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See the Signal: A Practical Framework for Cosmetic Adverse Event Investigation

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TODAY'S AGENDA:

01 MoCRA

02 Documenting Adverse Events

03 Post-Market Surveillance

04 Investigating Adverse Events

05 Identifying and Evaluating Emerging Safety Signals

06 Using PMS Data for Decision Making

07 Case Example

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MoCRA

Modernization of Cosmetics Regulation Act of 2022 (MoCRA)

Facility Registration

Product Listing

Safety Substantiation

GMP Standards

Mandatory Adverse Event Reporting

- Serious adverse events must be reported to FDA within 15 business days
- Must maintain records of ALL adverse events for 6 years (3 years for a small business)

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Documenting Adverse Events

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Intake Channels

Direct consumer contact

Phone lines

Email

Web forms

Postal mail

Social media

Retailer complaints

Adverse Event Reporting

Mandatory elements for reporting

1. an identifiable patient
2. an identifiable reporter
3. a suspect product
4. a serious adverse experience suspected to be due to a product that has been used

Adverse Event Data Important Elements

Patient

- Age
- Gender
- Weight
- Medical conditions
- Concomitant medications
- Concomitant products
- Allergies

Product

- Lot number
- Expiration date
- Product use start and stop dates
- Dosing
- Route of use

Adverse Event

- Narrative
- Start and end dates
- Diagnosis
- Treatments
- Diagnostic testing/lab results
- Management site
- Consumer and/or provider attribution to product use
- MedDRA Term
- Outcome

Challenges with Obtaining AE Data From Reporters

- Email reports typically have limited information
- Unsuccessful follow-up
- Emotional and upset consumers decline to provide information
- Lack of health literacy can lead to misunderstanding and miscommunicating provider diagnosis or lab results
- Vast majority of reporters are non-healthcare consumers

Adverse Event Reporting

- Serious adverse events must be reported to the FDA within **15 business days**
  - A copy of the label must be included
- If medical or other information regarding the AE is received within 1 year of the initial report, it must be submitted to the FDA within 15 business days

The report can be submitted via:

- Electronic Submissions Gateway (ESG)
- Safety Reporting Portal (SRP)
- MedWatch Form 3500A
  - Email
  - Mail

Serious Adverse Event Criteria under MoCRA

An AE that results in:

- Death
- A life-threatening experience
- Inpatient hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An infection
- Significant disfigurement (including serious and persistent rashes, second- or third-degree burns, significant hair loss, or persistent or significant alteration of appearance), other than as intended under conditions of use that are customary or usual

/ An AE that requires, based on **reasonable medical judgment**, a medical or surgical intervention to prevent an outcome described above

Differences in Serious Adverse Event Criteria

Dietary Supplements

- Death
- A life-threatening experience
- Inpatient hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above

Cosmetics

The criteria for dietary supplements, **PLUS:**

- An infection
- Significant disfigurement (including serious and persistent rashes, second- or third-degree burns, significant hair loss, or persistent or significant alteration of appearance), other than as intended under conditions of use that are customary or usual

Challenges with Assessing Cosmetic AEs

- **Non-specific criteria**
  - What type of infection?
  - How long is a persistent rash?
  - What defines “significant” hair loss?
  - What defines “significant” alteration in appearance?
- Limited details from consumer and unable to follow-up
- Cosmetic SAEs are defined differently from other FDA regulated products

Challenges with Cosmetic SAE Reporting

- **Reporting SAE ≠ Causality**
- Client fear that reporting will tarnish reputation
- Disagreements in seriousness
- Lack of understanding or awareness regarding mandatory reporting and its importance

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Post-Market Surveillance

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POST-MARKET SURVEILLANCE

The Critical Distinction

Mandatory Reporting vs. Post-Market Surveillance

COMPLIANCE

Mandatory AE Reporting

Regulatory compliance requirement for adverse event documentation and submission

INTELLIGENCE

Post-Market Surveillance

Strategic safety intelligence: analyzing patterns, detecting signals, and informing action

POST-MARKET SURVEILLANCE

The Compliance Paradox

When Reporting Isn’t Enough

“What’s the issue? I reported all those AE allegations of my product causing serious adverse events, and we even submitted them early!”

