GHTF

FINAL DOCUMENT

Title: Manufacturer's Trend Reporting of Adverse Events

Authoring Group: SG 2

Endorsed by: The Global Harmonization Task Force

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The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide *non-binding* guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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Preface

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1.0 Introduction

The GHTF document "Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative" (GHTF SG2 N21 R8) specifies principles for reporting of adverse events by manufacturers. It also includes provisions about common and well-documented events that may be exempt by National Competent Authorities (NCA´s) from reporting or changed to periodic reporting upon request by the manufacturer and agreement from the NCA.

The present document describes the criteria for identifying a significant increase in the rate of adverse events and hence for submission of a trend report to the NCA, irrespective of whether such events are individually reportable, periodically reportable or currently exempt from reporting as agreed to by the NCA.

It is also important to recognize that there are circumstances when a manufacturer should take action immediately without waiting for a trend to occur. It may be based on the severity of the event, or by perceived risks associated with the adverse event(s) regardless of the number of events.

This document is not intended to define statistical techniques for trending or to place additional requirements beyond the trending of complaints, which forms an integral part of a manufacturer's quality system. Instead, it explains the reasons for the importance of adverse event trending and reporting and also provides some guidance on key aspects.

Remark:
The intention of GHTF Study Group 2 is to integrate "Trend reports for adverse events" into the document SG2 N21R8, "Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative" at the time of the next major update of this document. To expedite completion of the final version of "Trend reports for adverse events" it is temporarily placed as a stand-alone document on the GHTF web site for comments.

2.0 Definitions

For the purpose of this document, "manufacturer" is limited to the organization that establishes and maintains the QMS associated with the product, it does not include distributors of medical devices.

3.0 Trend Reporting for Adverse Events

A trend report should be made where there has been a significant increase in the rate of:

3.1 Already reportable events

A significant increase in the rate of reportable events presents a manufacturer with a new piece of information about his device or its performance in a clinical setting. Unless there is a corresponding trend in the product market as a whole, it is less likely that the NCA will be able to detect this change as only the manufacturer with complete access to his market data can create a reasonable facsimile of rates and can estimate trends.

3.2 Adverse events that are currently exempt from reporting

An exemption from reporting certain reportable events is usually provided on the basis that the NCA believes the event is well characterized and they and the industry have done as much as is justified at that time to prevent further adverse events. However, a significant increase (see explanation below) in the rate of these exempt events may indicate an underlying change in the performance of the manufacturer's product or in its use by clinicians, patients or other customers. Either situation would be of considerable value for the NCA and is an appropriate reason for submission of a report to the NCA as soon as the manufacturer becomes aware of the change in rate.

3.3 Adverse events scheduled for periodic reporting

The rationale for reporting a change in the rate of events for periodic reporting follows from the arguments above. Firstly, periodic reports of numerator (adverse event) data without denominators (devices on the market or in use) do not provide the NCA with the ability to estimate trends appropriately. Secondly, although periodically reported events may enable the NCA to examine general market trends, the individual manufacturer is responsible for indicating potentially important changes in product safety.

4.0 Adverse Event Trending

The decision to file a trend report should be based on the occurrence of a significant increase in the number of adverse events.

4.1 Trending procedure and significant increase

Based on the diversity of the medical devices in the market it is not meaningful to define a single trending procedure valid for all devices. Depending on the type of device (e.g. IVD, implant, diagnostic and therapeutic device, surgical and dental instrument, hearing aid,

compression, etc.), the devices risk classification, the number of products delivered, single or multiple use of devices, devices with traceability requirements, unavailable information on device disposals and other parameters a manufacturer must adopt a trending procedure which is applicable and adequate for his operations and devices. Basic methods for performing trending can be found in the literature (e.g. for statistical quality control) and will not be repeated in this document.

While for many manufacturers the use of simple graphs and charts will be sufficient, the implementation of more sophisticated methods will be advisable for others. It is important that valid statistical methods are used for trend evaluation. NCA´s may request the manufacturer to demonstrate that the applied method is appropriate for the particular case.

