Postmarket surveillance and the ongoing process of monitoring, assessing and confirming the safety of supplements and other natural medicinals

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SafetyCall™ International
Industry Poison Control

- A Multi-disciplinary clinical practice including Medicine, Veterinary Medicine and Pharmacy practitioners
- Core service is a 24/7 Human and Animal Poison Control and Post-marketing Safety Surveillance Center
- SafetyCall™ clinicians have been serving both Industry and the Public since 1984
- SafetyCall™ practice group has been responsible for the handling of over 2,000,000 consumer product incidents
- A customer intimate, knowledge-based practice

Post-Market Surveillance/ In-Market Support

What is it??

- The processes whereby manufactures, regulators, health professionals, the public at large, and others monitor the performance and experience related to a given products life-cycle in the open market.

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Post-Market Surveillance

What should it accomplish??

- Helps identify intended ***and*** unintended use patterns that may potentially contribute to "unintended effects"
- Allows assessment of how the product performs by itself or in the presence of other products or substances
- Helps insure that effects in "unique" populations are considered when evaluating risk
- Should also help define a relative *"Safety* profile"

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"Dietary Supplement and Nonprescription Drug Consumer Protection Act"

A corporate approach to implementation

- PART A:
  Meeting the "letter" of the law (s)
- PART B:
  Understanding the implications for liability, risk communication, and impact on public confidence

Adverse Event Reporting vs. Post-market Surveillance

Adverse Event Reporting:

- Meeting the Letter of the Law (s)
  - Prescriptive process of:
    - RECEIVING
    - DOCUMENTING
    - TABULATING
    - SUBMITTING

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Adverse Event Reporting vs. Post-market Surveillance

Post-market Surveillance: Meeting the Intent of the Law

- Performance based process of:
  - Incident investigation: Collecting, Documenting, Categorizing incident details for signal detection
  - Interpretation/Utilization
  - Analysis for Causation (*Association*), hypothesis generation
  - Corrective action or risk mitigation efforts when warranted

Quality Issue vs. AE

I used your product and it's defective because…….,

- There's something floating in it
- It's the wrong color
- I can't read the label
- It has no label
- It smelled terrible, looked terrible, was the wrong color in a bulging container and,….
  - I drank it anyway
    - What I was trying to treat was worse than what I thought it could do to me

Quality Issue vs. AE

"Your product is defective and it….."

- Could of made me sick!
- Did make me sick!
- Could have killed me!

- It did kill me!!

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Adverse Event Possibilities

I have an adverse event report (allegation),..is it due to…

- Inherent product vs. ingredient issue
- Manufacturing issue?:
  - Quality control issue before or after leaving the plant
    - Intentional/accidental
  - Contamination/adulteration after sale
    - Supply chain issue
    - Malicious action

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Adverse Event Possibilities

I have an adverse event report (allegation),..is it due to…

- Predictable adverse effect based on:
  - Inherent toxicology/pharmacology profile of one or more of the ingredients (*or contaminants*)
  - Known (possibly labeled) interaction potential with:
    - Drug
    - Food
    - Disease
    - Other consumer products, etc.

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Adverse Event Possibilities

I have an adverse event report (allegation),..is it due to…

- Unpredictable/Unexpected effect
  - Idiosyncratic (simply unknown, unpredictable)
  - Other unrecognized “reaction” (direct effect?)
  - Other unrecognized “interaction”
    - Drug
    - Disease
    - Food
    - Environmental issue
    - Biologic (gene expression)

Adverse Event Possibilities

I have an adverse event report (allegation),..is it due to…

- NONE OF THE ABOVE!!!

AKA……

"Background Noise"

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Adverse Event Possibilities

- Background Noise
  - Concomitant disease
    - Spontaneous disease
    - Exacerbation of existing disease
    - Disease out of remission
  - Direct toxic effect due to something else
  - Mis-identification of the potentially offending substance or product

Adverse Event Possibilities

- Background Noise
  - Herd mentality reporting "I heard it through the grapevine":
    - Media reports
    - Friends and relatives
    - Twitter chatter or other "social media"
    - Other phantom issues leading to a feeding frenzy
  - None of the above…"it really didn't happen"
    - "Syringe in the Pepsi Can" syndrome

Where We Are Today

- FDA Database of "Serious AE Reports"
  - Likely contains incidents that fall into one or more of each of the "adverse event possibilities" previously listed
  - How do regulators, manufacturers, scientists healthcare providers,..and the public sort that out

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“Not all adverse event reports are created equal”

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Role of "Spontaneous Reports" in Botanical Postmarket Surveillance

