

THE POST-MARKET PRIORITY

Understanding and Meeting Demand for Effective Post-Market Clinical Follow-Up

Introduction

In his recent paper, "Basic Anatomy of a Design Dossier," Dr. Hamish Forster, orthopedic and dental product expert for BSI Healthcare, provides an overview of the key elements required within technical documentation to demonstrate conformity to the Medical Device Directive 93/42/EEC. One such component is the requirements for a post-market surveillance (PMS) report.

As stated by Forster, "Post-market surveillance data may be provided for devices already marketed in the EEA and/or other geographical territories. A postmarket surveillance plan should also be provided specific to the device under review. A post-market clinical follow up (PMCF) study is expected as part of this plan. The elements of the post-market surveillance plan can be provided within the executive summary along with a brief description of the PMCF study. There should be an adequate rationale if a PMCF study is deemed unnecessary."

He continues, "It is recommended to detail how often key documentation used to demonstrate conformity to the Essential Requirements will be updated in response to information gained during post-market surveillance."¹ Following the publication of Forster's paper, revisions to the guidance documents regarding PMCF were made, and, as the recent revisions represent a larger shift in the medical device manufacturing community, it is beneficial to expand on his overview of post-market clinical planning and data as a critical part of the design dossier and/or technical documentation of a device.

Overview of Guidance Document Scope and Revisions

The revisions to the PMCF guidance document (MEDDEV 2.12-2, REV. 2) are reflective of an emphasis on long-term clinical data, articulating the importance of the details and documentation required for post-market clinical studies as a part of an appropriate PMCF plan. The new document is in accordance with the Global Harmonization Task Force (GHTF) and was driven by initiatives of European Union (EU) legislation. The document provides guidelines and support for the creation of risk-based PMS plans in accordance with existing guidance documents and ISO standards relevant to clinical data plans, analysis, and final reporting. It also provides details on the role of Notified Bodies in PMCF.²

With a more comprehensive understanding of these revisions, manufacturers can work more efficiently and seamlessly with Notified Bodies in the review/audit process and plan and execute the PMCF plan, as well as overall post-market surveillance.

It is important to note that PMCF plans, and the guidelines that inform them, are not only relevant for high-risk devices, but may also apply to a device of any class that is affected by defined parameters that contribute to residual risk – which is the primary type of risk addressed in the post-market phase. **Residual risk** is risk that remains after risk control measures have been taken (i.e. during the pre-market phase), including known or emerging risks, or potential risks due to statistical limitations.² MEDDEV 2.12-2, REV.2 outlines specific circumstances that contribute to residual risk.

As provided by the MEDDEV 2.12-2,REV.2, the circumstances under which PMCF may be necessary are as follows:

- Innovation: the device's design, materials, substances, principles of operation, technology or medical indications are novel
- Significant changes to the product or to its intended use for which pre-market clinical evaluation and re-certification has been completed
- High product-related risk
- High-risk anatomical locations
- High-risk target populations (e.g., children, elderly)
- Severity of disease/treatment challenges
- Questions of ability to generalize clinical investigation results
- Unanswered questions of long-term safety and performance
- Results from any previous clinical investigation, including adverse events
- Results from post-market surveillance activities
- Identification of previously unstudied subpopulations which may exhibit different benefit/risk-ratio (i.e., hip implants in different ethnic populations)
- Continued validation in cases of discrepancy between reasonable pre-market follow-up time scales and the expected life of the product
- Risks identified from the literature for other data sources of similar marketed devices
- Interaction with other medical products or treatments
- Verification of safety and performance of device when exposed to a larger and more varied population of clinical users
- Emergence of new information on safety or performance
- Where CE Marking was based on equivalence (i.e., circumstances whereby the manufacturer demonstrated conformity to the relevant essential requirements by means of substantial equivalence to similar devices, and no long-term clinical safety and performance data on the device itself was provided for its indications prior to CE Marking)

While this list is not all-inclusive, registered Notified Bodies are equipped to assess manufacturers' PMCF plans, their proposed execution, as well as the assessment of a manufacturer's justifications that a PMCF is not necessary.

