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Pharmacovigilance Signal Monitoring:

Perspective of Marketing Authorization Holder & Regulatory

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PvNET
values patient safety

INTRODUCTION

Marketing authorizations of medicinal products should be backed by planning and analysis both, before and after the marketing approval.

Product Safety monitoring is one such prime activity that cannot be ignored

Every regulation is meant to affect one or more industrial sectors, such as the outsourcing agencies, the health care organizations, ethics committees, site management organizations etc. Thus, the Marketing authorization holder (MAH) has to take a call to comply or ensure compliance from stakeholders.

Undoubtedly, the life - cycle of pharmacovigilance is perpetual and continuous vigilant monitoring has to blend into their integral activity.

For example, a drug as old as propoxyphene, marketed since 1955 was recalled from the market owing to serious cardiac toxicity and number of

Pharmacovigilance catching all the required attention is indeed a good news for the population at large using medicinal products at some or the other stage of their lives. **The impact a small molecule in a packaged form can have in our lives is astonishing!**

Additionally, the MAHs and the Central Regulatory authorities have made all possible efforts so that absolute cautiousness is exercised at all phases of a product life cycle. The aim being to put safety and well-being of the patients as topmost priority, those who may already be living a compromised life due to their debilitating disease condition(s).

Planned and approved document on Safety crisis management is indispensable to prevent/minimize harm, if at all the safety crisis is witnessed in the post-marketing scenario. This is because a large number of patients will likely be exposed to therapy after marketing as compared to those in clinical trials**.**

With the number of regulations coming up at a global level, compliance to each marketing region becomes a challenge as it is essential to have dedicated resources, both human and technological, to keep an eye on the most recent updates on pharmacovigilance norms.

Eventually, it is **'their baby**' budding after immense research and development, of course for a worthy cause of innovation and treatment of the diseased population.

The pharmaceutical and biotechnology companies must be aware of the latest changes esp. those applicable to their sector or for which a major shift is demanded to suit the dynamics of regulatory environment. In addition to this, patient perspective also justifies sensitization to safety monitoring goals.

Signal management holds significant concern in pharmacovigilance and has its own set of predefined processes and timelines of information exchange between the responsible parties. Identifying a Signal and its subsequent management requires team work as well as coordination from predominant stakeholders i.e., marketing authorization holders (MAHs), National competent authorities, Agency and Pharmacovigilance Risk Assessment Committee.

Previous white paper (Concise Signal Management & Quality database: A prerequisite to Signal detection) discussed concise signal management and contribution of health care professionals and consumers to generating a quality database.

Objectives of this white paper are to elaborate on role of MAH and Regulatory Authority in Signal management. Regulatory here refers to European medicines Agency (EMA), the National Competent Authorities (NCAs) and the Pharmacovigilance Risk Assessment Committee (PRAC)

ISSUES DEMANDING ATTENTION!

Emerging safety issues should be documented and proactively informed to the Agency, in case it poses significant threat to the community or alters the risk benefit profile alarmingly.

Emerging safety issues may be:

- signal of a potential serious adverse event (i.e., signal of a significant fetal abnormality),
- major safety issues as an outcome of a planned non-clinical and/or post authorization study,
- Immediate safety concern(s) from a newly detected signal or new ICSR registered which poses threat to public health or needs urgent attention for safety recall/recommendations etc.

This implies that **a signal** may also qualify as a potential safety concern to be communicated to the Authority as an Emerging safety issue.

1. Marketing Authorization Holder(s): The Active 'Signal Monitors'?

There are all possibilities that even a single well-documented case report can be viewed as a signal, especially if the report describes a positive re-challenge or if the event is extremely rare in the absence of drug use.

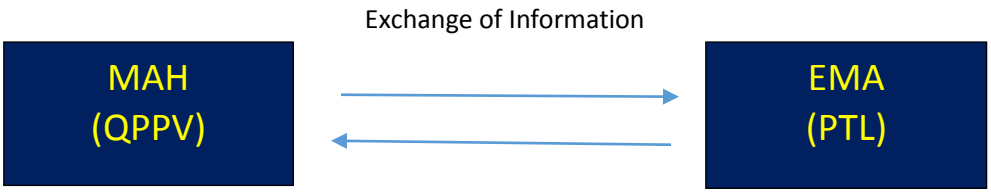
However, Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. Guidance document of FDA emphasizes follow-ups of serious adverse events, esp. those that are unlabeled.