It is less easy, however, to find in the medical device area a definition in the literature of what constitutes a significant increase in the rate of adverse events. The discussion below explains "significant increase" in statistical trending. Concurrently, this document provides guidance to manufacturers on how a creditable baseline for trending can be established and provides information to NCA´s that might facilitate decisions regarding reporting exemptions for devices with well-established baselines.

4.2 Complaint trending and adverse event trending

Complaint trending as an established quality system requirement provides the basis on which manufacturers are asked to accumulate and analyse their data. Since complaints come from the data source from which reportable adverse incidents are identified, trending of adverse events uses essentially the same methods as trending of complaints. For both trending processes the database, in the form of the complaint file, is the same.

The difference:

- Trending of complaints may lead to the discovery of a complaint trend (and the appropriate corrective and preventive action) but not necessarily to a report to the NCA.
- Trending of adverse events may lead to a report to the NCA.

To summarise: the method for the trend evaluation of both complaints and adverse events can be the same while the decision making process and following activities are different.

5.0 Statistical Trending Example and Significant Increase

5.1 Basic trending parameters

The raw data to be gathered for trending are the number of events (n) in a given time interval (t) and the related used product volume (by clinicians, patients) in the market (d) during that time interval. One data-point (i) = n/d is calculated for each time interval, and for the purposes of this document is defined as the observed incidence expressed as a percentage. Patient exposure over time will need to be measured or estimated for the denominator (d), in

place of the used product volume, for devices such as medical implants that are continually in use. However, where data about exposure to use are not known to a manufacturer, the number of products in the field may have to be used as the denominator (d).

If relevant, (e.g., for implants) trending might also be initiated for clinical findings or other variables such as age, weight and gender of patients, age of the device) and others.

The Baseline (I_B) and Threshold (I_T) against which the observed incidence is compared for establishing the trend are also expressed as percentages of the related used product volume in the market or exposure to use. If the used volume for a related manufacturer's product is too low for a meaningful statistical measure, each single adverse event should be reported to the NCA. The quality of the statistics increases with both the number of events and the installed volume in the market. Care should be taken when identifying the data to be used for trending. Only market areas where adverse event reporting is established should be included in the trending. Otherwise the frequency of known events may not match the used volume, leading to wrong results.

5.2 Baseline I_B

For establishing a realistic (e.g. to avoid under-reporting) baseline to start with, multiple tools and methods can be used such as risk analysis, analysis techniques for dependability and reliability testing (see also respective IEC standards and application guides) etc. Another important source of information is historical data from the manufacturer's or his competitor's equivalent devices. Further information can also be found in medical and scientific publications.

If there is insufficient information for the determination of a creditable and statistically proven baseline, individual adverse events should be reported.

5.3 Threshold (I_T) and Time Interval (t)

The typical number of events in a given time interval, e.g. one month, varies depending upon the product type and may range from 1 or 2 events up to a few hundred.

The time interval should be long enough to gather sufficient data for the analysis depending upon the volume of products sold and adverse events reported. For higher volume products a typical time interval is 1 month. It is important that the time interval is short enough to facilitate timely corrective action, especially in case of high-risk products.

The upper value of the normal range of variation that specifies the trending, Threshold I_T, will be different depending on the product category.

5.4 A significant increase in observed incidence

A sustained increase of the observed incidence (i) above the baseline over a certain number of time intervals will constitute a significant increase, and should trigger a trend report to