Also as defined in the guidance document, PMCF plans should detail the following:

- Patient population
- Inclusion/exclusion criteria
- Controls
- Selection of sites and investigators
- Endpoints and statistical considerations
- Number of subjects
- Duration of study
- Data to be collected
- Study endpoints
- Analysis plan, including interim reporting
- Procedures/criteria for early study termination.

PMCF studies may include extended follow up of patients involved in pre-market studies, new clinical investigations, or a review of relevant retrospective data from patients previously exposed to the device.

Elements of a PMCF studies include:

- Clearly stated objective(s)
- Scientifically sound design with appropriate rationale and statistical analysis plan
- Study plan
- Implementation of the study according to the plan, an analysis of the data and appropriate conclusion(s)²

Arguably, the requirements for PMCF studies do not differ greatly from those of other pre-market clinical study plans. While a PMCF study must demonstrate the clinical safety and performance of a device through its lifetime – for its intended use – and exhibit its performance to a broad spectrum of physicians and patients, it does not have to include randomization, excessive patient selection criteria, or control groups.

Balancing PMS and PMCF Data Guidelines

MEDDEV 2.12-2, REV. 2, in support of the MDD 93/42/EEC, and taking into consideration the amendments made by Directive 2007/47/EC, aims to create a manufacturing and clinical environment that better supports long-term safety and performance of medical devices through PMCF. But, if a manufacturer has existing long-term clinical data from the pre-market phase (whether through clinical investigation, literature search, market equivalence or another method), is PMCF still justified?

With regard to market equivalence, the European system has designated that if a device has gained CE Marking based on equivalency (even if the equivalent devices have long-term data that demonstrates their safety and performance) – PMCF will likely be required.

As a rule, if the manufacturer has provided long-term clinical data that demonstrates state-of-the-art safety and performance for its intended use, PMCF may not be necessary. In these cases, the purpose of the PMCF has already been met.

To help manufacturers determine when pre-market data is not sufficient to fulfill the purpose of PMCF, MEDDEV 2.12, REV.2 outlines the “limitations in the clinical data available in the pre-market phase,” including:

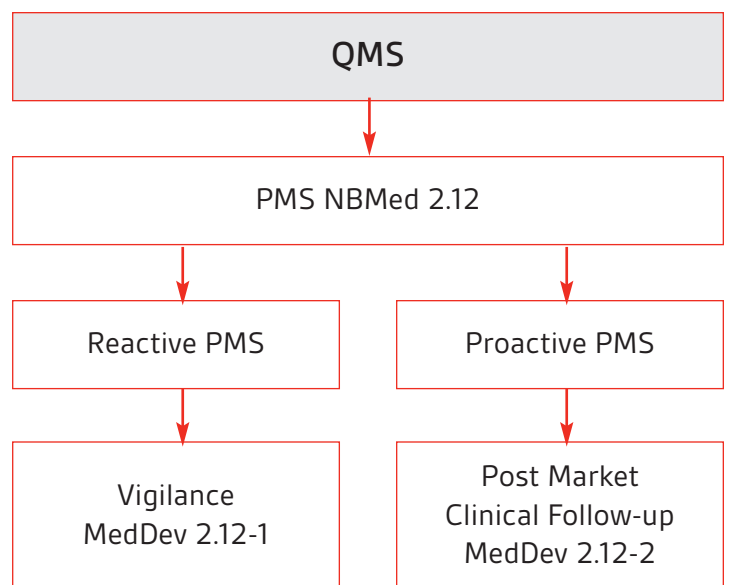
- Number of subjects
- Narrow population
- Relative homogeneity of subjects and investigators
- Control of variables vs. full range of conditions encountered in general medical practice

And the guidelines further suggest that “complete characterization of all risks may not always be possible or practical in the pre-market phase.”

