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Pharmacovigilance in the European Union:

Keeping Your Products Compliant Before & After Approval

Webinar

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Speaker: **Elisabethann Wright, BL**, partner, Hogan Lovells International

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I would now like to introduce our speaker. Elisabethann Wright, BL, is a partner in the Brussels, Belgium office of Hogan Lovells International. Her experience is in the area of European law and includes both periods in private practice and periods working with international institutions. She focuses on European Union, EU, law relating to life sciences, with particular emphasis on pharmaceutical law, medical devices, food law and the environment.

This includes assisting clients in classification of their products, establishment of a pathway to authorization and marketing of their products in the EU, including related regulatory obligations, pharmacovigilance obligations, promotion and marketing of products, sales agreements, clinical trial agreements, adverse event reporting, product withdrawals and challenges to national authority and EU Institution decisions concerning classification and marketing of medicinal products and medical devices.

I will now turn the floor over to Ms. Wright.

Wright: Thank you very much, and welcome to everyone who's here to participate in this event.

Pharmacovigilance in the EU, it started off many years ago, and remember this, as a part, an important part, of the marketing authorization. It has now become a very important part, both pre- and post-authorization, of the procedures relating to medicinal product. It is a somewhat complex area, but it is

Wright (cont.): essential that all related obligations are fulfilled, because since the entry into force of the Penalties Regulation failure to comply with pharmacovigilance obligations can have substantial consequences for marketing authorization holders.

So, what, exactly, is pharmacovigilance? Well, essentially, it's the collection, detection, assessment, monitoring and prevention of adverse events and other incidents associated with medicinal products in the EU. The European Commission's website defines pharmacovigilance as the process and science of monitoring the risk of medicines and taking action to reduce the risks and increase the benefits of medicines. This is the important part. It's not just the risk. It's the benefit.

So, when you have developed your procedures, your postmarketing vigilance obligations, then you have to—you must develop a structure in which you can monitor the risk related to the product, the efficacy of the product, and, to some extent, how the product is being used off-label for benefit or, indeed, for risk. Now, that last is an issue of some confusion and risk for marketing authorization holders, because to promote your product off-label—in other words, to promote your product for a purpose for which either product hasn't been authorized, or for an authorized product for which the therapeutic indication being promoted is not authorized, well, that's a criminal offense in the EU.

So, you have an obligation to monitor, but you must be able to execute that obligation in a way that does not abuse your prohibition on off-label promotion, and that can create a certain level of heartburn within the process of marketing authorization. All marketing authorization holders, without exception, for medicinal products in the EU are required to conduct pharmacovigilance activities. This includes innovative products, all kinds, generics, biosimilars, everybody has essentially the same obligation.

So, what is the guidance? How do we find out what it is? Well, a basic guidance is the Directive 2001/83, commonly known as the Community Code of Medicinal Products. It is a basic legislation governing the authorization of medicinal products in the EU. Then there is Regulation 726/2004, commonly known as the EMA Regulation. Essentially, this regulation governs the grant of authorization for medicinal products within the centralized procedure.

And, obviously, because Directive 2001/83 is a directive this is a piece of EU legislation which, per the Treaty, lays down the aims to be achieved but leaves to the member state the manner in which that aim is to be achieved. This means essentially in practice that where we have a directive for member states, 28 member states, each member state must develop national legislation which brings the provisions of the directive into practical effect in that country.

Now, as guidance there is also—there is the EudraLex, commonly known as the Notice to Applicants. These volumes are huge volumes of documents prepared by the European Commission with very useful guidance on various aspects, including how to fulfill your pharmacovigilance obligations. Then there's the European Medicines Agency's Good Vigilance Practice Guidelines—again, helpful procedures, a little bit less clear, because they're more condensed. They are very focused on regulatory obligation and not on the practical steps to be taken to achieve them. So, they really must be read in conjunction with your legal obligations that are granted that are imposed on you by the Community Code and the EMA Regulation and other—the legislation within the EU.

So, what are your pharmacovigilance activities? Well, these include data collection, data management, data concerning the safety of the medicinal product; signal detection if there is new and emerging safety concerns; the obligation to evaluate data and to take decisions with regards to safety issues that may or may not be identified; and a benefit-risk analysis. Your product before it was granted authorization, part of the application was a benefit-risk analysis. It is an ongoing procedure after grant of marketing

Wright (cont.): authorization. Has the benefit-risk analysis changed? Has it gone up? Has it gone down? You really have to keep monitoring that after authorization.

The importance of communicating with and informing stakeholders and the public, that means you are communicating with the competent authorities. Competent authority is a very EU term. Essentially it means the Medicines Agency, the European Commission, the member states' authorities, healthcare professionals, hospitals, clinics. Also communication with public—that in itself also brings its own risk, because the promotion of prescription-only medicinal products to consumers and patients in the EU is prohibited, another criminal offense if you do it. So, how you communicate to them about promotion is something you need to address.

Any regulatory action that you need to take—has the benefit-risk assessment changed—does that mean that you need to vary—make an application to vary your marketing authorization? The dosage level is incorrect, is the mode of delivery incorrect, should changes—the package information leaflet for patients be changed?

Perfect example of that, there was a case before the European Court of Justice a few years ago now in which generic manufacturers took an action against the innovative product and marketing authorization holder for their product. And essentially what the innovative manufacturer had done was he had—they had taken the SMPC, it's an authorization, for the product and the patient information leaflet, put them on the website, which they've got the right to do even if it's a prescription-only product.

But, in addition, to help the patient, the authorization holder simplified the patient information leaflet into a second document. And the generic manufacturers complained to the authority saying that second document is promotion, and to which the innovator was righteously indignant and said, "That's absolutely not the case. We're just trying to make things simple."