"***The safety of dietary supplements will be defined by spontaneously reported incidents (regardless of the quality and integrity of these reports)***"

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AE Benchmarking and Scoring

- Incident characterization in evaluating "causal links" and association scoring
  - **Expectedness**
    - **Including "relative incidence rates"**
  - **Temporality**
  - **Biologic, pharmacologic, toxicologic plausibility**
  - **De-challenge**
  - **Re-challenge**
  - **Confounding variables**

Top Supplement Adverse Event Possibilities

- Inherent pharmacologic/toxicologic effect issue with one or more of the product's ingredients
- Multiple ingredients synergistic/additive effects
- Contaminants

Top Supplement Adverse Event Possibilities

- Product “stacking”
- Interactions
- Allergy

Parting Shots

- Reviews or critiques of individual AE's represented in the current FDA Database

  …… all reports are not created equal

  most incidents have been collected to meet the "letter" not the "intent" of the law

Parting Shots

- Under-reporting is likely the current norm,…consider:
  - Approximately 1,000 events/yr being reported
  - ***Less than 50 companies have made up the reporting pool***
  - Over-reporting by a few companies contributing to numbers

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Parting Shots

- Under-reporting is likely the current norm,…consider:
  - The most serious adverse event related issue impacting the supplement industry post AE law was not reported by the company to FDA despite their knowledge of product associated illness

Parting Shots

- Under-reporting is likely the current norm,…but:

