Inside the EU's Next Generation of Pharmacovigilance

New legislation will promote the safe and effective use of human medicines.

Europe is redefining the practice of pharmacovigilance. New legislation that takes effect across the European Union (EU) in July 2012 promises to be the biggest change to the regulation of human medicines in the EU since 1995. The legislation aims for greater patient safety by—amongst other measures—managing risk proactively and proportionately, avoiding unnecessary administrative burden, and providing for a stronger link between safety assessments and regulatory action. It is designed to detect new safety signals and to detect them as early after marketing approval as possible.

At its core, the objective of the forthcoming legislation is to promote and protect public health. The European Commission projects a savings of up to 5,910 lives per year across the EU, and savings to society of up to €2.4 billion per year, due to more timely, more complete, and more effective pharmacovigilance.

The new pharmacovigilance (PV) legislation has significant implications for applicants and holders of EU marketing authorizations. The legislation applies directly to the European Economic Area (EEA)—the 27 EU member states plus Iceland, Norway, and Liechtenstein. And because Marketing Authorization Holders, or MAHs, as pharma firms are known in EU parlance, typically operate on a global basis, EU regulatory changes will have ripple effects in other jurisdictions.

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> **Starting in July 2012, MAHs may also need to report all suspected non-serious adverse reactions that occur within the EEA.**

Many pharma firms that operate in the EEA are focusing on what can seem to be a daunting list of new requirements for the expedited reporting of adverse reactions in the post-approval setting.

MAHs already report all suspected serious drug adverse reactions that occur both inside and outside the EEA, but expedited reporting requirements will change. Starting in July 2012, MAHs may also need to report all suspected non-serious adverse reactions that occur within the EEA.

"Many good things are coming in July 2012," said Sonia Araujo, London-based Manager of Product Management for Medidata Solutions Worldwide. "We are moving in the right direction with this legislation, moving in the direction of saving lives. There is some confusion in the industry because people don't realize that this is incremental change with clear transitional provisions. This new legislation can be a net benefit for MAHs as well as for patients, healthcare professionals and the European Medicines Agency (EMA)."

The Need for Change

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem, according to the World Health Organization (WHO). The EMA uses the WHO definition to guide its own activities, both in terms of existing pharmacovigilance legislation and the new provisions.

The package that is broadly referred to as "new PV legislation" includes two separate items—an amended regulation and an amended directive. Regulation (EU) No. 1235/2010 amends existing Regulation (EC) No. 726/2004. The new provisions come in effect on July 2, 2012 with immediate legal force throughout the EU. Directive 2010/84/EU amends existing Directive 2001/83/EC that established the community code relating to medicinal products for human use. The new provisions come into effect on July 21, 2012, but must be adopted by each member state.

The new legislation will be supported by a new set of guidelines for the conduct of pharmacovigilance in the EU. As these new good pharmacovigilance practices (GVP) modules are developed, they will replace the existing pharmacovigilance provisions found in Volume 9A of the Rules Governing Medicinal Products in the EU.

Peter Arlett, Head of Pharmacovigilance and Risk Management for the EMA, said the new provisions have their roots in an assessment of the existing pharmacovigilance system that was launched by the European Commission in 2003. While the investigation concluded that the then-current pharmacovigilance framework was functional, it needed improvements. The focus was on the reporting of adverse drug events. There was insufficient emphasis

on the scientific basis for adverse events and little integration of an assessment of the risks and benefits associated with medicines and the adverse drug reactions that were reported.

There was no systematic means to study the safety and efficacy of medicines that had already been approved. Some member states, most notably the United Kingdom, had a systematic program to assess the safety and efficacy of new agents as they were approved. New drug products approved for use in the UK typically carry a black triangle symbol on both professional and patient labeling to indicate an ongoing safety assessment. The EU did not have any similar program for post-approval evaluation of either safety or efficacy.