This case went all the way to the European Court of Justice, from a national court to the European Court, the most senior court in the EU. And the European Court of Justice agreed with generics, and they said, "You are—Mr. Innovator, you really should know that you can only provide information to patients for prescription-only product in the form of the SMPC, Summary Product Code of Characteristics, and the patient information leaflet. If you feel that the patient information leaflet is not sufficiently clear, you don't produce a new document. You modify the patient information leaflet." A lot of the regulatory actions here could be right from pharmacovigilance.

And, finally, conduct of regular audits, where audits can be internal, they can be third-party audits or they can be competent authority audits. It is not at all unknown for the auditors and the authorities to turn up, whether it is an actual unannounced audit, but you've got to let them in. You have to be able to present your pharmacovigilance, your drug master file, your pharmacovigilance files, to demonstrate how you fulfilled your obligation to pharmacovigilance.

So, what are the obligations? Well, these are the processes that you need to have. You need to have the risk management system. You need to be established a set of pharmacovigilance activities and interventions. The purpose is to identify, characterize, prevent or minimize risks relating to a medicinal product. And it is both taking those steps and assessment of the effectiveness of those steps. So, it is you need to take a step. You need to know the benefit-risk. You need to have a procedure in place in which you monitor it. And then you need to have a second procedure in place to determine the appropriate steps to be taken as a result of when you are facing the results of the monitoring.

You must have a risk management plan. It must be a detailed prescription of the risk management system.

Wright (cont.): You have to establish a pharmacovigilance system. What is it? It is used both by the authorization holder and by the member states to fulfill the tasks and responsibilities that are laid down in Title IX of the Community Code, Pharmacovigilance. And the purpose is to monitor, again, the safety of the authorized medicinal product, and, again, always iteration, always a fundamental principle, the review of the benefit-risk assessment of the product.

Finally, a pharmacovigilance system master file must be established. It is a detailed description of the pharmacovigilance system used by the marketing authorization holder in relation to one or more than one authorized medicinal products.

So, the obligations of pharmacovigilance don't only arise once marketing authorization is granted. In fact, their related obligations arise even before the marketing authorization is granted. As part of the application for marketing authorization applicants are required to provide detailed information concerning proposed pharmacovigilance systems.

This includes detailed information on the Qualified Person for pharmacovigilance. It's not enough to say we're going to appoint a QP. Qualified Person for pharmacovigilance is commonly referred to as a QPPV. Not enough to say yes, we know what our obligation is. We're going to appoint one. You've got to tell them. You've got to tell the authority who that person is, what are their qualifications, where are they established.

You need to say where is the location of the pharmacovigilance master file, which, in itself, means you need to have established a pharmacovigilance master file before you make your application. You must demonstrate the means by which you're going to fulfill your pharmacovigilance obligation. Again, it's not enough to produce the structure of what you want to achieve. You want to demonstrate how you're going to achieve that.

And you need to have the risk management plan established. You need to demonstrate what kind of a system is going to be implemented and provide a summary of this plan, as well. And, of course, it's not enough, again. You need to think what are you going to be—what did you achieve? Again, risk-benefit—the plan must not be too sophisticated. It can get overcomplicated. It has to be proportionate. It has to be practical. It has to mean that you will be able to identify potential risks and you will need to be able to determine how to act on those risks where they are identified.

Of course, where necessary the risk management plan must be updated. This is most likely to happen if you have perhaps sort of a serious adverse event which shows there are issues relating to your product, or, more importantly, that there are issues relating either to your reporting obligations—did you do it efficiently, did you do it on time, did you do it to the appropriate authorities—or what steps you took, were those accurate, were they adequate, were they long-term sufficient? You may require the risk management plan to be revisited as a result of this.

So, one of the things that, in fact, the guidance says that competent authorities may conduct postmarketing pharmacovigilance inspections. It is in our experience really common these days that the authorities will do that. And they will expect you to be able to demonstrate that you have thought about your pharmacovigilance obligations and that you know how this is to be achieved.

Again, this is not a theoretical exercise. If the competent authorities come and visit you and audit you, they're going to want to see the people who are going to conduct the pharmacovigilance obligation. They want to see where your pharmacovigilance master plan is going to be. They want to have an idea how do you plan to fulfill your—how do you monitor, how do you trend the uses of your product, the positive and negative effects thereof?

Wright (cont.): So, there are marketing authorizations in the EU. One of them is a conditional marketing authorization. It is a marketing authorization granted on condition that the authorization holder fulfills certain obligations. And among those are pharmacovigilance obligations. The authorization can include an obligation to develop specific safety measures that must be fulfilled in the risk management plan; must conduct post-authorization studies.

These are actually—until a few years ago the obligation to conduct post-authorization studies was relatively uncommon. Now it is becoming very common. As I guess you know, medicinal products have become more sophisticated, this obviously is requirement. But the procedure for granting of marketing authorization and postmarketing vigilance is obviously becoming more sophisticated, as well.

And we'll talk about this a little bit further on, but conduct of post-authorization studies is in itself a whole new project that requires a certain level of resources, precision, factual documentation. You need to demonstrate what you're going to do, and when you've demonstrated what you're going to do you have to make sure that you do it. And compliance with the requirements concerning recording and reporting of the suspected adverse events, and that are similar to those but are even more strict than those contained in the Community Code. "Strict" is probably too strong a word. They are more precise. They are more detailed.

And obviously any other conditions that are imposed by the conditional marketing authorization you have to fulfill those. Again, it is aimed at the safe and effective use of the medicinal product. The obligation is laid down in the authorization. After the authorization, commonly the marketing authorization holder will be required to submit a proposal to the authorizing authority to identify what the authorization holder proposes to do, what they want to achieve and the manner in which they are to achieve that.

