Management of Safety Data originating from Patient Support and Market Research Programmes

Current challenges from pharmaceutical industry and proposals to move forward

Pharmaceutical Industry Associations

Scope of Presentation

- Key objective
- Major concerns & observations
- Historical Perspective
  - As a basis of where we are today
- Key Challenges for industry
- Proposals for the future
  - As a means of meeting the key objective

Objective

To reach a pragmatic solution to the issues raised in a way which is logical, proportionate, feasible, meets legal obligations, has the appropriate governance and meets the common goals of all stakeholders – patient safety.

Concerns expressed by CIOMS V Experts

The quality of solicited cases (from these programmes) is very low and they should not be put into the same category as spontaneous reports regarding information content and potential usefulness. Doing so only floods the system with noise. The chances of learning something important and new from such sources is small, especially given the difficulty of obtaining detailed medical information. These considerations are important in trying to decide on the proper level of attention and regulatory reporting such reports should receive.

CIOMS V (2001)

Major Industry Concerns
PSPs and MR

- Disproportionate emphasis **in inspections** on PSPs/MR in relation to the overall PV/risk management system
  - **Differing interpretations between inspectors and inspectorates**
  - **Perception that all PSP/MR programmes are studies/organised data collection systems aimed at actively soliciting safety data**

- Significant & disproportionate focus **in MAHs** to manage expectations in relation to actual contribution to the PV system
  - **Diversion from activities which contribute more meaningfully to patient safety.**

- Potential to impede the detection of important new signals
  - **Potential to increase noise to signal balance**
  - **Unintended consequences**
  - **Consistent with CIOMS V concern in 2001**

Historical Perspective
The Bottom Line

- Current standards are effectively derived from guidance of another era
  - **Based on ICH E2D which , in turn was derived from CIOMS V (2001) and the FDA guidance to Industry (1997)**
  - **Situation very different in 2013**

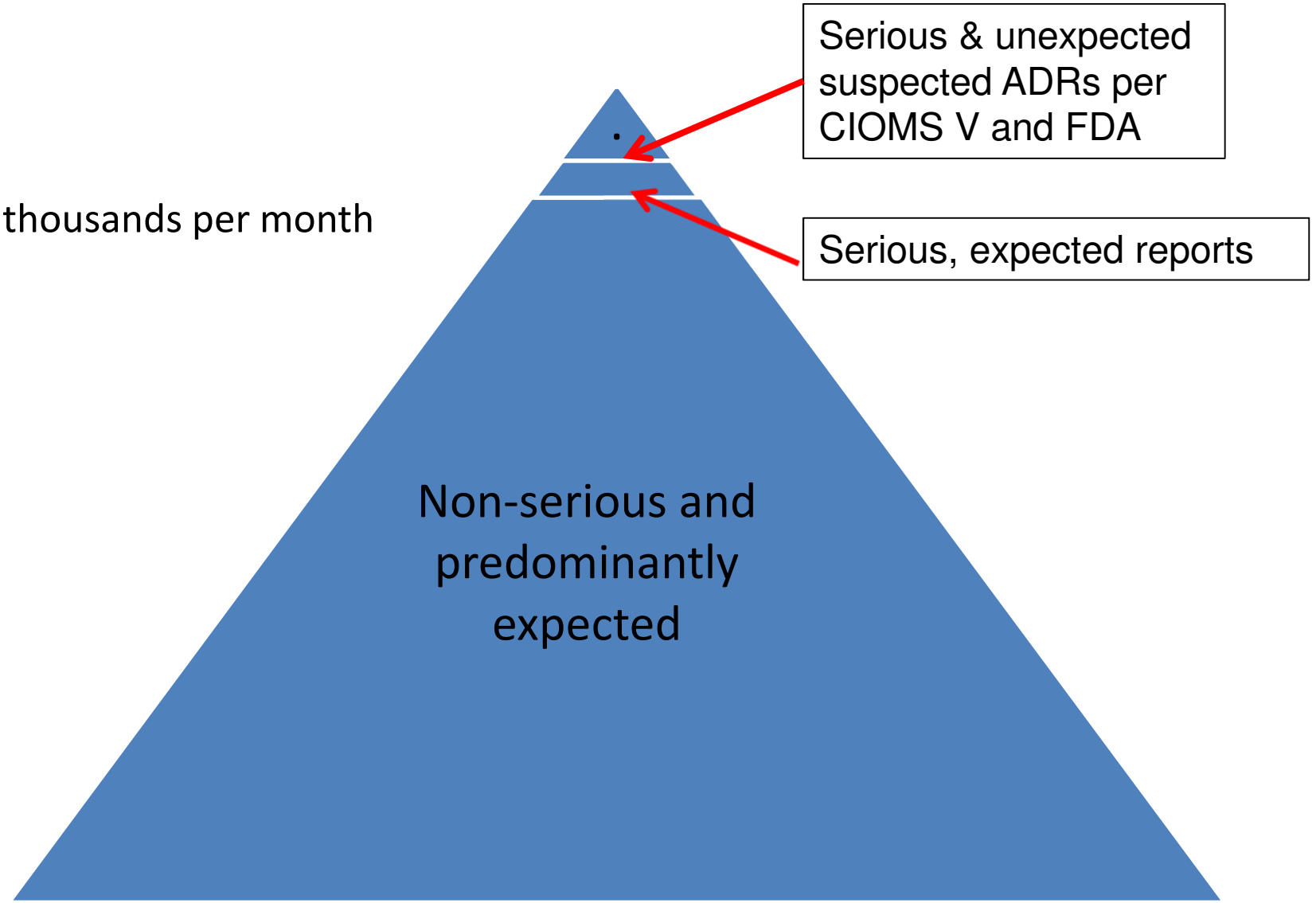
- Critical aspects of the original 1997 FDA guidance and CIOMS V recommendations have been “lost in translation”
  - **Aspect of “active solicitation”**
  - **Point made that reports from these programmes are neither spontaneous nor CT cases so CIOMS created a third class (solicited)**