The reality: Timely reporting does not equal safety assurance.

POST-MARKET SURVEILLANCE

Three Critical Questions for Manufacturers

The Foundation of Post-Market Intelligence

01

Do you know your expected incidence rates?

Are there significant deviations?

02

Is it a true safety signal?

Are the symptoms highly correlated to the product?

Could this be background noise?

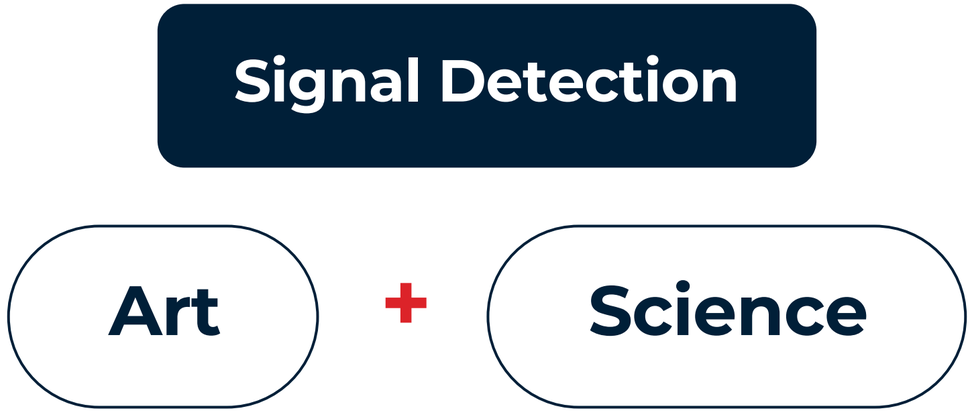
03

How severe are the AEs?

Is this acceptable risk?

Post-Market Surveillance

The Art and Science of Signal Detection



Combining clinical judgement with rigorous analytical methods to distinguish true safety signals from statistical artifacts.

Critical Principles

Foundation of Effective Post-Market Surveillance

“Not all adverse event reports are created equal”

&

“Not all adverse event reports are background noise”

The key to effective PMS lies in distinguishing signal from noise

Through systematic evaluation and clinical expertise

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Investigating Adverse Events

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Normalize Incident Rates

1 Define expected AEs

From toxicologic profile & product design

2 Characterize the AE profile

Collect data, calculate incident rates

3 Normalize incident rates

Compare periods, set acceptable ranges

Unexpected AEs

Require further investigation

Assessing Case Severity

1 Asymptomatic
No observable or reported symptoms

2 Minor
Mild and self-limiting

3 Moderate
Symptomatic; may require intervention or medical care

4 Major
Significant impairment; hospitalization or invasive treatment

5 Death
Adverse event outcome resulted in death

Correlation Scoring System

Published Framework: Regulatory Toxicology and Pharmacology (2021)

Peer-reviewed methodology for systematic adverse event evaluation in consumer products