  Expected to change with new FDA enforcement discretion with GMP's

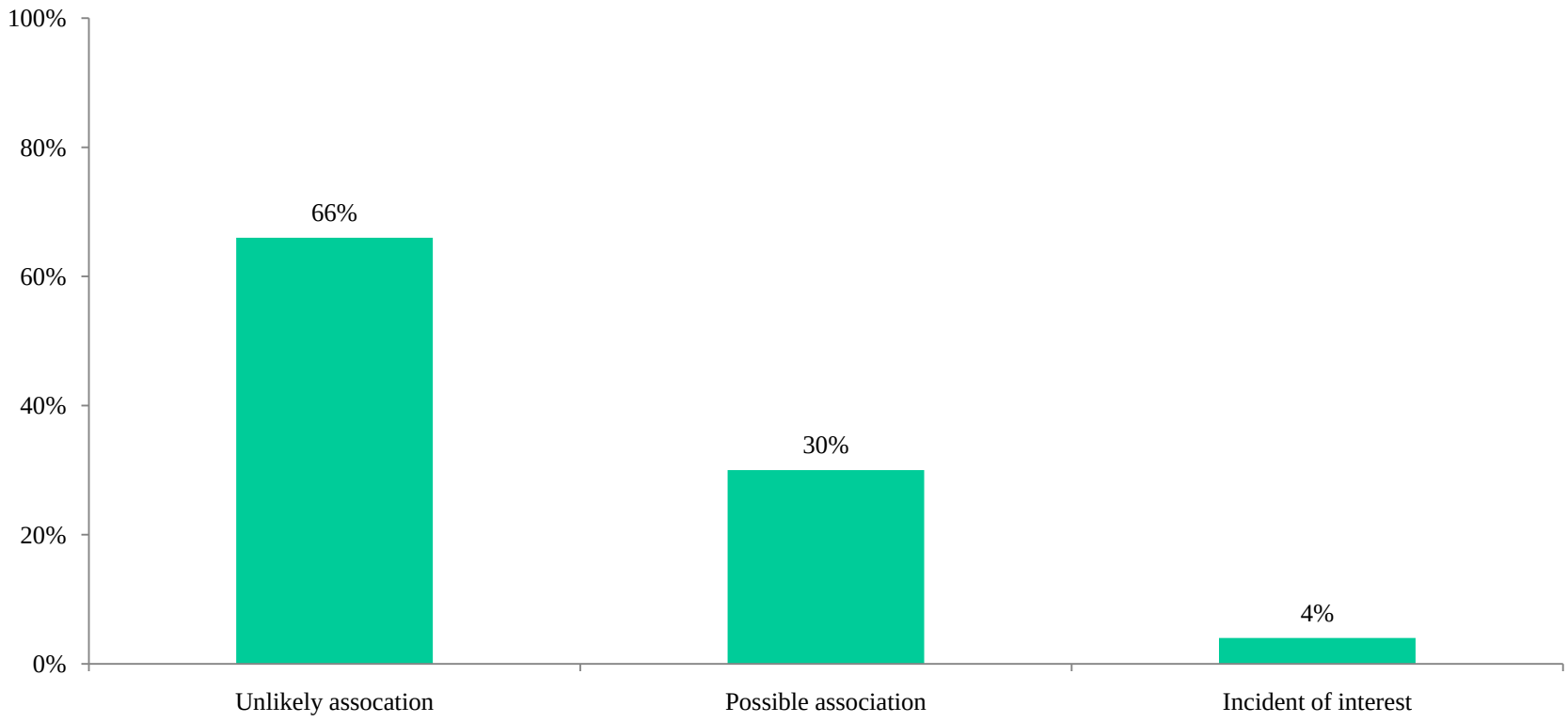
Parting Shots

- SafetyCall International Dietary Supplement Client Products:

  Average reporting score is <2

  0-2 Points: Unlikely Relationship – Incident details suggest that a relationship between the product use and the reported effect is highly unlikely;

Representative Dataset with Assessment



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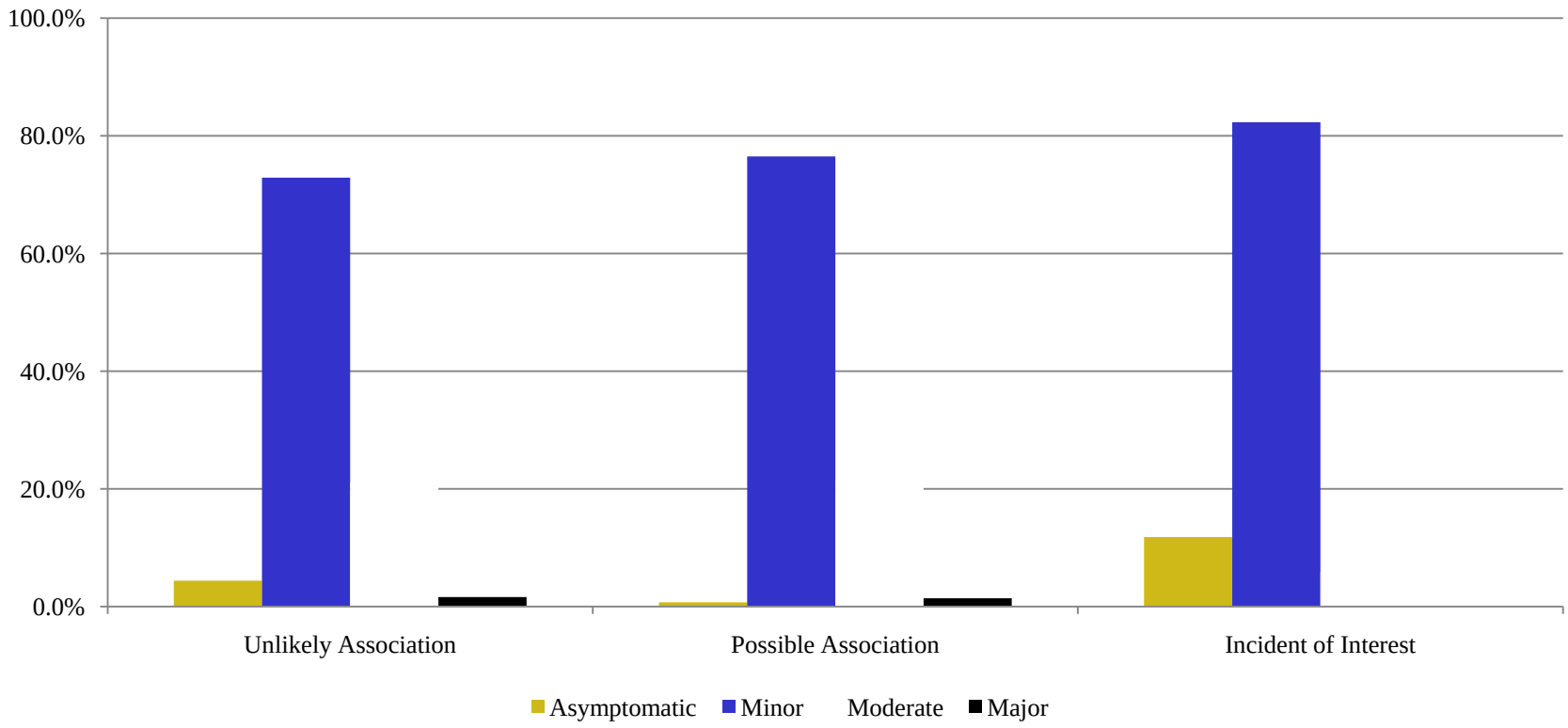

Thank you!

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