Now, it may take several rounds of negotiation and discussion and needs to be fairly precise, but this is a two-way street of negotiation with the authorities, and, again, as I said earlier, if you have this obligation, if you take on this obligation, you really must fulfill it. You could jeopardize your marketing authorization's validity if you don't. And, of course, a conditional—any marketing authorization, but particularly a conditional marketing authorization, it is essential to demonstrate that an adequate pharmacovigilance plan has been established.

So, what is a marketing authorization holder's obligation after grant of marketing authorization? Well, they are required to provide the competent authorities at the European Medicines Agency—the European member states or the European Commission with any new information that might influence the evaluation of the benefit and risk of medicinal products. So that means–includes both the positive and negative results of clinical trials or of other studies in all indications (important) and in the population. Now, in all indications, that means in practice that the fact that a clinical trial has been conducted on a therapeutic indication for which your product was not authorized does not exclude you from the obligation to trend and report that.

This is something that has changed in recent years with the evolution of pharmacovigilance. You are essentially required to have resources either in-house or externally that you can use to determine whether or not—determine that you know that clinical trials have been conducted, even if they are off-label, even if they are investigator-initiated. You need to have some way to trend that and to trend results and to determine if the results suggest that the benefit-risk of your product has changed, whether it's positively or negatively.

And obviously there is obligation to provide data on the uses of medicinal product, particularly, again, off-label use. It's not just the clinical trials. It is normal use within the normal treatment of the patient by a

Wright (cont.): physician. And, in addition, the Medicines Agency, the European Commission or the competent authorities may require the Marketing Authorization Holder to provide the latest copy of the pharmacovigilance system master file. An important part—point of that is you need to hold this in the EU, and you need to have a general principle of a standard operating procedure established and put in place, so that if Medicines Agency, the authorities, competent authorities, somebody shows up at your door and says, "I want to see your pharmacovigilance plan," you don't have to spend an hour trying, "I wonder where we have it. Who has it? Which country is it in?" You need to know. You need to have organization, a structure in place. It really upsets the authorities if you're not able to answer that question in an efficient way in a reasonable amount of time.

So, how are you—what is the guidance to what you do post-authorization? Well, the European Commission's Implementing Regulation it's called was adopted in 2012. It's really fairly detailed guidance as to what you should do to fulfill your obligations.

So, you are required to provide the list of the things that you need to do. You need guidance on the content of the pharmacovigilance system master file, again. You really should have done this before you had grant of marketing authorization, because chances are you wouldn't get marketing authorization if this was not developed, but it's something you need to know while you're preparing your submission.

You need the guidance from the pharmacovigilance quality system. It lays down minimum requirements for monitoring of data in the EudraVigilance database; and guidance on the transmission of reports for suspected adverse events; information regarding post-authorization studies; the format and content of risk management plans; the use of internationally agreed terminology, formats, standards for the performance of pharmacovigilance activities.

Again, it seems counterintuitive, but it is not at all unknown to have companies, particularly if you've got several sites and you've got a site in a number of EU member states, you want to have a single reporting system, and you discover that the software used in the individual member states don't talk to each other. It can be as simple as that, that the issue that your software has to be compliant in each member state.

So, it also sets down some specific requirements for the master file, the pharmacovigilance master file. It must have key information and documents covering all aspects of the pharmacovigilance activities, and that includes information on the tasks that have been subcontracted. Your obligation to fulfill pharmacovigilance obligations are yours. You're the marketing authorization holder. The legal obligation will remain with you always. You can subcontract the practical fulfillment of the obligation. You can never subcontract the legal responsibility. Important point.

And also the—how are you going to contribute to the appropriate planning and conduct of audits by the marketing authorization holder and the supervision of activities of the QPPV? You need to—it's not enough to appoint a QPPV, and indeed most QPPVs are very—fairly feisty people, and if they feel like you're not achieving what you want to achieve, well, they will be very blunt and say, "This is my responsibility. You have either appointed me or hired me. You're going to do this, you're going to do this, you're going to do this, and I'm going to do this, and you're going to make sure that you do it." So, you do need to have a fairly controlling, sophisticated QPPV and give him or her the resources to fulfill his obligations or her obligations.

And there must be evidence in the pharmacovigilance system master file to enable national competent authorities to verify compliance concerning all aspects of the system. There must be a way that when they come to audit you, they are able to see exactly what you're doing. And, obviously, again, quality, you must have evidence that your pharmacovigilance system is controlled by an efficient quality system. It's

Wright (cont.): no point in having a very sophisticated pharmacovigilance system master file if you have no way to ensure that its enforcement in practice is adequate and efficient.

So, what are the obligations of the marketing authorization holder post-authorization? Well, as you see, they must operate, maintain and regularly audit their pharmacovigilance system through the QPPV. They must establish and regularly update, again, pharmacovigilance system master file. I know we keep repeating this. It's a very important document. Must operate and update the risk management system for every medicinal product. There's no exceptions to that. There's not one or two that you can do it. No, you have to do it for all.

At the request of the competent authorities they may be required to appoint a contact person in the member state to report to the QPPV. Now, the QPPV that is appointed when you grant a marketing authorization, whether it's centralized or decentralized, is a QPPV for the product in the EU. That means there is only one of those people.

Now, for quite a number of years there have been some member states saying, "Well, that's not enough. We really need to have somebody in our territory." And in the most recent update of the pharmacovigilance legislation the member states were given the power to do that. Not all member states have done that, but there are a number of member states who require marketing authorization holders whose authorization extends to their territory to appoint a person in that territory, who has to be established in that territory, who reports to the QPPV and also reports to the competent authorities in the member state in relation to pharmacovigilance obligations.