The applicable legal requirements state that the Eudravigilance database shall be monitored by the MAH, at least once in a month. However, the frequency of monitoring can vary depending on various factors like identified risk, potential risk and need for additional information.

As stated in the Good Pharmacovigilance Practices Module VI: Management and reporting of adverse reactions to medicinal products, safety issues which do not qualify as valid individual case safety reports (ICSRs) but still carry crucial information to be communicated to authorities need documentation as **emerging safety issues**.

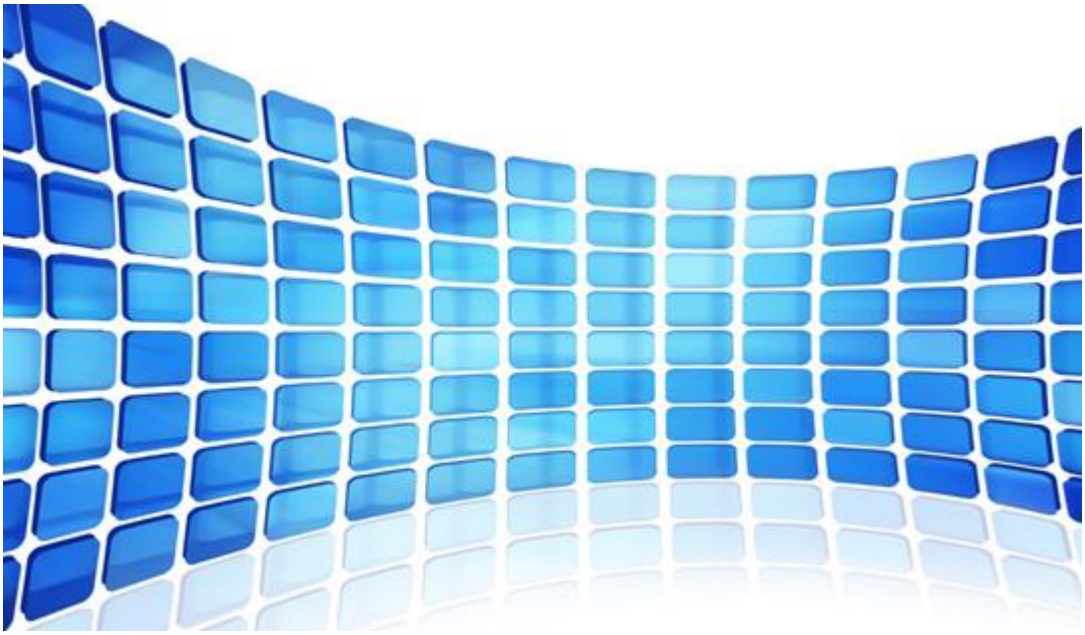
Two-way communication can be channelized if there are dedicated human resources in a robust pharmacovigilance system.

Figure 1: Responsible personnel for exchange of information



The MAH should assign a **Qualified Person for Pharmacovigilance** (QPPV) for products authorized in the EU or its respective member states. Likewise, European Medicines Agency's (EMA) **Product team leader** (PTL) is assigned for centrally authorized products in case the MAH has any questions regarding specific signal.