It may also be prudent for manufacturers to ask themselves the following questions, helping guide the justification for either conducting or foregoing PMCF:

- Does pre-market clinical data reveal any unanswered questions about safety or performance?
- Did any adverse events occur that warrant further investigation?
- Was pre-market clinical data improperly generalized?
- Does the lifespan of your device extend beyond the time frame that pre-market clinical data was collected?
- Has new information emerged that affects pre-market data?
- Has the use of the device been extended to populations that were not included in clinical trials?
- Has the product been altered in any way from the product that was used to gather pre-market clinical data?

It's important to remember that long-term data derived from PMCF is only one aspect of post-market surveillance and there are additional elements that must be fulfilled. No matter the particular device or PMCF plan, manufacturers still need to perform the more reactive post-marketing activities such as complaint handling, vigilance reporting, and monitoring the clinical literature and clinical databases.



Overview of Additional Guidance Documents Informing PMCF

The guidance in MEDDEV 2.12-2, REV.2 are further supported and supplemented by additional guidance documents and ISO standards that provide direction for obtaining relevant, long-term data from any clinical investigation (whether a part of pre- or post-market plans). Among these guidelines are common factors and priorities that guide the competency of clinical studies and help determine if clinical data is substantive and robust.

ISO 14155:2011 is referenced as a basis for clinical studies in MEDDEV 2.12-2, REV. 2. The standard defines good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.

ISO 14155:2011 specifies general requirements intended to protect the rights, safety and well-being of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices. The principles set forth in ISO 14155:2011 apply to all clinical investigations and should be followed as accurately as possible, depending on the nature of the clinical investigation and the requirements of national regulations.

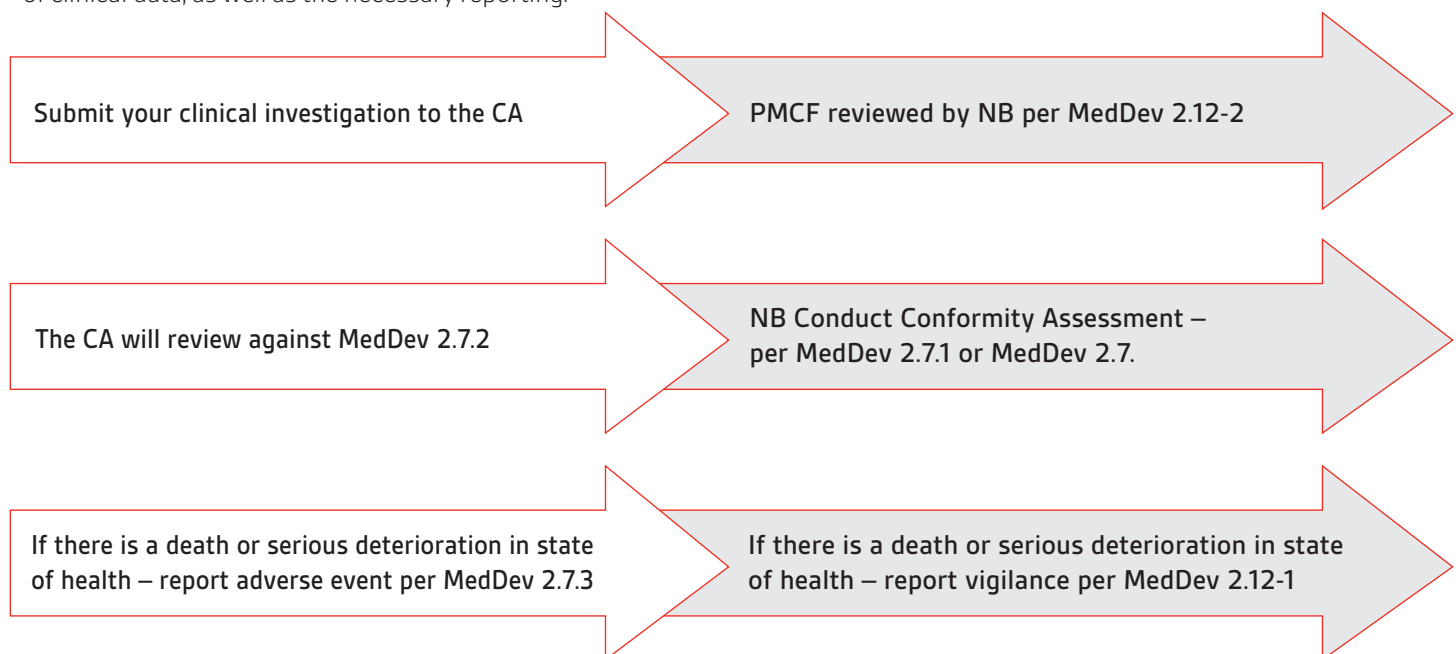
- MEDDEV 2.7.1, REV. 3 outlines the stages of clinical evaluations, the general principles of a thorough, objective and ethical clinical evaluation, the sources of data, appraisal and analysis of clinical data, as well as the necessary reporting.

