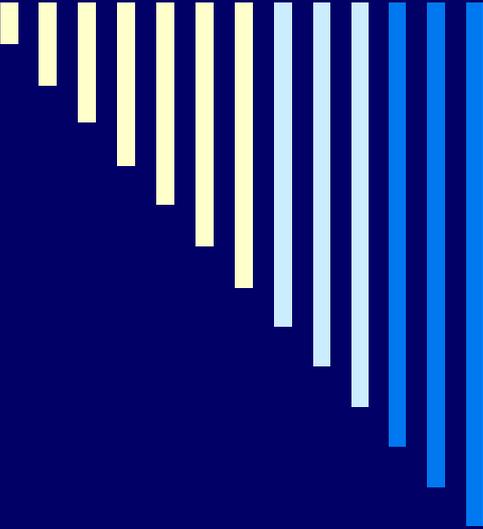


Adverse Event Reports Associated with Injection of Restylane for Lip Augmentation

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Outline

1. Methodology

2. Limitations of data analysis

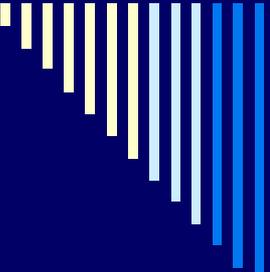
3. Findings

- Overall data (119 reports)

- Lips + other sites (22 reports)

- Lips as single site (15 reports)

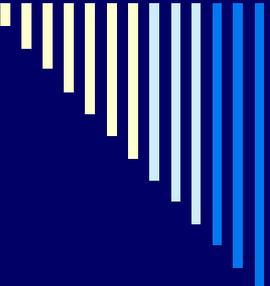
3. Conclusions



Methodology

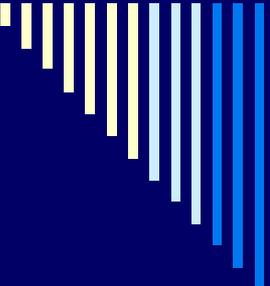
➤ MAUDE Search Criteria:

- Variations of brand names for “Restylane”.
 - Generated 119 reports since first marketed.
 - Sorted the reports indicating injection into the “lips”, “upper/lower lip”, and “vermillion border”.
 - 37 reports injection to lips (31%).
 - ❖ 15 reports: Lips (single site).
 - ❖ 22 reports: Lips (multiple sites).
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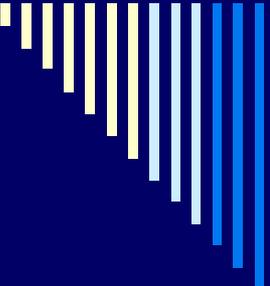
Limitations of Data Analysis for Lip Augmentation Reports

- ❑ Ambiguous terms used to describe the adverse events, i.e. lumps & bumps, lesion, mass, etc.
 - ❑ Direct association of the adverse events with the injection of the product is not always identified.
 - ❑ Unknown pre-injection local anesthetic used in some reports.
 - ❑ Injection of other products; at the same time or in the past.
 - ❑ Multiple sites of injection besides injection in the lips.
 - ❑ Relationship between patients' past history of Restylane injections to adverse events cannot always be identified.
-



Findings: Overall data- All Reports (n=119)

- Reports' source: 103 manufacturer & 16 voluntary reporters.
 - “Type of Events”- after individual report review:
 - No death, 117 Injury, 2 “Other”.
 - Country: US 109, UNK 10.
 - Age: Range 28-73 yrs. (99 reports), UNK (20 reports)
 - Gender: 110 Female, 8 Male & 1 UNK
 - *Only 1 male in the lip augmentation group
-