And one of the most important obligations of the marketing authorization holder, submission of periodic safety update reports, PSURs. And these include the results of any studies with potential impact on the authorization, again, not just negative, positive, and an estimate of the population exposed to the product, which again creates a problem of its own. How do you know what population is exposed to the product?

Well, there are various ways of finding out. You can do it through your sales. You can do it through speaking with your physicians. But there is, of course, the problem that the—you can't ask a physician whether he is using your product off-label, because if you do so that's off-label promotion. It's very easy in the EU to get into promotion. And asking that sort of a question is off-label promotion and something that the authority or indeed the physician themselves can get very upset at.

So, we talked about the qualified person for pharmacovigilance. You are required to appoint him. You won't get your marketing authorization without it. So, what's the role of a QPPV? The establishment and maintenance of a pharmacovigilance system. The QPPV must reside and operate in the EU, in one of the 28 EU member states, and must be available to the marketing authorization holder on a permanent and continuous basis, 24 hours a day, seven days a week. It is essentially what normally happens is that there is a QPPV and there is a co-QPPV, so if one isn't available the other one is. And, as I mentioned earlier, some member states require the company—I said request, but in fact it's not really a request, if the authorities say to you to do it you do it—to appoint a contact person in their territory.

So, one of the recent changes in the Community Code in medicinal products was change in the definition of a marketing—what constitutes a marketing authorization or a serious adverse event. Know what an adverse reaction is. It is a response to a medicinal product which is noxious and unintended. Now, it used to be that this statement was expanded and said, more or less, response to a medicinal product noxious and unintended in the purpose for which it was authorized. But the purpose for which it was authorized statement has gone, which essentially means that the marketing authorization holder is now required to record and if necessary report an adverse event that occurred in the off-label use of their product.

Wright (cont.): Again, the issue how can you consider—how can you determine whether a serious adverse event has occurred in the off-label use of your product? You need to have a procedure for reporting. You need to have a procedure for monitoring and trending. But you need to have it in such a way that you do not be perceived as stocking or off-label trending or off-label promotion. Difficult thing to achieve.

So, definitely an adverse event reaction essentially is it's occurring in the use of the medicinal products for its authorized and unauthorized products. It also covers overdose, misuse, abuse and medication errors, very broad scope. And obviously it includes suspected adverse reactions outside the EU. So, if you have—your product is authorized in the EU and outside the EU, you need to establish a procedure whereby you can be sure that any adverse reactions, you learn about them, you learn about them within an appropriate time, and you report them to the authorities within an appropriate time.

Again, the basics, like getting software that talks to each other, agreeing who is responsible for reporting to who, agreeing who holds the database in which this information is developed, and if both in the EU and for example in the U.S., there's going to be a database in each, how can you be sure that any update to one is also an update to the other? This has to be something that is very organized, because it's something of an organizational nightmare if it goes on.

So, the marketing authorization database has to be centralized and has to be in a single location in the EU. It is part of the pharmacovigilance system. The report and marketing authorization holder is also required to submit the reports of suspected serious adverse reactions reports and of suspected nonserious adverse reactions through EudraVigilance.

EudraVigilance is a software process, program that is established in the EU in which it is part of EudraPharm. If you've ever conducted clinical trials in the EU you will know and submitted a marketing authorization you'll know that you have to have your procedures registered through EudraPharm. It's a European-wide database. And, of course, submission of reports must comply to related reporting timelines, and they're established in the EU laws and regulations, and in the appropriate format.

So, we mentioned earlier the PSURs. This is a very important part of the postmarketing pharmacovigilance obligations. The marketing authorization holder must prepare and submit through the Medicines Agency a PSUR in relation to the medicinal product. It has to be done electronically these days. No paper versions.

The PSUR must contain summaries of postmarketing data relevant to the benefit and risks, again, benefit and risk of the medicinal product, and discussion of the potential impact of the data on the marketing authorization of the product, and the result of all studies conducted with the medicinal product, and a related discussion of the potential impact of the results on the marketing authorization. And it can be—it's not just the therapeutic indication. Is the dose appropriate? Is the delivery system appropriate? Is the patient information leaflet appropriate? All of these issues—it's a very broad scope that needs to be considered.

Again, a scientific evaluation of the risk-benefit balance of the product, all data related to the volume of sales of the medicinal product—again, that's fine when you're talking about the issue of on-label use. You need to proceed to establish a process for trending also this information on the off-label use. And any data relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product, which, again, there are procedures, there are third-party service providers who can do this with you. You need to be careful that you have a detailed procedure, that you have a continuously updated procedure, and that you have a procedure that complies with all technical rules.

Wright (cont.): Now, how often do you need to produce and submit a PSUR? It will depend on what is provided in the marketing authorization. This quite often reflects the risk profile of the medicinal product. The more their risk is considered to be presented the more often you will need to do a PSUR. Normally marketing authorization holders are required to submit PSURs every six months for the first two years after grant of marketing authorization, and then annually for the third and fourth year and after that every two years.

Obviously it can change. Indeed, not only can it change over that period, it can change in the marketing authorization, and events can cause it to change. If your product is—has been on the market for two or three years, for example, and suddenly it becomes evident that there is a certain type of concern with it relating to the product, the authorities, Medicines Agency, have power to impose an obligation on you to produce and submit PSURs even every three months. We have recently had a situation where a client was obliged over a period of a year to submit every three months and then every six months and then went back to the normal reporting obligation periods.

So, pharmacovigilance can also impact the renewal of marketing authorization. In principle, a marketing authorization is, at its first step, valid for five years, and once it has been reviewed at the five-year period it becomes an open-ended authorization. And so to ensure that you get that open-ended authorization you're required to submit the PSURs. It's an application for authorization renewal, and it includes evaluation of your data contained in the suspected adverse reaction reports and the PSURs.

