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New Paradigm for Transparency Practice for Greater Openness and Accountability in the Pharmaceutical Sector in Europe



BY LINCOLN TSANG, SILVIA VALVERDE AND JACQUELINE MULRYNE

In a climate of increasing scrutiny of conduct of public and private institutions, engagement with stakeholders through openness has been viewed as an accepted mechanism to demonstrate accountability. The pharmaceutical sector is not immune to this public demand for greater corporate and societal responsibility in conducting their affairs. It has been said that sharing and disseminating factual and accurate information can prevent misinformation, or misleading information. As a result, a well-functioning market place can be promoted, based on mutual trust and a set of guiding principles reflecting the core ethical values shared by all who have an interest in the sector, by enforcing standards and preventing anti-competitive behavior.

The transparency agenda, including the disclosure-of-payments initiatives and the growing campaign for registering and reporting the results of all clinical trials, are the latest developments that will have a significant impact on reshaping how research and development data and how the pharmaceutical industry's interactions with its stakeholders are managed at a global level. It has been argued by some that transparency may engender better regulatory decision-making and corporate governance. It also has been said that policies that promote transparency in the clinical research process, through improved and expanded disclosure of investigators' contributions and funding, comprehensive publicly available trial registration and independent analysis of clinical trial data, may improve accountability among industry and investigators to protect the integrity of clinical research.

Lincoln Tsang is a partner based in Arnold & Porter's London office specializing in regulatory, compliance and enforcement matters affecting the life sciences sector.

Silvia Valverde is an associate in the firm's London office providing regulatory and compliance advice to the life sciences sector.

Jacqueline Mulryne is an associate based in the firm's London office providing advice on regulatory matters.

The European Medicines Agency (EMA) has consistently defended its transparency and data access policies as a necessity in the delivery of its service to patients and society at large because (a) they instill trust and confidence in the regulatory system; (b) there is an ethical responsibility to the patients enrolled in the trials; and (c) data-sharing can open up new horizons for future research for the benefit of patients and public health. Constructive public engagement with the relevant stakeholders has been viewed as important in the new paradigm of research and development based on cooperation and collaboration.

Demand for greater transparency of regulatory decision-making has led to the ongoing debate for greater public access to data held by regulatory authorities for approved medicinal products, as well as those in clinical development. There is a perception that companies have in the past withheld data that may not have led to product approval but may still be considered as useful to guide future research. Companies have not been pro-active in publishing negative data. This has led many to believe that companies cannot be trusted to release data about their products. And yet, key regula-

tory authorities, such as those in the United States and Europe, have considered data sharing as integral to private-public partnerships to evaluate and validate innovative research methods that are important to accelerate testing of new drugs and new medical technologies.

The EMA's position on data access has received the support of academic researchers and patient groups through their related campaigns. On the other side of the divide, industry has been more cautious about the wholesale disclosure of its data, particularly where such data can be accessed by competitors. The level of information that is capable of being released to the public should take account of (a) the stage in the product lifecycle, (b) the type of information that could be legitimately disclosed by the competent authorities and (c) the impact on the future value of the products and the underlying technologies (especially for those products in development).

Similarly, the integrity of the decision of a health-care professional to recommend or prescribe a particular medicine is one of the pillars of the European health system. EU pharmaceutical law provides that health-care professionals must be able to carry out their professional duties objectively without being influenced by direct or indirect financial inducements. In recent years, there has been growing public interest in the pharmaceutical industry's relationships with these professionals. The public wants to know that such relationships do not influence or otherwise compromise clinical decisions and that they can trust their doctors and the allied professions in making an independent clinical decision on treatment options. Although these interactions are strictly controlled in Europe by a combination of legislation and industry codes of practice, by creating greater transparency, it is intended to improve the relationship between industry, health-care professionals and health-care organizations.

That said, in an increasingly collaborative research and development environment where external expert input is frequently enlisted to inform the study design and the assessment of unmet medical needs, interactions between industry and health-care professionals are invaluable.

It is against this background that this article is written to provide an overview of recent regulatory and compliance developments that seek to improve public engagement in every aspect of the product life cycle, and the challenges for the regulatory authorities and industry bodies to workably put these new requirements into practice. Most critically, there is a need to ensure these requirements are applied with a sense of proportion based on ethically sound and legally robust governance principles that strike the right balance in serving public interests and protecting private individual rights.

European Transparency Policy

The concept of transparency and the underlying principle are consistently set out in various versions of the Treaty establishing the European Union. The Treaty requires the European institutions to conduct their work as openly as possible, and that any EU citizen and legal entity should have a right of access to documents of the Union's institutions. Regulation 1049/2001/EC (Public Access Regulation) confers an express legal right to access documents held by European institutions. The right to access is not unfettered as it needs to be balanced against certain public and private interests by way of exceptions, such as protection of commercial interests of a natural or legal person. Regulation 726/2004/EC governing the centralized procedure requires that the Public Access Regulation should be applied to documents held by the EMA to enable public access.