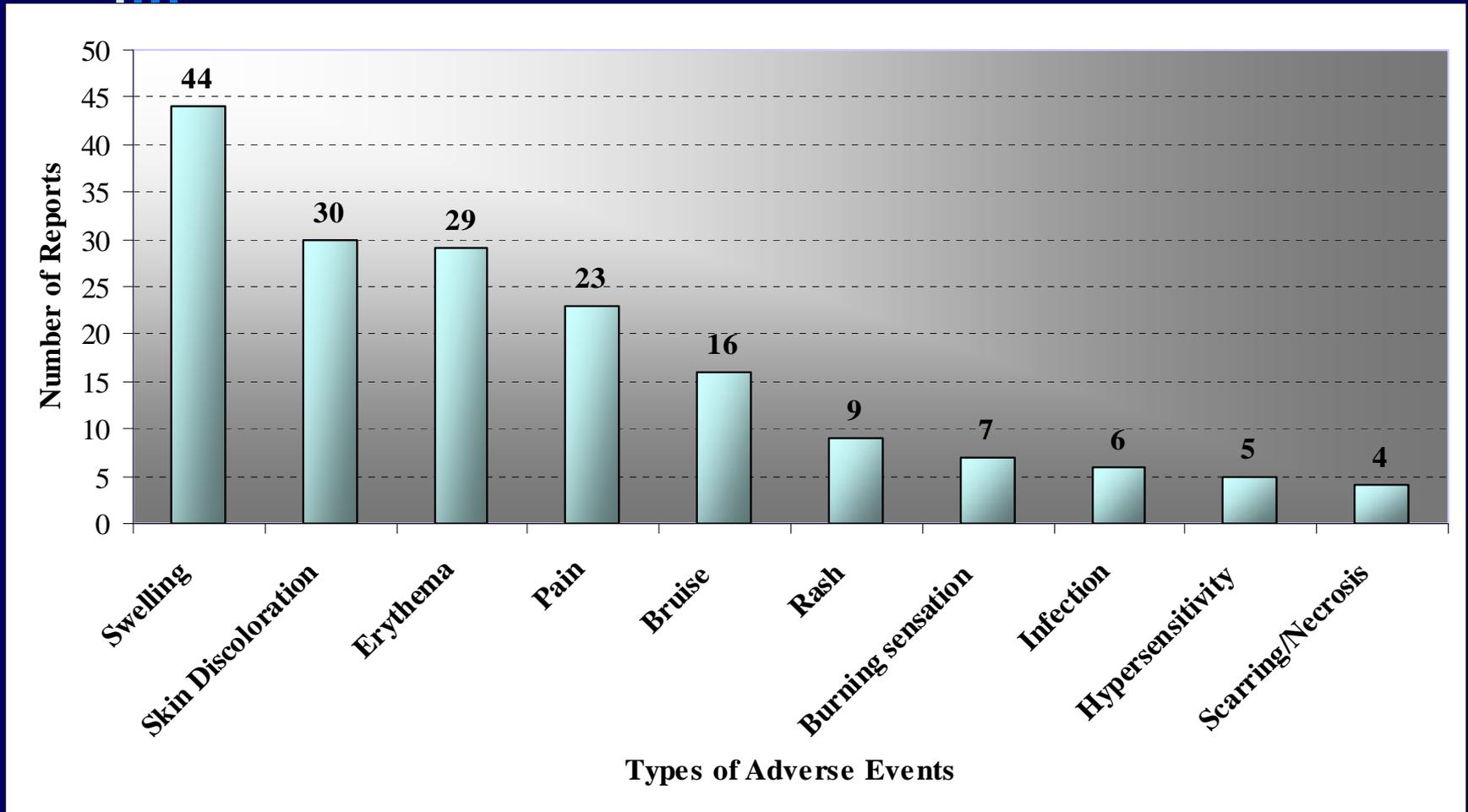


Overall Data: Table 1-Number of Reports by the Year Reports received (n=119)

| Year Report Received | Q-Med's MDRs | Medicis MDRs | Total # of MDRs |
|-------------------------|-----------------|-----------------|-----------------|
| 2003 | 1 | 0 | 1 |
| 2004 | 2 | 3 | 5 |
| 2005 | 23 | 1 | 24 |
| 2006 | 11 | 5 | 16 |
| 2007 | 23 | 0 | 23 |
| 2008 | 23 | 2 | 25 |
| 2009 | 1 | 20 | 21 |
| 2010 | 0 | 2 | 2 |
| 2011 | 0 | 0 | 0 |
| TOTAL | 84 | 33 | *117 |

*2 reports were missing MFR's name

Overall Data: Figure 1. Top 10 Adverse Events (n=119)



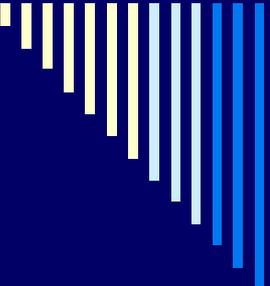
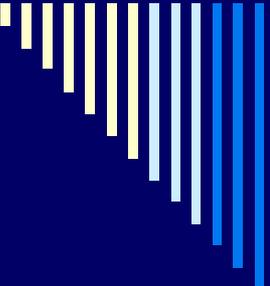


Table 2: Number of Reports by the Reported Sites of Injections in the Lip Augmentation Reports (n= 37)

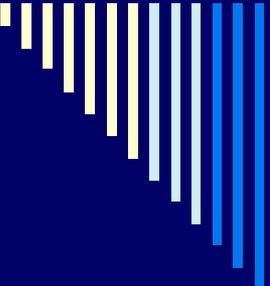
| Sites of Injections | # of MDRs |
|---------------------------------------------------------|-----------|
| Lips. lower lip, upper lip, vermillion border | 15 |
| Lips, upper or lower lip and nasolabial fold | 7 |
| Lips and other unknown sites of the face | 7 |
| Vermillion border and nasolabial fold | 4 |
| Vermillion border, nasolabial fold & lower or upper lip | 2 |
| Vermillion border, nasolabial fold, lips & smoker line | 1 |
| Vermillion border and Botox | 1 |