BUT

  - **Leap from causality assessment advocated by FDA and CIOMS V on <u>suspected serious unexpected AEs/ADRs only</u> to causality assessment on <u>ALL AEs</u> to determine if they are “ suspected”.**

So to be very clear……

n = thousands per month



Industry Observation

- Where information from PSPs is helpful
  - **Can provide good insights into what is important to patients in relation to their disease or treatment**
  - **Generating information on what may impact ability of patients to comply with treatment (i.e. optimise benefit)**
  - **Can help direct where advice and support are needed with respect to seeking medical help or where reassurance is needed to avoid discontinuing treatment inappropriately.**
  - **Confirms what is already known**

Industry Observation

- Where information from PSPs does not appear to be helpful
  - **As a signal detection or PV tool**
  - **As a tool to collect effectiveness information**
  - **As a tool to provide new safety information that would otherwise not be provided by other methodologies already a component of the PV system.**
  - **As a tool to inform risk management**

Industry Challenges

- Volume and variety of programmes
  - **Not designed as studies with a safety objective**
  - **In general ,not designed to actively solicit safety data**
  - **May not even be specific to one product (disease education)**
  - **Current definition of PSP does not fully encompass the sheer breadth of activities undertaken**
    - **Very difficult to operationalise**

- Volume and nature of reports
  - **Can be in excess of several thousand per month**
  - **Generally generate non serious and expected reports**
  - **Most "reports" either spontaneous /"stimulated "**
  - **Many "reports" are not suspected ADRs at all**
  - **Many interactions involve completely incidental " noise"**
  - **Meaningful causality assessment precluded**
  - **Significant effort on follow up with very poor response**
    - **Disproportionate focus and effort**

Industry Challenges

- Typical examples of reports from one PSP programme
  - **Weight loss attributed to impending divorce**
  - **Injection in the upper limbs or in the bottom, no AE**
  - **Use the pen more than 28 days, no AE**
  - **Not following a set time pattern for the injection, no AE**
  - **Have been in treatment for more than 24 months, no AE**
  - **Patient was told to inject every 48hrs instead of every 24hrs, no AE**
  - **Patient does not feel any improvement**
  - **Missed dose, no AE**