1.1 Signal Management: A shared domain



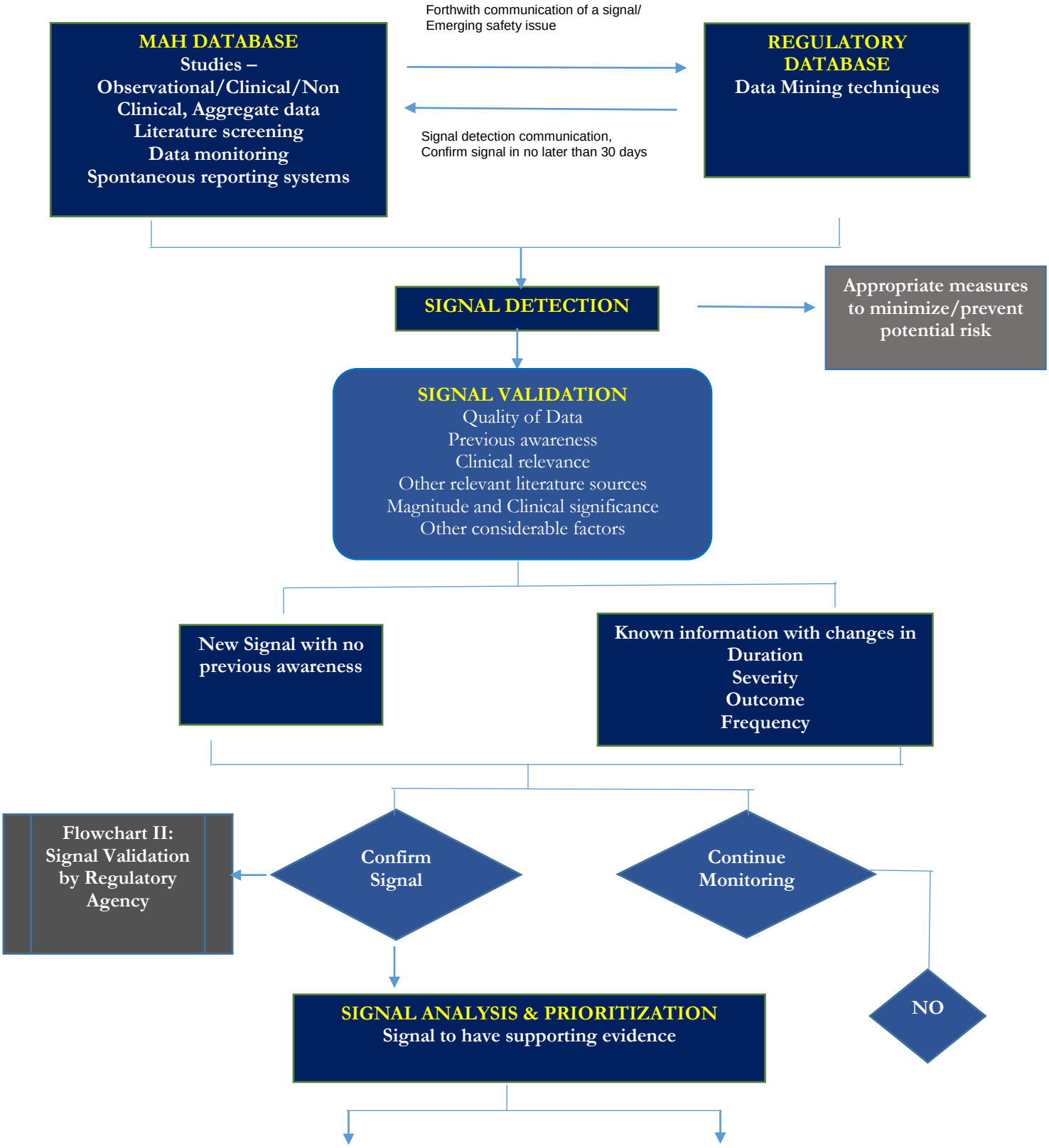
After detecting a probable signal, its validation by MAH is a verification step in concluding that a safety signal could be a potential health threat. In a nutshell, it is validating an identified signal with further support evidence and excluding all the cases of likelihood of event occurrence due to other factors such as co-morbidity, concomitant medications or progressive illness i.e., evaluating and excluding the likelihood that the event is a result of confounding factors.