Objectives and Scope

The European Commission assessment led to a formal law making process in the Council and the European Parliament. Regulation (EU) No. 1235/2010 and Directive 2010/84/EU were published on December 31, 2010, for implementation 18 months later, in July 2012. The regulation, directive, and GVPs apply to all medicinal products authorized for marketing in the EU, whether the authorization is central (by the EMA) or at the national level (by a member state).

The high level objective of the new legislation is to promote and to protect the public health by reducing the burden of adverse drug reactions and optimizing the use of drug therapy, Arlett reminded a stakeholder meeting in late February. The intent is to provide

- Clear roles and responsibilities for robust and rapid EU decision making
- Engage patients and healthcare professionals
- Create a science-based framework that integrates benefits and risks
- Make regulation more risk-based and proportionate to the risks/benefits involved
- Increase proactivity and planning
- Reduce duplication and redundancy
- Increase transparency and provide better information on medicines

The scope of the changes ranges from a new and unified list of medicines approved for marketing in the EEA to greater encouragement of patients to report suspected adverse reactions, public hearings on pharmacovigilance, mandatory post-approval studies with sanctions for failure to comply and new fees for industry.

"The expected increased public participation and exposure is both brilliant and daunting," Araujo commented. Patients themselves will be able to report adverse drug reactions directly to national competent authorities through web portals, playing an active role in identifying adverse reaction patterns. Additionally, patients will be able to attend public hearings on medicines, and patient representatives will be included in the new

> **"The new provisions will likely affect industry and regulatory practices on a global basis."**

Impact of ADRs (adverse drug reactions) in the EU

- 5% of all hospital admissions are due to an ADR
- 5% of all hospital patients experience an ADR
- ADRs are the 5th most common cause of hospital death
- ADRs cause an estimated 197,000 deaths per year
- The total cost to society of ADRs is €79 billion

Source: European Commission, 2008

Pharmacovigilance and Risk Assessment Committee (PRAC).

In the context of her interaction with the industry, Araujo highlights the move to risk/benefit decision-making and the revised structure for expedited reporting as far-reaching changes to pharmacovigilance.

"The net effect is that drug makers must rethink, redesign, and redeploy the entire life cycle of drug products marketed in the EEA," Araujo continued. "The new provisions will likely affect industry and regulatory practices on a global basis. ICH (the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use) is almost certain to become involved as one of its three key constituencies rewrites its rule book. Pharmacovigilance is poised to become a key consideration starting with the very earliest phases of drug development, not an addendum that may appear sometime after marketing approval has been granted."

Implementation Practice

The new legislation comes into force in July 2012. That is not to say that it comes without hurdles. For example, final EMA guidance documents for all provisions will not be available at the time of implementation.

"We will be implementing some provisions before the guidance comes out," predicted Sue Rees, MSc, Head of Pharmacovigilance & Safety Risk Management and EU Qualified Person for Pharmacovigilance, Eisai Europe Ltd., during a webinar sponsored by *Applied Clinical Trials* in late 2011.

Rees' prediction seems safe. The EMA plans to issue a total of 16 guidance modules on good pharmacovigilance practices (GVP). Seven draft modules were published in February.

The EMA has assured the industry that these seven modules will be finalized before July, but has not committed to a firm publication date. The remaining nine modules will be published by the end of the year.

Arlett noted that the agency has very specific priorities in creating and publishing its guidances. The top priority goes to modules that guide activities directly contributing to public health, namely:

- Module I: pharmacovigilance systems and their quality systems
- Module II: pharmacovigilance system master file
- Module V: risk management systems

- Module VI: management and reporting of adverse reactions to medicinal products
- Module VII: periodic safety update reports
- Module VIII: post-authorization safety studies
- Module IX: signal management

Later modules will offer guidance on activities that will improve transparency and communication, followed by modules on activities that streamline processes.

"This is proactive pharmacovigilance," Arlett said. "It asks deliberate questions about safety, efficacy, the ratio of benefits and risks, and more rapid decision making. The new legislation strengthens the legal basis for regulators to impose studies on companies and therefore on their ability to follow up and ensure that companies comply."