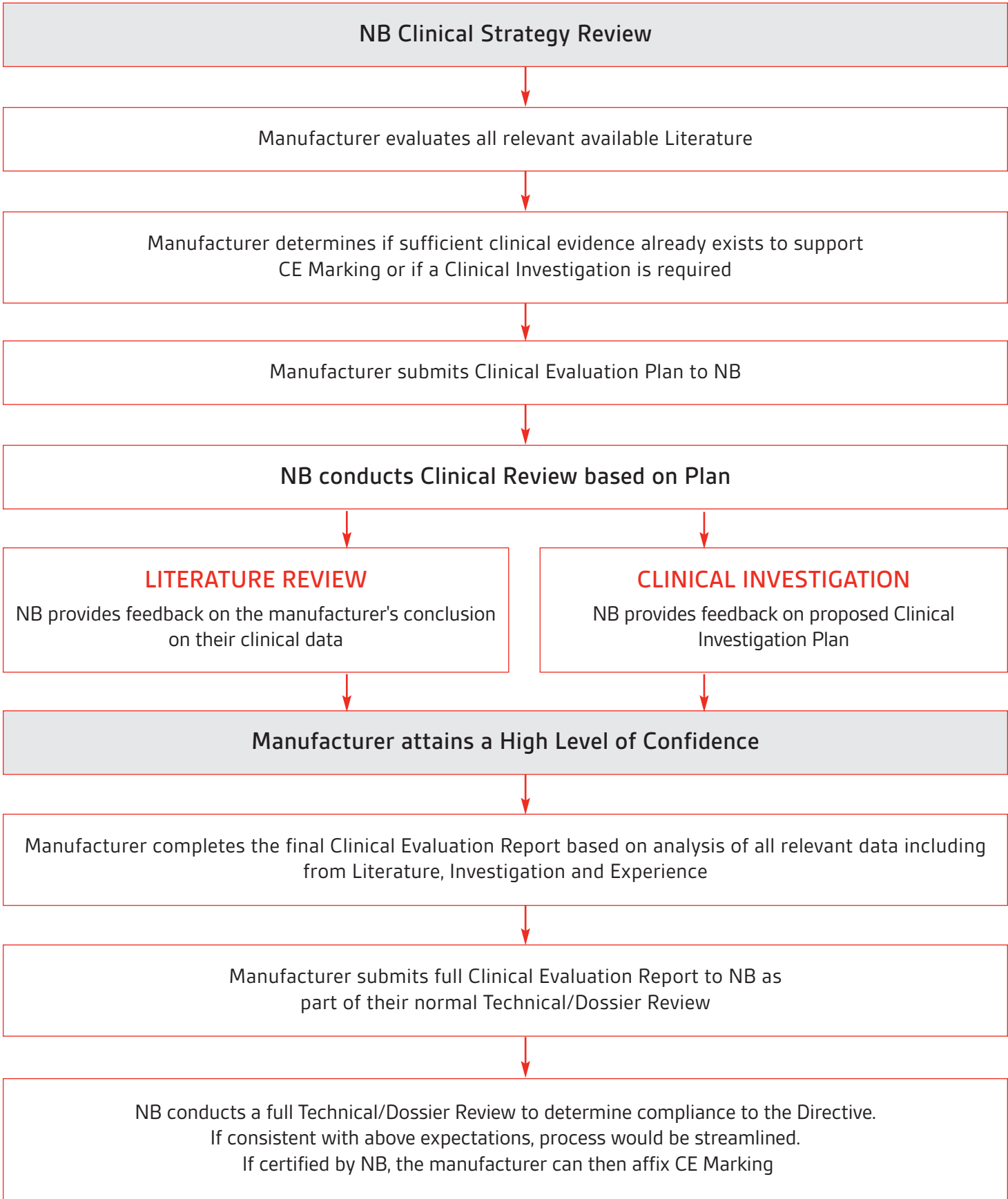
Appropriately conducted clinical evaluations include:

- Appraisal of individual data sets and suitability and contribution of results to demonstration of performance and safety
- Analysis of relevant data to assess strength of overall evidence and derive conclusions about performance and safety
- Compliance with relevant essential requirements⁴

- With regard to good clinical practice, MEDDEV 2.7.4, updated in late 2010, focuses namely on pre-market clinical investigations, but provides relevant best practices for any clinical investigation. In terms of investigation design, the guidelines emphasize that studies are able to capture clinical data relevant to issues such as clinical performance, safety and side effects, and residual risk elements – which is especially pertinent to PMCF investigations. The document provides general parameters to which clinical investigations must conform:

- An investigation must be part of a larger clinical evaluation process (e.g., post-market surveillance)
- Adequate risk management procedures should be in place
- Legal and regulatory compliance must be ensured
- Investigation design should be appropriate
- Adherence to all relevant ethical principles⁵





Maximizing the Support of a Notified Body

Given the presence of several interacting and authoritative guidance documents and standards – all of which create a set of larger, more comprehensive guiding principles for PMCF – a good working relationship between the manufacturer and the Notified Body is essential. A positive and communicative partnership promotes the successful and efficient creation and execution of a PMCF plan that results in compliance with all Essential Requirements.

According to MEDDEV 2.12-2, REV. 2, the role of a Notified Body in PMCF is to “review the appropriateness of the manufacturer’s general post-market surveillance procedures and plans, including plans for PMCF, as relevant.” This responsibility includes all of the guidelines in MEDDEV 2.12-2, REV. 2, as well as any other relevant presiding documents and/or standards.

When working with Notified Bodies to review a PMCF plan, the process is most efficient and beneficial to manufacturers when it’s initiated during the early stages of development. At this time, manufacturers can present and revise ideas for the PMCF, and Notified Bodies can challenge any elements that will not stand up to scrutiny.

In addition to submitting the PMCF plan, an experienced and knowledgeable Notified Body will work with manufacturers and provide reasons why a plan does not meet requirements.

Common examples of problem areas include:

- Insufficient clinical measures (e.g., assessment time intervals and overall duration, assessed outcome measures)
- Insufficient patient enrollment numbers, which should account for potential loss to follow-up over the study duration
- Covering all indications
- Covering all devices related to the design dossier or technical Documentation

Manufacturers should maximize the expertise of registered Notified Bodies so that the review process is not hindered. Working early and maintaining consistent communication with a Notified Body will help ensure that any necessary changes can be made in a timely manner.

A Global Shift: The Need for PMCF Data

The purpose of any medical device is to make significant improvements to patients’ quality of life. Manufacturers are facing increasing pressures to provide detailed technical documentation of clinical data – beyond pre-market findings – that demonstrate continued safe, effective use and support any and all of a device’s claims and indications.

The emphasis in legislation on post-market clinical data is becoming increasingly more prevalent. The revisions to MEDDEV 2.12-2 are indicative of the laws that currently govern EU requirements, and there are continued legislative efforts to make PMCF and post-market surveillance an even more authoritative presence within the law.

A good example of the need for this focus is seen by evaluating real-market situations. After recent complications with PIP breast implants, the EU Commission urged member states to tighten controls, increase surveillance, and restore full confidence in the EU CE Marking regulatory system.