In some of the—one of the occasions in which you could have issues is if an insufficient number of patients have been exposed to the medicinal product and the authorities may agree to decide to impose an additional five-year renewal. Of course, and unhelpfully, the term "insufficient number of patients" is not defined. It's essentially determined on a case-by-case basis. It will depend on the patient population. It can depend on the mode of administration. It can indeed depend on the cost of the product. There's all sorts of reasons that it can be determined. That's why it is on a case-by-case basis.

So, we talked before about postmarketing obligations, how that can be imposed. One type of that is a noninterventional study. Now, these can be either voluntary or can be imposed by the authorities. Now, one of the—there's a very specific procedure that must be followed in relation to post-authorization noninterventional studies, and one of the most important things is the draft protocol must be submitted to the PRAC, to the Pharmacovigilance Risk Assessment Committee. Now, we will discuss that later. So, this is a fairly new committee, but it does have an important role to play in this procedure, also to the competent authority of the EU member state if the authority asks, and the role will be for endorsement before the study is initiated, or, quite often, not at all excluded, if there is a need to modify the protocol.

And these type of studies must be initiated, organized and financed by the marketing authorization holder. It relates to the collection of data from patients or from healthcare professionals, essentially registry studies. Must not have a promotional aim, and, again, no clinical study should. And payment to healthcare professionals restricted to compensation for time and expense, fair market value, again, like any clinical study.

And the—again, not only is there a need to submit the draft protocol before the study begins, the authorization holder may also be required to submit the progress reports to the competent authorities on a case-by-case basis on a period-by-period basis, depending on the nature of the study and the purpose of the noninterventional study. And the results are communicated to the authority by the PSURs. We mentioned earlier that PSURs included results of clinical studies, including noninterventional studies. And the final report should be sent to PRAC, or the authorities of the EU member state where the studies first took place. The manner in which the study is presented is in the Implementing Regulation, Annex III thereof.

Wright (cont.): Post-authorization efficacy studies—again, there are occasions when these sort of studies are either voluntary or imposed, quite often imposed after marketing authorization. Now, what are the purposes of efficacy studies? And essentially depending on the nature of the product, depending on the therapeutic indication, depending on the patient population, and it may be that the efficacy of the product can only be resolved after the medicinal product has been placed on the market, because of urgency or because of ethical reasons a long and detailed clinical investigation was not possible.

If the understanding of the disease, the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluation might be revised significantly, again, efficacy studies may be necessary. Again, these are things that can be found through conduct of pharmacovigilance trending and presentation and preparation of PSURs.

So, when postmarketing and efficacy study is to be conducted, where there's an initial efficacy study based on surrogate endpoints that need to be verified by a clinical outcome, essentially, to determine the outcome, the disease progression or confirmation of previous efficacy assumptions; where there is inadequate detail; if it hasn't been conducted for a sufficiently long time because there still has not been three months, six months, 12 months, 18 months follow-up prior to authorization. Again, that's one of the reasons that efficacy studies may be required.

Where further efficacy data is necessary for the use of the medicinal product in combination with other products. Now, this is becoming something that is become more common. This used to be fairly unusual, but now with increasing sophistication and the increasing focus on the use of products in combination with other products, post-authorization efficacy studies are coming more often.

And to clarify uncertainties that weren't addressed when the medicinal product was authorized, and this second part, this is if there were uncertainties but the benefit-risk analysis, the balance was considered to be appropriate for grant of authorization in any event, there would be a fairly good possibility that the marketing authorization will be conditional, and we talked about those before, that post-authorization efficacy studies be conducted to make sure that these uncertainties are addressed.

And where there is a potential lack of efficacy in the long term that raises concerns in the maintenance of a positive benefit risk-balance, for example, if a product was, when it was first authorized, it was considered to be the risk-benefit balance was great, the primary endpoints were addressed, were a success, the product was effective and safe, and the patient at six months and 12 months, marketing authorization granted, 18 months, 24 months the effectiveness suggests that it has been diminished. Again, efficacy, postmarketing efficacy studies may be imposed or, indeed, recommended.

And where the benefit of the medicinal product in clinical trials is significantly affected by the use in real-life conditions. In a clinical trial they are in a limited, selective environment and a limited, select version of the patient population. The EU is a big, big, big geographical region. If its use was determined to be less effective or create risk in relating to an element of the population, postmarketing efficacy studies may be conducted to see if this is actually a practical result, whether it's a concern, whether it should be used, whether you then need to do with the actual product itself, and where there's a change in the understanding of the standard of care for a disease, and that's something that, again, happens with the evolution of medicine.

Where things have changed, the determination of appropriate standards of care are changed, or the pharmacology of the medicinal product requires additional evidence of its efficacy. Anything—essentially, all of these are the same. It's the evolution of the use of a product in a therapeutic indication in an environment which is much, much broader than the clinical trial environment in which the data was

Wright (cont.): generated on the base of which marketing authorization was granted, and where new concrete and objective scientific factors may constitute a basis for finding that previous efficacy evaluations might have to be revised significantly. Essentially, progress in science and medicine may cause that.

So, we mentioned earlier the pharmacovigilance risk assessment committee, the PRAC. And this is fairly new. It's only been going since 2013—2012, 2013, and feisty group of people. We have—it is made up, by and large, of the heads of pharmacovigilance of the health authorities of the 28 EU member states. Its role is to review all aspects of risk management concerning the use of medicinal products, and that includes detection and assessment and minimization of risk, particularly where these—should these information involve some PSUR that they feel should be reviewed, and communication related to the risk, and, an important part, design and evaluation of post-authorization safety studies and pharmacovigilance audits.