Clear Transition Rules

The EMA recognized that it is not practical or even desirable to institute so many sweeping changes at one time. Nor could it afford to, due to budgetary cuts amidst the current European economic recession. Instead, the EMA opted to introduce changes on a staggered schedule, beginning in July 2012.

The agency accepted public comments on its 2011 concept paper and incorporated the results in the draft GVPs published in February 2012. The original concepts laid out by agency staff in 2011 are largely unchanged in the draft GVPs. While it cannot be known how the agency might act on public comments to the draft GVPs, it rarely shifts course without advance warning.

Pharma firms see themselves in a quandary. While MAHs know that change is coming in July, they do not and cannot know the precise direction or degree of change until the final GVPs are published.

But the quandary is less complex than it might appear. While all of the transitional details will not be known until just before implementation, the EMA has been very clear as to its intentions, directions and limits. The agency is unlikely to produce any major changes in its final GVPs.

Araujo said, "It is a tremendous stress on industry to learn about a thing one day and be ready to fall into place with it the next day. It helps to look forward to the ultimate goal and work backward through the transition."

Take expedited reporting. The ultimate goal will be to report on all suspected adverse reactions to the EMA's EudraVigilance database. The universe of reportable adverse reactions will include all suspected serious adverse reactions that occur worldwide within 15 days, and all suspected non-serious adverse reactions from inside the EEA within 90 days. All reporting is to be electronic (i.e., using the industry-standard E2B format). This ultimate legislative goal is expected to be in place no earlier than the second half of 2015—after EudraVigilance's new functionality is in place and has been inde-

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Post-Marketing Expedited Reporting by MAHs

for products authorized in the EEA

	Suspected Serious Adverse Reactions occuring in the EEA			Suspected Serious Adverse Reactions occuring outside the EEA			Suspected Non-Serious Adverse Reactions occuring in the EEA		
	To Whom	How	When	To Whom	How	When	To Whom	How	When
Currently	MAH-> MS where reaction occurred + Reference MS + Rapporteur MS	Electronically (E2B)	Within 15 days	MAH-> MS(s) where MP is authorized MAH -> EV	Electronically (E2B)	Within 15 days			
From July 2012 (Transitional Provisions)	MAH-> MS where reaction occurred	Electronically (E2B)	Within 15 days	MAH-> MS(s) where MP is authorized, if it requests serious reports* MAH -> EV	Electronically (E2B)	Within 15 days	MAH-> MS where reaction occurred, if it requests non-serious reports*	Electronically (E2B)	Within 90 days
Future (est. no earlier than Q3/Q4 2015)	MAH-> EV	Electronically (E2B)	Within 15 days	MAH-> EV	Electronically (E2B)	Within 15 days	MAH-> EV	Electronically (E2B)	Within 90 days

Key

EEA – European Economic Area (the 27 EU MSs + Iceland + Norway + Liechtenstein)

EMA – European Medicines Agency

EU – European Union

EV – EudraVigilance (EMA's reporting platform/database)

MAH – Marketing Authorization Holder

MP – Medicinal Product

MS – Member State (of the EU)

* - List of MSs who will require reporting not yet published; expected just before July 2012

pendently audited, and the EMA has given the industry six months' notice. Meanwhile, as of July 2012, the following transitional provisions will apply.

MAHs must report suspected serious reactions that occur within the EEA to the member state where the reaction occurred. There is no change in reporting by the member states compared to the current expedited reporting requirement, but MAHs will no longer have the requirement for multiple member state reporting.

If suspected serious adverse reactions occur outside the EEA, the MAH may generate either one or two reports. The MAH must report each reaction to EudraVigilance. The MAH must also report each reaction to the member

state(s) where the medicine is authorized—but only if the specific member state requests such reports. It is not yet known which member states will request them, but this transitional provision is likely to decrease the reporting burden for most MAHs.