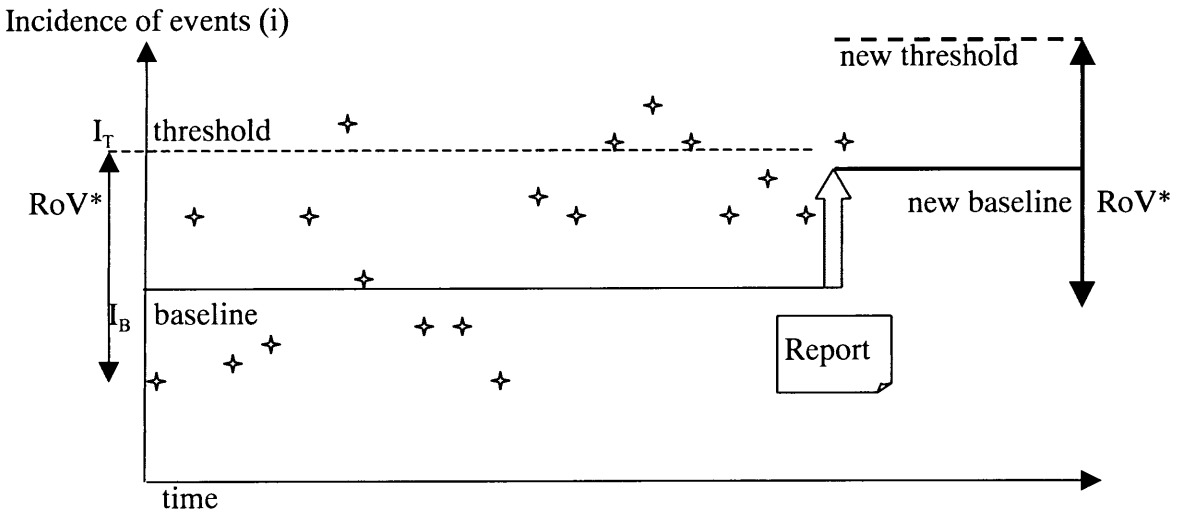
the NCA (see figure 1). Whether or not the increase is considered to be sustained is tested and determined by the chosen statistical methodology. The trend report should be filed as soon as the significant increase is identified.

Depending on the product volume in the market, a "significant increase" might be identified as a result of any of the following:

(a) a rapid and continuous increase in (i) over a limited number of time intervals for high volume products (eg over 1 - 3 months)
(b) a slow and continuous increase in (i) over a larger number of time intervals for low volume products (eg over 3 - 6 months),

Although an upward shift in the baseline will follow identification of a significant increase, as a basic quality system requirement, corrective and preventive actions needs to be initiated to evaluate and eliminate the root cause of the problem in order to reverse the upward trend of the baseline and return it to the previous level or lower.

Figure 1: Upward Shift of baseline and trend report filing



* normal Range of Variance

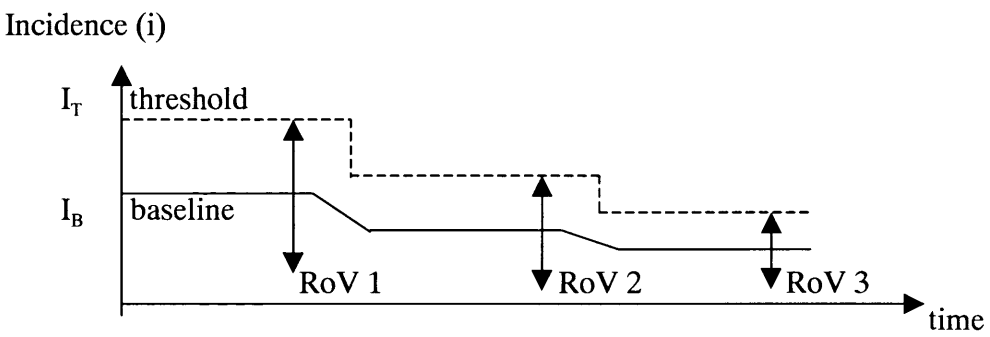
Note: Only one datapoint per time interval

5.5 Baseline Improvements

If there is a sustained decrease in incidence over successive time intervals this will lead to a reduction in the baseline and threshold which should then be used for future trending. (see Figure 2).

Such downward shifts in the baseline, which can relate to product/process improvements, or refinement of clinical indications/usage - are positive developments leading to reduced numbers of adverse events and, to cost savings on the manufacturer's side and to the overall healthcare system.

Figure 2: Baseline improvements



5.6 Exceptional cases

If there are sudden large increases in the incidence (i) or number of events (n), whether or not they are sustained, it is recommended to file a report with the NCA even if the trend evaluation does not trigger a report or the time interval for the actual trending period has not finished. A report should be filed as soon as the exceptionally high value is identified and an associated corrective action initiated even before the trend is confirmed.