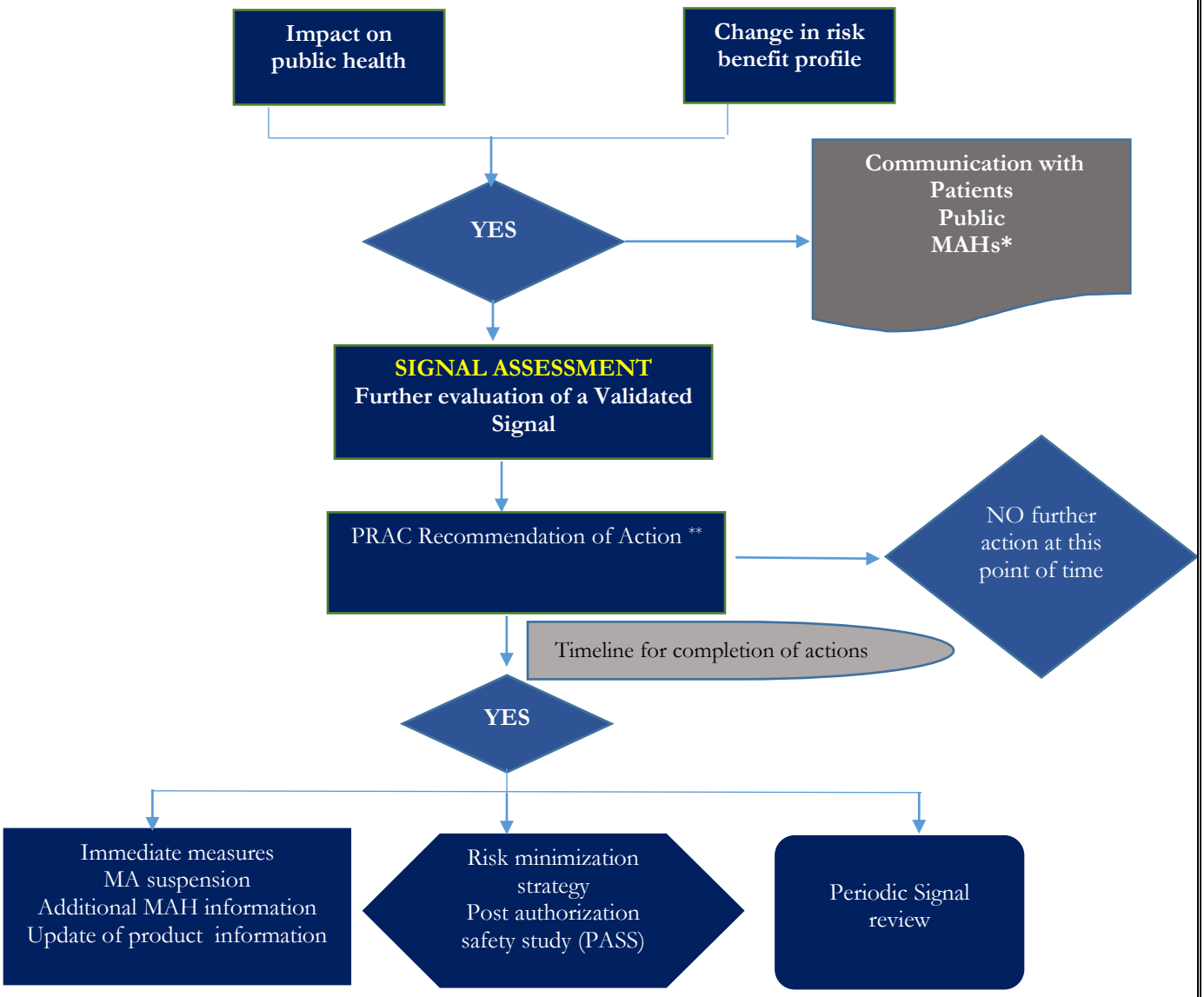
Signal management comprises number of key processes and is a shared domain of the MAHs and the Regulatory. The following flow chart specifically mentions key operational steps involved in the process. It also highlights the intermittent processes that may precede or overlap in order to take immediate measures or for appropriate reasons of priority.

If a signal is being monitored, but has not been validated, it may be useful to describe this in periodic safety update reports (PSURs) and risk management plan (RMP) updates, where applicable

- Pharmaceutical Information and Pharmacovigilance Association (PIPA) guidelines on Signal management

Flow Chart I: Procedural segregation in Signal Management process





NOTE:

* Communication with MAHs is done by the Regulatory Agency when the signal is validated by Regulatory authority

** Other actions may be recommended by CHMP or CMDh for CAP or NAP respectively

1.2 Potential pharmacovigilance risk: Monitoring key updates

Marketing authorization holders should keep an eye on the Regulatory updates on EMA website

- Confirmed signals
- Product information updates
- PRAC Minutes of meeting
- Comply to PRAC recommendations in stipulated timeline

The following are the critical areas for pro-active monitoring by MAH:

- EMA's website for all the confirmed signals listed in the agenda of PRAC after each meeting, usually the day for publishing being Monday.
- A vigilant monitoring is legally mandated for all updates on product information on EMA website including the meeting minutes of PRAC and other information from the concerned Member states.
- Compliance to variations asked in the recommendations of PRAC, *the timeline for which starts from the direct communication date of regulatory authority or date of PRAC recommendation publication on website, whichever is first*.