01

Temporality

02

Plausibility

03

Alternative Causes

04

De-challenge

05

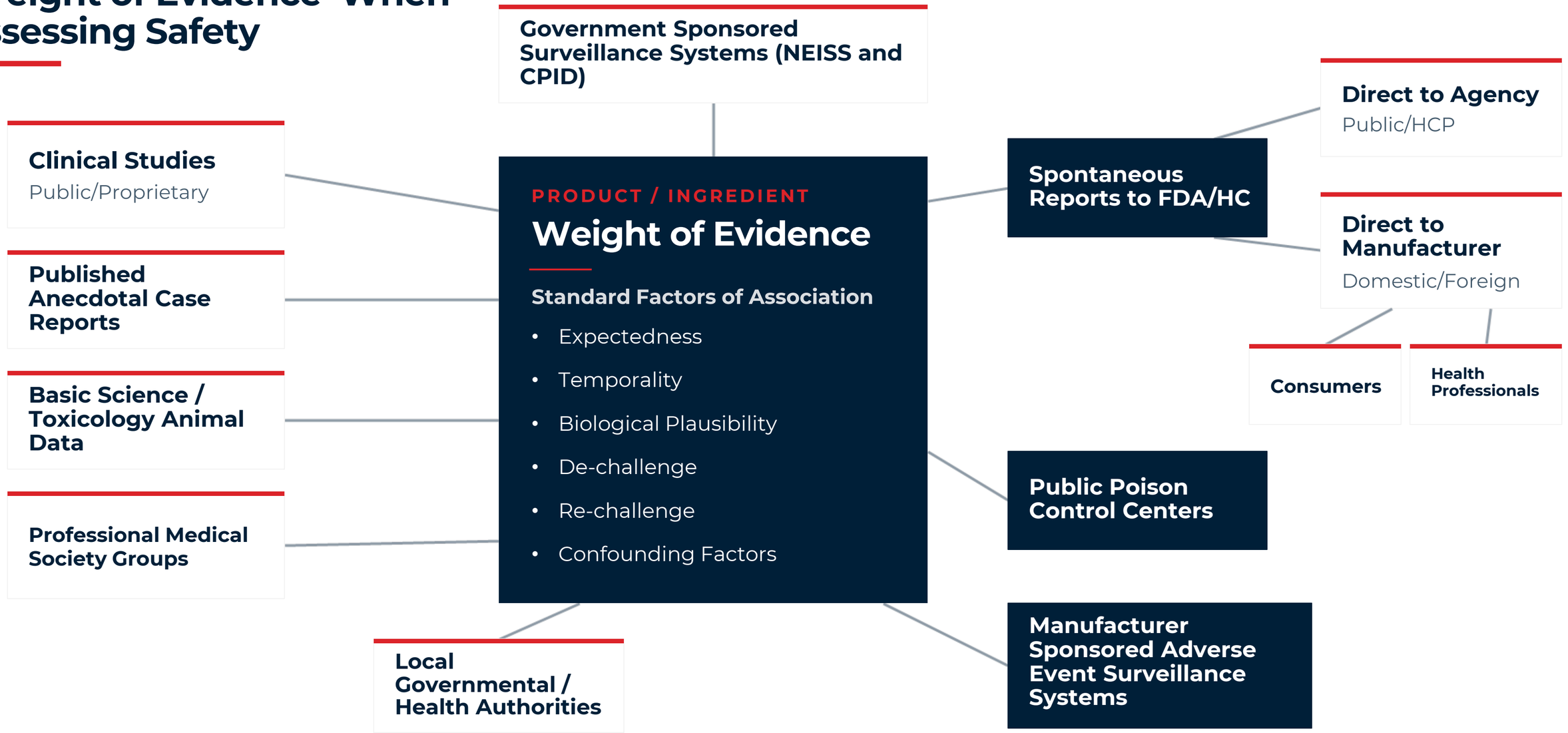
Re-challenge

06

Medical Opinion

Kingston R, Sioris K, Gualtieri J, Brutlag A, Droege W, Osimitz TG. Post-market surveillance of consumer products: Framework for adverse event management. Regul Toxicol Pharmacol. 2021 Nov;126:105028. doi: 10.1016/j.yrtph.2021.105028. Epub 2021 Sep 3. PMID: 34481892.

‘Weight of Evidence’ When Assessing Safety



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Identifying and Evaluating Emerging Safety Signals