The Commission proposed the following:

- Verify the designations of Notified Bodies to ensure that they are designated only for the assessment of medical devices and technologies that correspond to their proven expertise and competence.
- Ensure that all Notified Bodies in the context of the conformity assessment make full use of their powers given to them under the current legislation which including the powers to conduct unannounced inspections.
- Reinforce market surveillance by national authorities, in particular spot checks in respect of certain types of devices.
- Improve the functioning of the vigilance system for medical devices for example by giving systematic access for notified bodies to reports of adverse events; encouraging healthcare professionals and empowering patients to report adverse events; enhanced coordination in analyzing reported incidents in order to pool expertise and speed up necessary corrective actions.
- Support the development of tools ensuring the traceability of medical devices as well as their long-term monitoring in terms of safety and performance, such as Unique Device Identification systems and implant registers.⁶

These objectives, however, are not isolated to the EU. At the start of this year, the Center for Devices and Radiological Health (under USFDA jurisdiction) released its 2012 strategic priorities, the first of which emphasizes the complete implementation of a “total product lifecycle approach” and includes the following post-market goals:

- Develop a comprehensive strategy to assess real-world device performance.
- Post a proposed strategy (online) to assess real world device performance and seek public input.
- Develop a comprehensive framework for the timely evaluation and management of significant post-market signals.⁷ This market-wide shift, particularly as it is proposed in the U.S., aims at providing more transparency for the medical community and patients, and importantly, works toward a better guarantee of long-term safety and performance.

In addition to the broad commitment to better deliver on the promise of long-term safety and efficacy, industry trends have contributed to the need for a greater emphasis on PMCF. With a global economic downturn that has shaped commerce over the last three years, medical device manufacturers (much like those in other industries) have made a strong commitment to investing in new technology and research and development in order to overcome financial challenges. Innovation means more efficient and economical devices, but it also presents manufacturing and implementation challenges.

The continued development of these highly innovative medical devices, while positive for the industry, patient and global community, creates an even greater need for clinical data (especially in the post-market phase). Government regulators, Notified Bodies and manufacturers alike are realizing the importance of this long-term clinical data to not only the well-being of patients, but to continue the development and manufacture of innovative, effective, affordable and life-changing medical devices.

With these ever-growing challenges and demands for innovation, manufacturers benefit even further from the support of Notified Bodies who – through their feedback and knowledge of MDD requirements – help balance the need for long-term clinical data with innovation.

Translating the Value of Clinical Data

The value of clinical data extends beyond compliance and the foremost benefit of identifying and eliminating any residual risk to patients. Long-term clinical data can also translate into economic value for medical device manufacturers: Having robust clinical data for a medical device is an excellent marketing tool that can drive sales and payer reimbursement.

Moreover, with a global legislative shift that is directing the need for a particular emphasis on PMCF requirements – as well as the benefits of partnering with an experienced and well resourced registered Notified Body in the assessment of such plans – manufacturers, physicians and patients stand to benefit greatly from strict compliance to EU Essential Requirements and a long-term commitment to post-market surveillance.

¹Forster, H. (2011). “Basic Anatomy of a Design Dossier.” BONEZONE.

²NB-MED. MEDDEV 2.12-2, REV. 2. (2012)

³International Organization for Standardization. ISO 14155:2011. (2011)

⁴NB-MED. MEDDEV 2.7.1, REV. 3. (2009)

⁵NB-MED. MEDDEV 2.7.4. (2010)

⁶European Health and Consumer Policy Commission. (2012, February 9). Medical devices: European Commission calls for immediate actions - tighten controls, increase surveillance, restore confidence [Press Release]. Retrieved from www.europa.eu

⁷U.S. Food and Drug Administration. (2012). CDRH 2012 Strategic Priorities. Retrieved from www.fda.gov

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BSI is a trusted partner to industry and government with a focus to support their business objectives through the transfer of knowledge of best practices, assurance services to identify and measure performance indicators, training services to aid the building of organizational competency and enable continuous improvement, and the tools to monitor, enhance and report on compliance against the customer's management system objectives.

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