Essentially, the role of the PRAC is to monitor the benefit-risk balance of medicinal products after they're authorized, and to review any postmarketing observational studies, the protocol, as I mentioned a bit earlier, and to determine if the PSUR over a period of time suggests that there is an increased—potential increase in risk. PRAC will become involved. It will discuss, will decide that appropriate clinical trials, for example, need to be conducted, or propose that the therapeutic indication for its product as authorized should be varied. These are the sort of activities in which PRAC becomes involved.

As I mentioned, it's composed of all member states, one expert and one alternative from each member state; six experts from the Commission, some pharmacology and some epidemiology; one representative for the healthcare professions; one representative for patients. And which sector of the population is not represented? Yes, industry. Industry there's no representative. And each member has a three-year renewable mandate.

And, as we discussed earlier, delivers opinions on referrals to the agency, Medicines Agency, regarding evaluation of data relating to pharmacovigilance in relation to an authorized medicinal product; conducts initial analysis and prioritization signals for new or changing risks in relation to product. We mentioned and discussed the endorsement of draft protocols in relation to noninterventional studies, and provides recommendations regarding EudraVigilance organization and function. Now, the PRAC hasn't been, as I say, it hasn't been in action very much, or, sorry, very long, but it is an active and opinionated committee. It's got a lot of expertise.

So, then there is the CHMP, which I'm sure many of you have heard of before. And the CHMP—PRAC reports to the CHMP. The CHMP is essentially the committee that gives the opinion in relation to an application for marketing authorization as far as centralized procedure. That's its main role. It's not its only role, but it's its main role within the EU. It can rely on the PRAC's assessments and recommendations when agreeing and monitoring risk management systems. And it will review them. It doesn't always follow them, but it will review them. And they cooperate closely with each other.

And the CHMP, their positive opinions, CHMP's opinions on the grant of marketing authorization, it will include recommendations on the frequency of the PSURs, as I mentioned earlier, that in principle it should be every six months, then every year, then every two years, but it's not always like that if there is a risk concern; and details of any measure for the safe use of the medicinal product contained in the risk management system; that is, if there is postmarketing obligations to be followed, the committee will propose those; and, indeed, the written requirement to conduct post-authorization safety studies, or requirements on suspected adverse events. They can also propose issues such as should there be

Wright (cont.): educational materials provided to physicians. Should there be training provided to physicians? If so, in what form and for how long? These are the sort of issues that the CHMP will propose.

Then there is the CMD(h), which is essentially the best way to describe, I guess, CMD(h) is that the CMD(h) is the CHMP for decentrally authorized products. It is made up of the heads of the Medicines Agencies of the 28 member states, and it will review pharmacovigilance issues in relation to medicinal products authorized by the decentralized authorization procedure. And it will agree and monitor risk management systems, and, of course, it as well relies on the scientific assessment and recommendations of the PRAC.

And the Executive Director of the Medicines Agency and representatives of the Commission are entitled to attend all the CMD(h) meetings. In fact, they always do. And, again, if there is a case of absence of consensus, which I have to say doesn't happen too often in my experience, CMD(h) decisions will be taken by the majority of the representatives of the member states.

So, where a medicinal product is subject to additional monitoring, the new legislation, original the Community Code, said that the European Commission would develop a symbol to identify these products. And there was a great deal of discussion and a great deal of proposal as to what was the appropriate symbol. And after a great deal of time the decision was to use the black triangle that is beginning to be used already.

It must be accompanied by text encouraging patients and professionals to report any unexpected adverse events experienced in the treatment of these products, and it is required obviously when any medicinal or any marketing authorization holder who had a medicinal product subject to additional monitoring that didn't have, which virtually nobody had, this black triangle on their product, they had to actually go and get a variation to the marketing authorization to add the triangle to the product.

So, I mentioned about obligations to report. One of the more controversial elements of the revision between pharmacovigilance laws and the Community Code was the addition of the obligation on the marketing authorization that they should make a statement in the patient information leaflet and the SmPC encouraging healthcare professionals and patients to report adverse events. And, again, explicit statements had to be made to healthcare professionals and patients to report any suspected adverse events. And there was information to be provided as to how to report by post, electronically and other means.

And this created two sets of issues still being addressed, indeed. The first is there are obviously going to be patients who will be dying and at death's door before they would ever report, and then there will be patients who will report at the drop of a hat. The second is how does a patient report it without breaching personal health data obligations?

As you may be aware, we have very strict rules on data protection here in the EU, and offering, inviting the patient to submit data to you on your website brings with it a whole array of data privacy issues, because the presumption of the competent authorities is that the person reporting is probably going to be a patient. So, essentially any personal information related to that patient in that context must be considered to be personal health data, which is subject to high levels of security and which must be—you must establish a very detailed informed consent process for.

And the Medicines Agencies in the member states are also to be encouraged—to encourage patients and pharmacists and healthcare professionals to report suspected adverse events. And the obligation, and this is becoming increasingly active—it's taking a little while, but it is getting there, that the Medicines Agency — I'm sorry, the, yes, Medicines Agencies of the EU member states and the

Wright (cont.): European Commission to publish marketing authorization, patient information leaflets and SmPCs on their websites, and, of course, any related conditions relating to the marketing authorization, without delay. With a bit of a relative term, not all member states have yet done all of that. So, we talked about that. So, those two established portals, they are getting there, they're getting there, but it's been a while to get to where some member states processes' publication.

We're nearly at the end. Falsified medicinal products—this is—there's a relatively new Directive on Falsified Medicines since 2013, and essentially the obligation is to help avoid the purchase by patients, among other things, online of falsified medicines. And this has been—it's very controversial. It is difficult to enforce. It is something that the authorities are very focused on, and, as you see there, since 1st of July this year online pharmacies and retailers that offer medicinal products in the EU must require to display an EU-wide recognizable logo on the website that they are acknowledged to be suppliers.