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Trending Your Data

Adverse event profile over time

Trend across periods

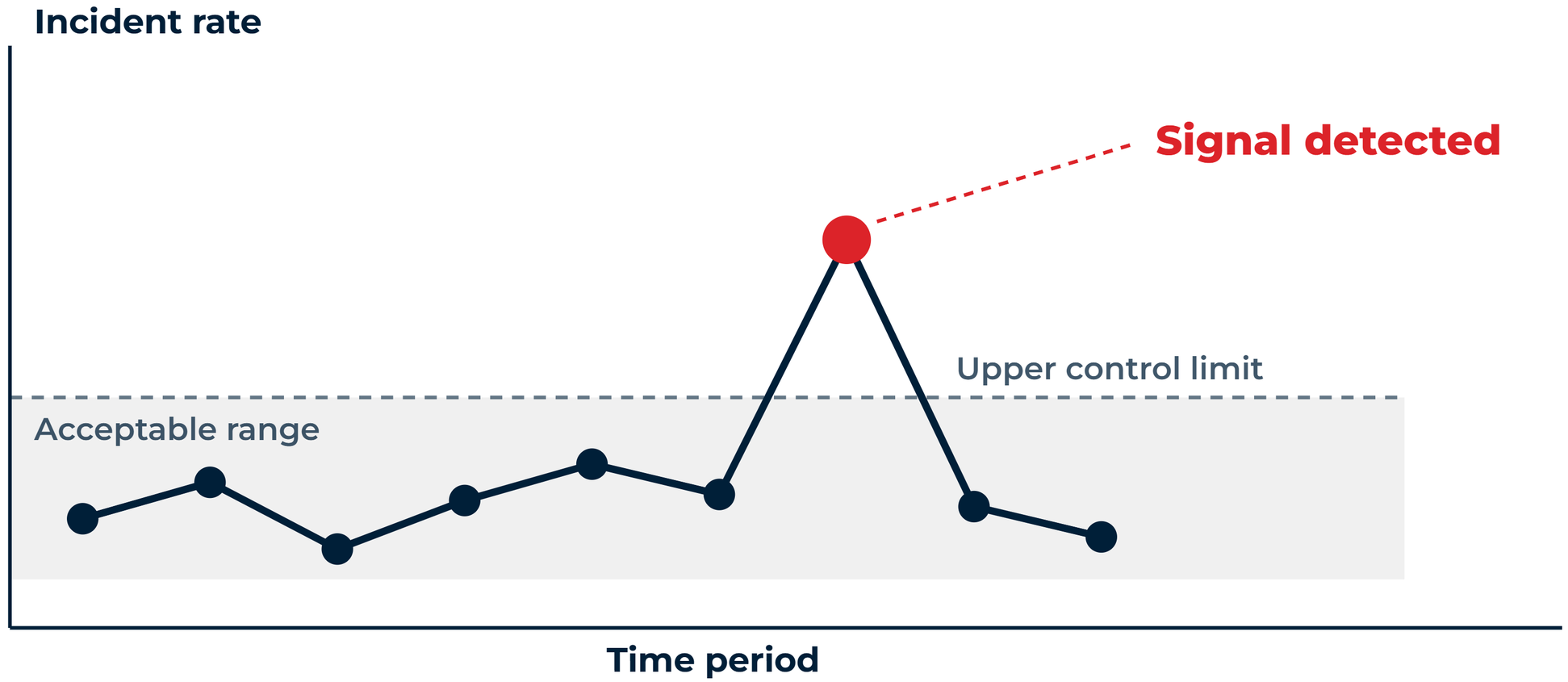
Severity and correlation

Assessed for each AE

Comparing incidence rates

By product and period

Trending Your Data



Sorting Out the “Background Noise”

- Direct toxic effect due to something else
- Concomitant disease
- Spontaneous disease
- Disease out of remission
- Mis-identification of the potentially offending substance or product
- Incentivized AE reporting resulting in reports made for ulterior purposes (eg. Refund justification)

Sorting Out the “Background Noise”

Interaction related event involving use of the product and:

- Other drugs
- Disease
- **Counterfeit Product**
- Environment
- Food

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Using PMS Data for Decision Making

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A signal is found… now what?

01

Analyze lots that have common AEs

Determine if a recall is needed

02

Reformulation if there is an uptick in specific complaints

03

Labeling changes for clarity

Why PMS Data Matters

Building a defensible audit trail for regulatory inquiries or FDA Form 483 scenarios

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Case Example

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CASE EXAMPLE

Cosmetic A is a leave-on facial serum with retinol sold nationally through mass retail and e-commerce.