List of Adverse Events: Reports of Lips & Other Sites of Injection (n= 22)

| | |
|-------------------------------------------------------------------|---|
| ■ Swelling..... | 9 |
| ■ Skin discoloration..... | 5 |
| ■ Bruise..... | 4 |
| ■ Allergic reaction/hypersensitivity & anaphylactic shock..... | 4 |
| ■ Vascular accidents and necrosis..... | 4 |
| ■ Hyperpigmentation..... | 4 |
| ■ Erythema..... | 3 |

Cont'd next slide



Cont'd: Adverse Events in the Lips & Other Sites' Reports (n= 22)

- Lumps & bumps.....3
 - Herpes break out (+ 1 possible).....3
 - Broken capillaries.....2
 - Infection.....1
 - Angioedema.....1
 - Delayed hypersensitivity.....1
 - Desquamation, peeling.....1
 - Numbness.....1
 - Hypertrophic scar tissue.....1
-

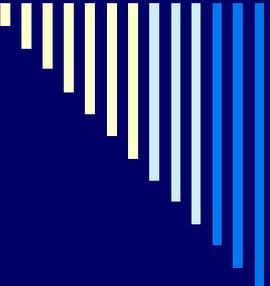


Table 3. Adverse Events in Lips; Single Site Injections (n=15)

| Adverse Events | Immediate (first 24 hrs.) | Delayed (after 24 Hrs.) | Total |
|--------------------|------------------------------|----------------------------|-------|
| Swelling | 3 | 4 | 7 |
| Lumps & bumps | 0 | 5 | 5 |
| Skin discoloration | 0 | 4 | 4 |
| Erythema | 0 | 2 | 2 |
| Allergic reaction | 2 | 1 | 3 |

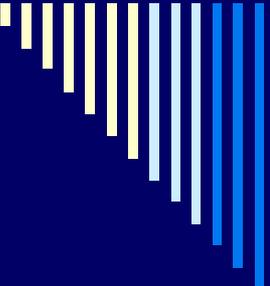
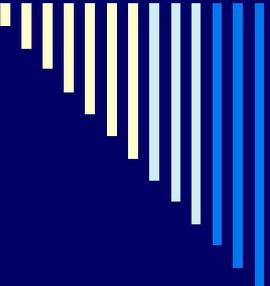


Table 3 Cont'd. Adverse Events in Lips; Single Site Injections (n=15)

| Adverse Events | Immediate (first 24 hrs.) | Delayed (after 24 Hrs.) | Total |
|----------------------------------|------------------------------|----------------------------|-------|
| Angioedema, severe | 1 | 0 | 1 |
| Infection & Abscess | 1 | 1 | 2 |
| Vas. accident & necrosis | 1 | 0 | 1 |
| Broken capillary & granulomas | 0 | 1 | 1 |
| Desquamation | 0 | 1 | 1 |



Treatment of Adverse Events

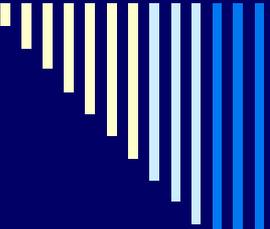
□ Treatment with medication

- Steroids: Topical, oral, & intra-lesion injections
- Oral & IV antibiotics
- Antihistamines

□ Surgical treatment

- combination therapy
- I & D of abscess
- Excision of lesion & biopsy

□ Hospitalization & ER admission



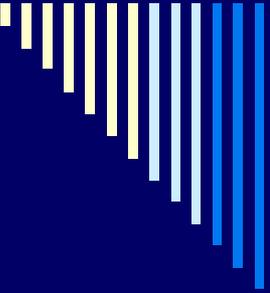
Conclusion

□ Adverse events not reported in clinical study:

- Severe allergic reaction, hypersensitivity, and anaphylaxis
- Severe swelling
- Skin discoloration
- Infection and abscess
- Vascular accident, necrosis & scarring
- Severe angioedema

□ Off label use of the device

- Product was used in sites other than indicated such as molar region, glabella, lips & marionette line
-



Conclusion; cont'd

- True incident of adverse events in US cannot be identified due to small number of reports, and low quality of reports.
 - Voluntary reporting of adverse events to FDA such as filling out a MedWatch form by the health care professionals becomes crucial in having a stronger set of data.
 - Should FDA decide to approve this product for lip augmentation, the presented MDRs' data here hopefully will assist the panel members to:
 - Determine the premarket assessment of approvability, and
 - The appropriateness of the post approval studies.
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