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On Behalf of the National Center for Health Research
Before the FDA Advisory Panel Convening to Discuss Dermal Fillers
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Thank you for the opportunity to provide this written statement regarding strategies to improve the safety of dermal fillers and ensure that patients are making informed decisions. I am Dr. Diana Zuckerman, president of the National Center for Health Research, a nonprofit think tank that scrutinizes the safety and effectiveness of medical products. We don't accept funding from drug or medical device companies or any companies that make products that we evaluate.

Improving Safety Information

We agree with the statement in FDA's Executive Summary that enrollment in premarket clinical studies has been too small to identify less common adverse events, such as vision loss or stroke. However, as thousands of serious adverse events have been reported through the FDA's passive reporting system, it is clear that better data are needed to determine how frequently these serious events occur and whether there are certain patient, provider, or procedure variables that increase the risks. **FDA should require larger studies, and should not lower approval standards when a new indication is being considered for a previously approved product**, because we now know that new indications can create different risks.

In addition, the size of the studies is not the only reason why real world evidence differs from the safety profiles reported in the clinical trials. These products are being used by many different types of patients, and so they need to be tested on those diverse patient populations. And what about the healthcare professionals involved? When companies seek approval, their clinical trials will be based on data from the best trained clinicians the company can recruit. Our Center has learned that unfortunately, these procedures are being performed by healthcare providers who are not well trained. And, on YouTube there are videos on how a patient can inject themselves.

Whether in pre-market or post-market studies, the FDA should determine the risks when these procedures are performed by different types of healthcare professionals, and also determine if special training should be required to reduce those risks for certain products or procedures. The FDA has the authority to require the companies to limit access to their products to those who are best trained to safely use the product. This won't be 100% effective and preventing unskilled practitioners from using the products, but it puts pressure on healthcare professionals who consider ignoring those requirements.

Informed Patient Decision-Making Undermined By Online Information

If you wonder why patients say they were not informed of the risks, just go to google or another search engine and type in the name of one of these products with the term "risks". You will be bombarded with ads and other promotional information, and you will see how difficult it is to find any meaningful risk information. Going directly to a company's website for a specific product is not necessarily helpful. Let me give one example: Juvederm. Go to Juvederm.com and you will find very attractive, colorful promotional information that encourages people to use

the product. The more attractive parts of the website do not include risk information, but if you are persistent you will finally find the following "Important Safety Information" which I have quoted directly here:

"IMPORTANT SAFETY INFORMATION

Are there any reasons why I should not receive any JUVÉDERM® formulation?
Do not use these products if you have a history of multiple severe allergies or severe allergic reactions (anaphylaxis), or if you are allergic to lidocaine or the Gram-positive bacterial proteins used in these products.

What precautions should my doctor advise me about?