Estimated annual units sold:
480,000

CASE EXAMPLE · STEP 01

Adverse Event Intake

A consumer submits a report through the brand's adverse event line. The intake specialist captures the four minimum elements needed for a valid case, plus supporting details.

Field	Captured Information
Identifiable patient	Female, age 41 (initials on file, no full name provided)
Identifiable reporter	The patient herself, self-reporting by phone
Suspect product	Retinol Serum, lot #RR-2603, purchased via brand website
Adverse event	Facial redness, burning sensation, and peeling beginning ~18 hours after first application; sought urgent care on day 3 when peeling did not resolve
Onset/latency	18 hours post first use
Concomitant products	Reports no other new skincare products in past 30 days, no meds/supplements
Medical treatment	Urgent care visit; prescribed topical corticosteroid
Outcome at time of report	Recovering, not yet resolved

CASE EXAMPLE · STEP 02

Seriousness Assessment

The reviewer evaluates the case against FDA's definition of a "serious adverse event" under MoCRA

ASSESSMENT

The patient was not hospitalized, and the event is not life-threatening. Medical intervention (prescription treatment) was required to manage the reaction, but it does not rise to the threshold of “significant disability” or “persistent alteration of appearance” based on the information provided (no scarring, no lasting impairment reported).

DETERMINATION

Non-serious adverse event.

This means the case does not trigger the 15-business-day mandatory FDA reporting clock, but it is still logged, retained per the 6-year recordkeeping requirement, and factored into ongoing trend monitoring.

(For contrast: if the patient had instead developed a secondary infection at the site requiring antibiotics, the case would be classified serious, triggering mandatory reporting to FDA within 15 business days via MedWatch Form 3500A.)

CASE EXAMPLE · STEP 03

Correlation Scoring

Criterion	Assessment for this case	Score contribution
Temporality	Onset at 18 hours post-use	+1
Dechallenge	Patient discontinued use; symptoms began resolving within 5 days	+1
Rechallenge	Not attempted (not clinically advisable)	0
Alternative etiology	No new concomitant products or medications, no significant sun exposure	+1
Plausibility	Retinoid-induced irritation/exfoliation is a well-documented effect	+1
Medical opinion	Reaction is consistent with first-time exposure to retinol at labeled concentration	+1

CASE EXAMPLE · STEP 04

Trending and Incidence Rate

Over the trailing 12 months, the PMS team compiles all AE reports associated with this product and lot family to calculate a reporting rate:

Total reports of erythema/burning/exfoliation:

14 cases

Units distributed in the same period:

480,000

Observed reporting rate: 14 / 480,000 =

~2.9 per 100,000 units

Benchmarked Against internal baseline.

The brand's broader retinol-serum portfolio (three other SKUs, similar concentration range) shows a historical background rate of **1.1 per 100,000 units** for comparable irritation-type events

CASE EXAMPLE · STEP 05

Determine if corrective action is warranted

Corroborating factors:

- Positive dechallenge across multiple cases in the batch, not just this one
- Consistent temporal clustering (18–36 hour onset window across cases)
- Biologically plausible, consistent mechanism (retinoid irritation)
- No confounding pattern of concomitant product use across the case series
- Majority of cases scored "probable" on correlation assessment
- Seriousness distribution across the 14 cases: 1 serious (secondary infection, reported to FDA within the 15-day window when it occurred), 13 non-serious.

Recommendations to Consider:

Labeling enhancement

strengthen the existing patch-test and gradual-introduction instructions and add a more prominent irritation warning specific to first-time retinoid users.

Formulation review

evaluate whether the formulation requires any tweaking to decrease risk of reaction.

Continued enhanced monitoring

regardless of which action is taken, the product is flagged for a shortened surveillance review cycle (e.g., quarterly rather than annual trend review) for the next 12 months to confirm the reporting rate.

A recall is unlikely to be recommended at this stage

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Thank you

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