue contour deficiencies, such as wrinkles and acne scars." Please discuss the adequacy of these indications based on the fact that only nasolabial folds were treated in the PMA. The panel recommended using the terminology "soft tissue effects" instead of "acne scars."**

**5. As shown by Genzyme, the duration of effect of this device is short, and multiple maintenance doses will be needed to maintain the desired cosmetic effects. To assess safety of these repeated doses the sponsor has provided serum hylan B IgG levels for the repeat study population. Clinically, no significant changes in adverse events were noted in this group. Does this data support the safety of the device for repeated use, or do you believe that a post-approval study is needed to address this issue? The panel felt there are limited 12-week studies on immunologic reactions, and post-approval studies should be considered to address this issue.**

♦