Industry Challenges

- Potential for under-reporting or over-reporting
  - **Under-reporting as most reports lack sufficient information to assess whether or not there is a reasonable causal relationship**
  - **Over-reporting: MAHs default to the most conservative option (presumed causality)**

- Significant inconsistency across multiple data sources; all currently classified as spontaneous reports:
  - **A sales rep asks the question of an HCP " How is the product performing?" and HCP volunteers a suspected ADR**
  - **Class action law suit reports which effectively solicit cases through advertisements**
  - **Reports from EPPV (an "organised data collection system ")in Japan**

Industry Proposals

Aims of Industry Proposals

- Gain a common understanding that patient support programmes:
  - **Are not studies and not necessarily organised data collection systems**
  - **Generally do not involve active solicitation of safety information**
  - **Denominator may be known but still can only estimate " reporting rates" so no advantage over spontaneous reporting**
- Determine what is and what is not actively solicited
  - **Assign classification of information appropriately**
  - **Simplification which reflects reality**
- Redefine PSPs/MR based on current situation
- Restore proportionality of focus in relation to :
  - **Contribution to the pharmacovigilance system vs other PV activities**
  - **Active solicitation or not**
  - **Re-focus on what is medically important.**

Industry Proposals

It should be made clear in the respective definitions that, unless the information is actively solicited, neither MRPs nor PSPs are designed or intended to collect data on safety and efficacy (or effectiveness)

Industry Proposals
Revised definition of PSP

A Patient Support Programme is a service that involves direct interaction with patients and/or patient carers for the purpose of :

- Helping to manage a patient's medication and/or disease outcomes (e.g., adherence, awareness, education), or
- Helping patients understand their condition and provide advice on managing disease e.g. lifestyle (exercise), diet or
- Providing a service or arranging financial assistance for patients (e.g. reimbursement support, product discount)

These programmes are not usually designed or intended to elucidate safety, effectiveness or efficacy information on the product(s)*

* Similar wording added to definition of market research

What is Active Solicitation?

- HCP or non HCP at company or vendor speaks directly to a patient (outbound communication)
- Entails as a minimum :
  - **Focused line of questioning designed to capture suspected ADRs from patients in the programme**
  - **Ideally should aim to capture clinically relevant information to allow meaningful assessment**

These would be solicited reports

What is Not Active Solicitation?

- Reports arising from non specific questions not designed or intended to elicit safety information (**stimulated**) e.g.
  - **How is your well being?**
  - **How are you feeling ?**
  - **Are you still taking your tablets?**
  - **Do you have concerns about taking your medication?**
  - **What worries you about your disease ?**
- Unprompted mention of an event during the course of another interaction (**incidental**) e.g.
  - **Call centre phones patient`s home as device needs replacing to be told that patient passed away last week; no mention of suspected relationship to drug**
- Reports arising from any incoming call from a patient

Re - Classification of Reports

Solicited

- Design of programme **does** involve active solicitation of safety information/product complaints via structured questions
- **Reporting** of serious and non-serious events to EMA is **driven by the causality assessment** and non-related events are not reported
- Excluded in EV for signal detection (per current practice)

Spontaneous

- Design of programme **does not** involve active solicitation of safety information/product complaints
- Includes information obtained through “stimulated” reporting
- Ideally would exclude “incidental” reports
- Expedited reporting in line with requirements for suspected ADRs
- Included in EV for signal detection (per current practice)

Industry Proposals
Re-define Focus

On what is serious, unexpected and important from a patient safety perspective

Industry Proposals
For Further Discussion

- Remove misleading reference PSPs as an example of "CTs/studies" from GVP Module VII (PSURs) !