Alert: Here, though the term 'recommendation' is referred to, it is a legal requirement for compliance by MAH and not a voluntary one.

2. Safety Signal Processing through Regulatory Eye

The EMA considers all signals of active substance, irrespective of its strength or indication or route of administration. The procedural guidelines are bifurcated as for centrally authorized product (CAP) or nationally authorized product (NAP)

The confirmed signals will be transmitted to database of PRAC for signal prioritization and recommendations. Meeting recommendations include update of the product, additional data submission, urgent safety precautions, conduct of additional studies etc.

One such study recommended by Regulatory Authority aimed to evaluate use of Phosphodiesterase type 5 inhibitors and an enhanced risk to developing Non-arteritic Anterior Ischemic Optic Neuropathy (NAION). The study was requested on receipt of a number of reports of NAION by the Regulatory after marketing of PDE5 inhibitors and is likely to complete in the current year (2015).

2.1 Significant Timelines for exchange of information

- MAH to submit requested data in 60 days
- Regulatory recommendations released after 60 days
- Regulatory recommendations released after 30 days in urgency

Though the timeline for submission of data requested may vary depending on the seriousness criteria, voluminous data or the risk benefit profile, it is usually 60 days. It is subject to variation on a case to case basis.

The PRAC starts its signal assessment (of additional data) process 2 days later of the submission deadline and gives its recommendations at the end of 60 or 30 days, latter so in case of urgency of a signal. A comprehensive list of questions and answers on signal management, published by the agency provides timelines for reporting as well as for getting response.

The Regulatory authority (Agency) has a range of activities to perform for the Signal management as listed in the Table below, including but not limited to:

Table 1: Responsibilities of Agency pertaining to Signal Management

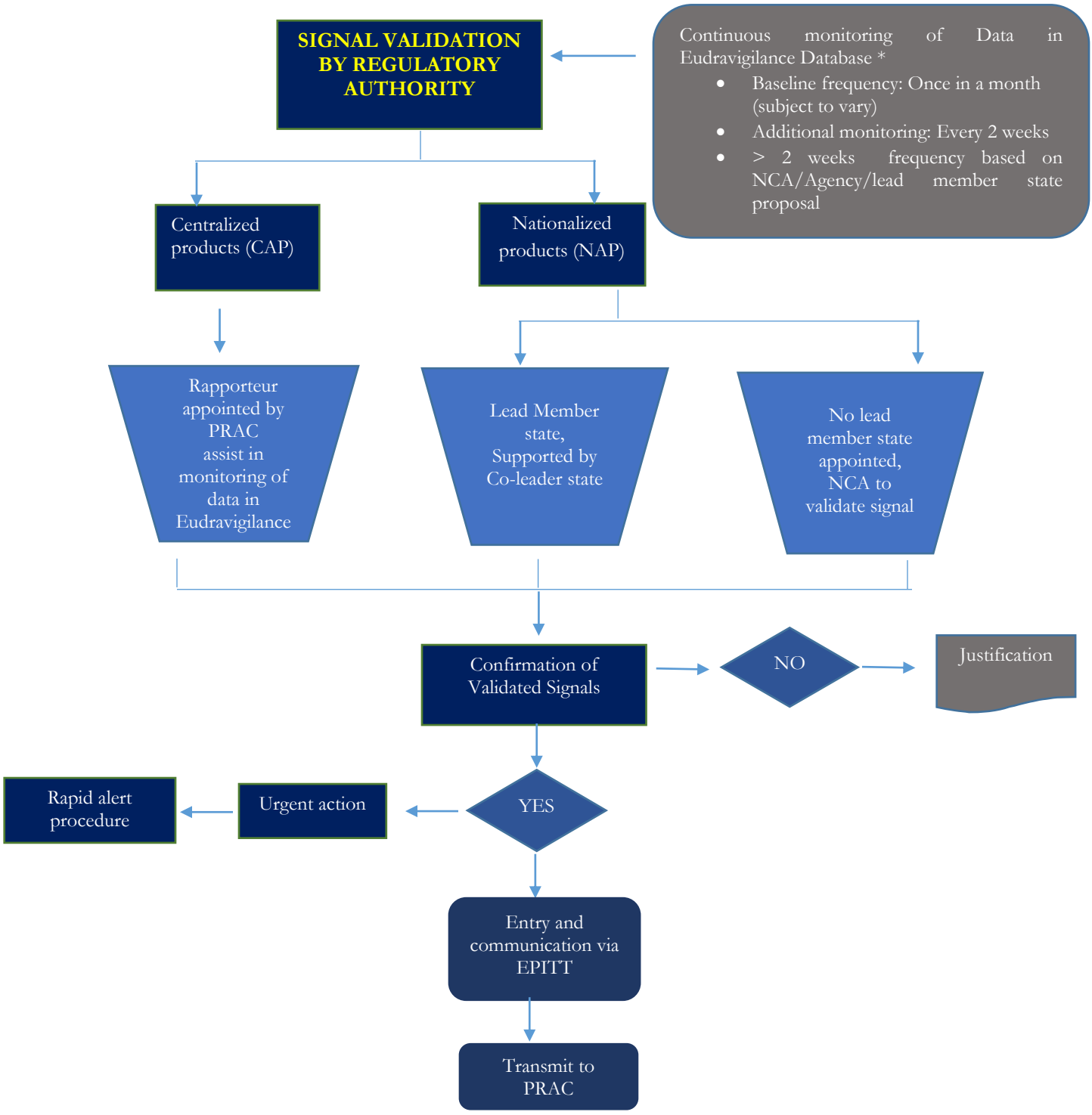
Monitoring the Eudravigilance database
Coordination with MAH or other MS or NCA for any query pertaining to signal management
Applying statistical tools for signal detection methods
Thorough documentation on signal detection activity and statistical reports generated
Maintaining and updating Eudravigilance Pharmacovigilance Issues tracking tool (EPITT) to enter a validated signal
Confirmation of a validated signal communicated by MAH (in NMT 30 days)
Signal transmission to PRAC for analysis and prioritization
Audit trail of its signal detection activities