And I talked before about the EudraPharm and EudraVigilance. EudraVigilance is an emanation of EudraPharm, and EudraPharm is a database with all information on all medicinal products authorized in the EU, both centrally and decentrally authorized. And it is—the website, the first part of the website has been in existence for quite a number of years. If you go to conduct a clinical trial in the EU you get to know this site, because you have to have—be registered in the site before you start.

There are still issues. There are still issues with some elements, particularly there is an element of EudraPharm that should permit you to report information, changes, variations to the Medicines Agencies for approval. And that element of the website, which is much needed, was supposed to come into application in March, and then in June, and then in October, and we have now been told it will come into force but we weren't told when. So, it's definitely a work in process.

But the database has and will do into more or less greater, it'll have the SmPCs and patient information leaflets, public assessment reports, summary of risk management plans, list of medicinal products, and information on how to report. Now, that information, some of this information is accessible to the public and some of it isn't.

We also talked before about inspections, Article 111 of the Community Code and, of course, the GVP Modules. Both pre- and post-authorization competent authorities of the EU member states in cooperation with the Medicines Agency can conduct inspections of pharmacovigilance obligations. And they can be product related, system related. That means there are issues. They can be routine or they can be for cause, again, pre- and post-authorization. They're always pre-authorization and increasingly they're post-authorization.

They can be announced or unannounced. In our experience the unannounced ones occur when you've had issues with your, among others, with your pharmacovigilance. And it can be an initial or reinspection. If there's a real issue you get a first inspection and then the authorities will come back and check that you've done what you've said you would do. And of course they can do remote inspections that are increasingly common. That means that you're required to make available access by the competent authorities to your databases so they can check the type of procedures you have and to reaffirm pharmacovigilance procedures. Issues of access to documents, copying of documents, disclosure of documents, all sorts of issues of intellectual property, IT issues, data privacy are linked to that. But, again, they're getting there.

And, finally, the Penalties Regulation. Now, this regulation has been around for a while, but essentially one of its bases are to say that—this only relates to centrally authorized products—but if you don't fulfill your obligations, postmarketing obligations, including your pharmacovigilance obligations, you can face a fine that is 10 percent of your annual turnover—not 10 percent of the annual turnover in medicinal product, off your entire annual turnover in the EU. And in fact it has not ever been applied. No penalties

Wright (cont.): have ever been imposed yet. But this could change. And there is in all EU member states there is an equivalent version for decentrally authorized products.

So, there have been a few changes, just there are a few fragmented changes essentially at the moment. The Medicines Agency is, of course, now required to monitor medical literature for reports of suspected adverse events in medicinal products. They have—the Agency have published a list of substances in relation to which it is now monitoring medical literature in relation to identify suspected adverse events.

And there are advantages in that, and you can, if you are a marketing authorization holder, you can actually go to that site to determine if there has been anything. It helps you to develop particularly your PSURs and fulfill your pharmacovigilance obligations. Important is practically if there is a serious adverse event that occurs in relation to one of those products on that list marketing authorization holder doesn't need to report to EudraVigilance simply because the agency already knows it.

So, that is a quick run through the rather complicated area of pharmacovigilance. So, I am happy to answer any questions you may have.

Operator: All right, we're now ready to take some questions. Thank you. Ladies and gentlemen, now is your opportunity to have your questions answered by our presenter. Please remember this portion of the conference is also being recorded, and please limit yourself to one question at a time.

[Operator gives instructions for calling in or submitting questions.]

Our first question will come from Kyle Asay, from FDAnews. You may go ahead, Kyle.

Asay: Hi. I received a number of questions both via the Q&A panel and via email, so in the interest of time I'm going to proceed to those. The first question is from North Chicago, and they were asking about they think India also requires the QPPV. So, if you're a global company you would have two QPPVs, one for the EU and one for India?

Wright: Well, I'm afraid I don't—I'm not in a position to opine on India. I don't really know much about how it functions. I would say, just by extrapolation, that the answer to that is probably yes, in the sense that a QPPV for the EU must be established in the EU. I would anticipate that—for effectiveness I would anticipate that the QPPV for India would probably have to be established in India, which would have the net effect that yes, you probably would need two QPPVs.

Asay: OK. The next few questions come from Richmond. This one is in reference to Page 9 in the slides, so if you wanted to flip over to Page 9. It's in reference to talking about how both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorization, and here is the question. This is a little long, so bear with me.

Is it sufficient to inform the European Commission or the competent authorities of the EU member state of clinical trials that positively influence the benefit-risk of the medicinal product only via the PSUR? Does this statement intend to infer that if, for example, clinical trials aimed at an indication or adding new pathology or new dosage must be submitted as formal variation to the marketing authorization even if the authorization holder has determined that there is no medical need nor commercial return?

For example, it is not unusual to register lower doses for medicinal products in Japan on the basis of differing pharmacology and average body weights. Would submission of formal variation to add the lower doses to EU marketing authorizations be required, and the statutory time frame for the submission of such variations?

Wright: Right. That's actually two different issues. The first is if you're positioned—well, you have an obligation, essentially you have an obligation to report on the results of your clinical trials in your PSURs, whether those results are positive or negative when you tote your results. It is not necessary to go into every detail, but it needs to be reported. PSURs are not publicly available, by and large. They're not normally subject to Freedom of Information requests. But they do need to be addressed.

Now, the fact that you have conducted a clinical trial and there's been results that do not impact—and this is prominently important—the results do not impact the benefit-risk balance, then in principle if you come to the conclusion that there is no need to vary your marketing authorization results because there's no commercial need, even if you have had someone, even if there was an investigator-initiated study that discovered that the use of your medicinal product in the treatment of a therapeutic indication for which the product is not yet authorized is very effective, that doesn't mean you're required to vary your marketing authorization. That's your decision. It's your marketing authorization.