- Potential Impact of PSP reports on Signal Detection
  - **Currently no systematically collected data on the utility of PSPs/MRs as a source of safety signals or their impact on signal detection.**
  - **Need for evidence to support industry concerns on increasing noise to signal balance and possible adverse impact on signal management**

- Disproportionate focus in PV Inspections
  - **Need to restore a pragmatic balance**
  - **Establish a consistent and proportionate scope**

Back up Slide

Not intended to present only if question arises

Historical Perspective
ICH E2A (1994)

CLINICAL SAFETY DATA MANAGEMENT:DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

Causality assessment is required for ***clinical investigation cases****. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.*

For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

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The expression "reasonable causal relationship" is meant to convey in general that ***there are facts (evidence) or arguments to suggest a causal relationship.***

Historical Perspective
FDA Guidance to Industry (1997)*

III. ***INDIVIDUAL CASE REPORTS BASED ON SOLICITED INFORMATION***

The FDA has determined, for purposes of post marketing safety reporting under 21 CFR 310.305, 314.80, 314.98, and 600.80, ***that information concerning potential adverse experiences derived during planned contacts and active solicitation of information from patients (e.g., company-sponsored patient support programs,*** *disease management programs) should be handled as safety information obtained from a post marketing study*

Historical Perspective
CIOMS V (2001)

In relation to patient support & disease management programmes , CIOMS V acknowledged:

- Reports may not be generated in the usual spontaneous manner; they are usually obtained incidentally to the main purpose of the programme . Neither are they a result of a prospective /retrospective clinical study
- Reporting them as " spontaneous" would undermine, possibly corrupt, the objectives of the SRS for **the generation of important new safety signals**
- Such reports are regarded as solicited in nature and one cannot infer implied causality. ……..but,
    - **Assumes that the company or vendor have contacted the patient**
    - **And another important but……..**

Historical Perspective
CIOMS V (2001)

Suspected serious unexpected ADRs *should be regarded in the same way as would be for a CT *, thus* ***for the purposes of regulatory post- marketing drug safety reporting*** *on an expedited basis a causality assessment should be conducted by the manufacturer.*

Footnote in the CIOMS V report

* **At least one regulatory authority (US FDA) has already adopted such a stance via a guideline**

Historical Perspective
ICH E2D (2003)

- Paraphrased but directly based on FDA guidance

3.2 Solicited Sources

Solicited reports are those derived from organised data collection systems*, which include clinical trials, registries, post-approval named patient use programs,* ***other patient support and disease management programs,*** *surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance.*

Adverse event reports obtained from any of these should not be considered spontaneous. ***For the purposes of safety reporting,*** *solicited reports should be classified as study reports, and therefore should have an appropriate causality assessment by a healthcare professional or an MAH.*

Historical Perspective

- 2007 : Volume 9a guidelines on PSPs :
  - **Based on ICH E2D Step 4 guideline**
- April 2012 :Draft GVP Module VI guideline refers to classification of reports from PSPs as :
  - **solicited, if actively sought**
  - **spontaneous, if not actively sought**
- July 2012 : Final Module VI stipulates that **all** reports from organised data collection systems, including PSPs should be classified as solicited
  - **Compassionate use or named patient programmes exempted if AEs not actively sought**

Industry Proposals
Classification of reports by source

The classification of safety information from PSPs/MR should reflect its source and the extent to which an HCP in a programme is involved in the care of the patient in whom a suspected ADR has occurred and been reported. Reports from PSPs/MR should be classified as consumer reports, when the HCP (e.g. a nurse) involved in the programme is not involved in the care of the patient and does not have access to sufficient information to verify the events reported (e.g. access to their medical records)

What is Incidental?

A driving principle of spontaneous reporting systems is the suspicion of possible causal relationships between adverse events (AEs) and drugs, which prompts the reporter to submit a spontaneous report. In the course of investigating these reports, drug safety personnel may receive information on events, adverse or otherwise, that occurred after the drug was administered, **but were not the intended subject of the spontaneous report**.

Events which did not **prompt contact with the pharmaceutical company or regulator and for which there is no indication of drug causality** are proposed to be defined as 'incidental events'

CIOMS V Working Group (2001)

What is Stimulated?

Stimulated reporting can occur in certain situations, such as notification by a “Dear Healthcare Professional” letter, publication in the press, or questioning of healthcare professionals by company representatives*. **These reports should be considered spontaneous.**

ICH E2D (2003)

* Added to take into account Japanese Early Phase Pharmacovigilance (EPPV - organised data collection system) where reports are classified as spontaneous.