If suspected non-serious adverse reactions occur inside the EEA, the MAH will generate one report to the state where the reaction occurred, if requested by the member state. Again, it is not yet known if any member states will request reporting of suspected non-serious adverse reactions. For those affected MAHs, this transitional provision will increase their reporting burden as non-serious adverse reactions are not currently reported in an expedited manner.

Throughout the transitional period, expedited reporting shall be done using E2B electronic reporting. Once a MAH has taken knowledge of the reaction, they have 15 days in which to report serious reactions and 90 days for non-serious reactions.

Global Challenges

While MAHs will be required to file expedited reports to fewer entities beginning in July 2012, their data collection burden could increase if they are requested to file expedited reports for suspected non-serious adverse reactions.

The challenge: many pharmas continue to rely on manual data collection using paper forms that are faxed to a central office to be assessed, collated, and digitized for reporting. Adding an unknown, but undoubtedly large number of suspected non-serious adverse reactions will only increase expedited reporting volume, stress, and the likelihood of missing reporting deadlines.

One solution: collect data electronically from the outset. That significantly reduces or eliminates the enormous costs associated with paper data collection and record storage as well as the associated personnel costs. Electronic data collection also helps to improve data integrity and audit performance. Electronic data collection gives companies more flexibility in meeting reporting requirements for other jurisdictions that have yet to match the new EU provisions.

Global scope is a baseline business requirement for successful pharma operations, but doing business globally also exposes companies to differences in reporting requirements and in basic terminology. ICH has made significant strides in harmonizing practices between the US, Japan, Europe, and other regions, but significant gaps still exist, and these span across pre-marketing and post-marketing settings.

Take causality in the context of clinical trials. In the EU and Japan, causality can be based on either facts or arguments supporting a cause and effect relationship between an event and a drug.

"In the US, facts and facts alone can establish a causal relationship," Araujo said.

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For more information contact Medidata Solutions:

79 Fifth Avenue, 8th Floor
New York, New York 10003
E-Mail: info@mdsol.com
Phone: 212-918-1800

There are equally significant differences in who has the last word on causality assessment in clinical trials across global jurisdictions, she continued. In the EU and in Japan, the trial investigator has the last word in determining causality. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided to a regulatory authority.

In the US, the sponsor has the final word. If the sponsor disagrees with the investigator's assessment and believes the event is "not related" to the drug, then the sponsor's assessment stands. However, if there is a EU component to the trial, both causality assessments will need to be reported. And one could say that, ethically, the sponsor should provide the full causality information to US investigators too.

Another area of potential confusion is medical terminology. Whilst MedDRA, the Medical Dictionary for Regulatory Activities, is commonly adopted for structured data in reporting, its usage varies by region. The EU uses lower level terms, or LLTs, in both pre-marketing and post-marketing reporting. Japan uses preferred terms, or PTs, for both situations. In the US, there is no requirement whatsoever for coding in pre-marketing reporting and only voluntary PT coding for post-marketing reporting.

"Whilst appropriate standard operating procedures (SOPs) can and should be in place at pharma organizations to deal with such interpretation and implementation regional differences," Araujo continued, "it leaves scope for further and future harmonization across the board. Having witnessed discussions with our global clients on such topics I, for one, look forward to that day."

An Unstoppable Force

"Pharma firms and software vendors have a pressing need to cooperate on electronic data collection," Araujo said. Pharma firms with any ambition to succeed in the global market must have the ability to collect all data required by any of the appropriate regulatory authorities. Firms must also have the ability to filter the data set and tailor final reports to meet the different requirements that seem likely to coexist across the EU, Japan, and the US for the immediate future.

Like the incremental introduction of GVPs themselves, a stepwise approach is the most practical way forward. MAHs can expect missteps and bumps in the road but the final goal is a practical improvement over the current situation.

"The only absolute certainty is that change is coming in July," Araujo concluded. "The negative consequences of doing nothing to prepare are far greater than the consequences of adapting proactively and adjusting your course as more GVPs are published and the full extent of the new PV legislation is made effective. The firms that accept change and prepare for it will emerge in a stronger competitive position."