So, the obligation—you don't need to vary your marketing authorization just because you conduct a clinical trial. On the other hand, if your clinical trial results demonstrate that there is a change in the benefit-risk analysis, yes, then in that case it would be very advised that you seriously consider doing that and you discuss it with the competent authorities as to what you're going to do.

As a tangent to that, there are, as some of you may be aware, changes going on in the disclosure of clinical trial data in the EU at the moment anyway. We have the already existing European Medicines Agency access to documents, disclosure. You then have from the 1st of January of this year you have the Medicines Agency's own disclosure of the clinical data, their own decision to disclose clinical data relating to applications for marketing authorization. And this is causing some controversy, because they can—the agency can itself decide to disclose this information.

It discloses it in two ways. One, it discloses to people who agree that they are researchers and that they will not use the data for anything other than research, and they will have access to the documents. They already do. And then there are people who are not researchers, and they are permitted to have access to data relating to clinical trials that are the basis for marketing authorization only on the screen. And the agency acknowledges that there is a—says that this sort of data should not be used by accessing parties to submit a marketing authorization application anywhere in the world, but then says and if somebody does do that it's not our responsibility. That's the second one.

The third one is EFPIA, members of EFPIA, which is the European equivalent of PhRMA, have given an undertaking to disclose the results of their clinical trials on their own websites on a voluntary basis. And you can see some of them, the members of EFPIA, have started to do that.

And, finally, from at earliest the middle of next year, when the clinical trials regulation comes into force, clinical trials—companies conducting clinical trials will be obliged to publish the results of the clinical trials on their websites within 30 days of the data being locked. And you need to provide fairly detailed information, and you need to provide a layman's version summary of that data, as well.

So, I'm sorry, that was quite a long answer.

Asay: Not a problem. Do you have anything to address the second part of the question, that there was the issue of the lower doses for different body weights?

Wright: That to me—I'm not sure how—I don't—I'm not familiar with the Japanese provisions, but if you—the permitted dosages are the dosages on—that are given on the marketing authorization, so if a

Wright (cont.): physician chooses to use different dosages due to different body weights, well, that's his prerogative, but you cannot encourage him to do so, because that would be off-label promotion.

Asay: OK. Next question is what is the definition of the implementation or safety-related changes to the SmPC in the EU, and what are the expected timelines for implementation?

Wright: Could you say that again?

Asay: What is the definition of implementation or safety-related changes to the SmPC in the EU? What are the expected timelines for implementation?

Wright: I'm afraid that that all depends. This is all a factual issue, and it's all governed by the Variations Regulation. The procedure to be followed in relation to a variation to your SmPC will depend on the nature of the change, and it is dictated by the provisions of the Variations Regulation. The procedures to be followed and their timelines are also laid down in the Variations Regulation, and they vary.

Asay: OK. Is the scope of this legislation limited to the EU or the EEA? Is there an expectation that the legislation applies globally? Does the European Commission have the legal right to demand that this legislation be applied to countries outside the EU or the EEA?

Wright: No. No, this is EU legislation. It applies in the EEA EFTA states, so that's Lichtenstein, Iceland and Norway, through various procedures. It cannot apply outside the EU. That would be giving extraterritorial effect to the legislation, which is just—that's not possible.

Asay: OK. Next question has to do with the wording, the marketing authorization holder's database in which suspected adverse reactions are recorded should be centralized and accessible at a single location in the EU. They're looking for clarification on this. The question is, does the server need to be in the EU? Does it mean it has to be accessible from at least one location in the EU, only one location in the EU? It's not entirely clear what this means in practice.

Wright: This is a very factual issue. You need to have a server in the EU that has this—in which this data is stored. It's part of your pharmacovigilance obligations. You have to have it in a site in the EU. And who has access to it? That's up to you. If you give access from outside the EU, particularly to other countries like the U.S., you're giving yourself rise to EU data privacy issues. It's not the subject of this talk, but they are very important. It's very important that you keep access to those, because those are personal health data issues.

And essentially who has access to that is practical. And if you have—if your product is for sale in four or five or six different member states, then access for your sales reps or your representative people in those sites to the database, there is an argument that you should be given it. And, again, this is purely practical. Do you want to give access to these people so that they fulfill the information, or do you want to have a recipient in where the data is stored who will triage the information and make sure that it's altered in an appropriate way, in a consistent way, and that the data is followed up? Again, these are all practical issues. The important thing is that in doing that you fulfill your pharmacovigilance obligations.

Asay: OK. And we have one more question here. This is regarding post-authorization efficacy studies. They're talking about on February 3, 2014 adopted Delegated Regulation 357/2014 concerning circumstances in which post-authorization efficacy studies may be required if the concerns relating to the efficacy blah-blah-blah can only be resolved, if the understanding of the disease, clinical methodology or the use under real-life conditions indicate that it might have to be revised. What they're asking here is

Asay (cont.): please clarify is this related to the study in the registered indication or for studies that are for new indications?

Wright: This is studies for the registered indication. It's the efficacy of the product for the purpose for which it's authorized.

Asay: OK. Let's see. I believe that's it for what I've got via email.

Operator: [Operator gives instructions for calling in or submitting questions.]

There are no further questions. Do you have any closing comments before we wrap up?

Wright: No, not really. I do appreciate this is a complicated area, but it is important that you follow it in detail. The ongoing validity of your marketing authorization can rely on it.

Operator: Thank you very much. On behalf of FDAnews, I would like to thank our speaker and you.

Just as a reminder, if you would like a recording of this session, you can order the CD and transcript package from FDAnews by visiting our website or contacting customer service. This now concludes today's webinar. To end this call, simply hang up your phone and close your browser. Thank you.