2.2 Regulatory procedure for Signal Validation

Signal validation activity is carried out by the Regulatory Agency, if the signal is detected from the Eudravigilance database.

Signal validation by EMEA is followed by a cascade of procedures depending on whether it is a Central authorized product (CAP) or a National authorized product (NAP). The flow chart below lists out the regulatory procedures for validation and confirmation of a Signal.

Flow Chart II: Signal Validation by Regulatory Authority



NOTE: * All the processes can be efficiently performed through IT intervention

3. Technology enabled Regulatory adherence to Quality Systems by MAH

Ever pondered how data and documentation activities can be adequately addressed! The most convenient way is a simplistic yet pragmatic solution that suffices your needs.

In accordance to Signal management guideline, the systems are to be well-defined and that MAH may be requested to produce evidence/documents for the quality system activities as a matter of compliance.

Till now, our talk was focused on 'What' should be done. But, which are the viable options and answers to '**How**' it should be done?

Figure 2: Quality systems elements for Regulatory compliance via technology solutions

- All Signal activities recorded including customized line listings and quantitative detection and qualitative analysis
- Queries, responses, follow-ups and other correspondences can be tracked
- Data lock (read only option) and restricted access at individual User level
- Transparent auditing due to legible, precise data entry and system validation checks
- Secure storage of data, reliable data entry and transfer to other parties
- Audit trail of all Safety signal activities

All the listed quality system elements (Figure 2) can be complied using a favorable technology solution. Signal management activity by MAH, esp. signal detection and validation mandates technological intervention to take immediate safety precautions.

PvNET is a user friendly application fine-tuned to perform 'Signal' management processes and comprises all of the quality systems entailed by the guidance document.

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ABOUT Sarjen Systems:

Sarjen, a "**Business Technology**" company, has been providing "Information Technology" solutions to diverse industries to suit their business needs. Sarjen provides solutions and services across several industries including pharmaceutical and healthcare research with exposure to regulatory guidelines.

Armed with technical expertise, domain knowledge and project management skills, Sarjen has developed custom applications (Finance and Wealth management). Sarjen boasts knowledge of global pharma, life sciences regulatory requirements, regulatory trends & updates... offers consulting, implementation and regulatory services.

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