- Minimize strenuous exercise and exposure to extensive sun or heat within the first 24 hours following treatment. Exposure to any of these may cause temporary redness, swelling, and/or itching at the injection site
- Tell your doctor if you are pregnant or breastfeeding. The safety of these products for use during pregnancy or while breastfeeding has not been studied
- The safety of JUVÉDERM® VOLUMA™ XC has not been studied in patients under 35 years or over 65 years for cheek augmentation, or under 22 years and over 80 years for chin augmentation. The safety of JUVÉDERM® VOLLURE™ XC and JUVÉDERM® VOLBELLA™ XC has not been studied in patients under 22 years, and the safety of JUVÉDERM® XC and JUVÉDERM® Ultra XC has not been studied in patients under 18 years
- The safety and effectiveness of JUVÉDERM VOLUMA® XC in areas other than the cheek area, JUVÉDERM® XC and JUVÉDERM VOLLURE™ XC for areas other than facial wrinkles and folds, and JUVÉDERM® Ultra XC and JUVÉDERM VOLBELLA® XC in areas other than the lips and perioral area have not been established in clinical studies
- JUVÉDERM® VOLUMA™ XC is intended for use in the chin and cheek areas. JUVÉDERM® VOLLURE™ XC and JUVÉDERM® XC are intended for use in facial wrinkles and folds. JUVÉDERM® VOLBELLA™ XC and JUVÉDERM® Ultra XC are intended for use in the lips and perioral area. The safety and effectiveness for treatment in other areas have not been established in clinical studies
- Tell your doctor if you have a history of excessive scarring (thick, hard scars) or pigmentation disorders. The safety of JUVÉDERM® products has not been studied in these patients and may result in additional scars or changes in pigmentation
- Tell your doctor if you are on therapy used to decrease the body's immune response (immunosuppressive therapy). Use may result in an increased risk of infection
- Tell your doctor before treatment if you are using substances that can prolong bleeding, such as aspirin, ibuprofen, or other blood thinners. As with any injection, this may result in increased bruising or bleeding at the injection site
- Patients who experience skin injury near the site of injection may be at a higher risk for adverse events
- JUVÉDERM® VOLUMA™ XC was not studied in patients with significant loose skin of the chin, neck, or jaw
- The effect of JUVÉDERM® VOLUMA™ XC injection into the chin on facial hair growth has not been studied

Information about allergies is important, but how many patients know that they are allergic to "gram-positive bacterial proteins"? And while the lengthy list of precautions has some useful

information for a small percentage of patients, most will probably stop reading midway through that list. It is only if they keep reading that they will get to the section entitled "possible side effects." That heading isn't much of a warning, and the patient would need to get to the 3rd paragraph to find out that blindness and stroke are possible side effects. Even then, those risks are not made especially noticeable, and are given the same attention as "temporary scabs." The exact wording from the website is as follows:

> **"What are possible side effects?**
> The most commonly reported side effects with JUVÉDERM® injectable gels included redness, swelling, pain, tenderness, firmness, lumps/bumps, bruising, discoloration, and itching. For JUVÉDERM® VOLBELLA™ XC, dryness was also reported. For JUVÉDERM® VOLUMA™ XC, most side effects resolved within 2 to 4 weeks. For JUVÉDERM® VOLLURE™ XC, JUVÉDERM® XC, and JUVÉDERM® Ultra XC injectable gels, most resolved within 14 days or less. For JUVÉDERM® VOLBELLA™ XC, most resolved within 30 days or less. These side effects are consistent with other facial injection procedures.
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> Most side effects will resolve with time. Your doctor may choose to treat side effects persisting over 30 days with antibiotics, steroids, or hyaluronidase (an enzyme that breaks down hyaluronic acid).
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> One of the risks with these products is unintentional injection into a blood vessel. The chances of this happening are very small, but if it does happen, the complications can be serious and may be permanent. These complications, which have been reported for facial injections, can include vision abnormalities, blindness, stroke, temporary scabs, or permanent scarring of the skin.
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> As with all skin injection procedures, there is a risk of infection."

FDA clearly needs to do more to ensure that companies provide risk information in a more prominent position, rather than inserted after much less important "safety" information. **A black box warning is needed, should be prominently displayed, and should include warnings about off-label uses as well as approved indications and well-trained providers. FDA should also warn against self-injections in the strongest possible terms.**

Patient Informed Consent Checklists

In addition to a boxed warning, FDA has a mechanism to improve patient information about risks: **Patient Informed Consent Checklists**. Such a Checklist was developed for Essure permanent contraception and FDA has a Guidance for a Checklist for breast implants. These checklists focus on the risks, since ads and widely available promotional materials already inform the patients about the benefits. In the case of dermal fillers, the checklist should be quite short, with separate sections for approved indications, off-label indications, and warnings regarding the importance that health professionals be well-trained in these procedures. As has been required for other Patient Checklists, the patients would be required to initial each warning, and the physician is required to sign it as well. It is essential that these checklists be read and signed at the time of the initial consultation, not at the time that the procedure is performed.