Public Access to Clinical Trial Data

European regulators already proactively release a large amount of clinical trial data that are submitted to support an application for marketing authorization once the product is approved. Articles 12 and 13 of Regulation 726/2004 require the EMA to explain the basis of its recommendations to approve or otherwise refuse an authorization in a European Public Assessment Report (EPAR). Similarly, national regulatory agencies are required under the Clinical Trials Directive 2001/20/EC to enter certain information about clinical trials onto the centrally held EudraCT database, and for certain information to be publicly accessible. European Commission guidance adopted in October 2012[1] expanded the scope of the information to be made public. It states that, for all trials, result-related information should be supplied and made public after the completion of the trial, and not only after the grant of the marketing authorization.

The EMA has embraced this principle of transparency and access to documents, and in November 2010, published a policy defining how it would respond to requests for access to documents under the Public Access Regulation.[2] This reactive policy describes the process for the EMA to release documents submitted as part of applications for marketing authorizations to any party that requests them, subject to fairly limited exceptions.

More recently, the EMA announced its commitment to adopt a policy for the proactive publication of data from clinical trials that are submitted to support product approval. This policy was adopted by the EMA's Management Board on Oct. 2, 2014,[3] following nearly 18 months of extensive consultation involving stakeholders with very divergent views on the topic. Under the policy, after the grant of a marketing authorization (or refusal, or withdrawal of the application), the clinical data within the application dossier will be available on the EMA's website. The data will be available in two forms: (i) available to view by all those who register for the website, and (ii) available to download and re-use by academics and for other non-commercial research purposes. All use is subject to the EMA's terms of use, whereby the use of the data must be for non-commercial purposes only.[4] In addition, commercially confidential information will be redacted. Commer-

[1] Commission Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation 726/2004/EC and Article 41(2) of Regulation 1901/2006/EC (2012/C 302/03).

[2] European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use), Nov. 30, 2010, EMA/110196/2006.

[3] European Medicines Agency policy on publication of clinical data for medicinal products for human use, Policy/0070, Oct. 2, 2014, EMA/240810/2013

[4] Data owners also have third-party rights allowing them to enforce the terms of use directly.

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cially confidential information means any information contained in the clinical reports submitted to the EMA by the applicant that is not in the public domain or publicly available, and where disclosure may undermine the legitimate economic interest of the applicant.

Clinical Trials Regulation

Consistent with the EU-wide policy towards increased transparency, the recently adopted Clinical Trials Regulation[5] also contains provisions aimed at increasing the information available about clinical trials. The original proposal for the Regulation created a revised EU-wide database which will be accessible to the public. In particular, sponsors are required to register clinical trials on the database, and provide certain information about the trial, including a summary of the results once the trial is completed.

During the legislative procedure in 2013, the Rapporteur Member of the European Parliament proposed some additional amendments to the Regulation requiring the full results of clinical trials, including the clinical study report, to be published on the database. The final text of the Regulation states that, as well as the original provisions on registration of the trial, the sponsor should submit a summary of the results to the EU database within a year of the end of the trial. In addition, where the trial was intended to be used for obtaining a marketing authorization, the applicant should submit the clinical study report 30 days after the marketing authorization has been granted (or refused or withdrawn). The Regulation also requires Member States to put in place penalties to cover non-compliance with these provisions.[6]

Implementation and Enforcement

The EMA's policy will apply from January 2015 for all new marketing authorization applications that are evaluated under the centralized procedure, and will apply to all line extensions of approved centrally authorized products from July 1, 2015. In contrast, the Clinical Trials Regulation is unlikely to apply until May 28, 2016, at the earliest. The EMA has described its proactive policy as ''a useful complementary tool'' ahead of the implementation of the Regulation. The scope of the two initiatives also is slightly different—under the Clinical Trials Regulation, disclosure will apply to all trials with a study site in the EU, regardless of whether the ultimate authorization is submitted via the centralized or national procedure. In contrast, the EMA's proactive policy applies to all data within a centralized marketing authorization application, regardless of where that study was conducted (but not to nationally authorized products).

However, the EMA acknowledges that the proactive policy has been developed in the absence of any clear legal provision mandating the EMA to proactively publish documents submitted by third parties. The Treaty and Public Access Regulations deal with requests for access to documents, and not to proactive disclosure. The Public Access Regulation was not intended to allow the wholesale disclosure of thousands of pages of detailed clinical trial data submitted by companies that may contain commercially sensitive information describing ongoing and future internal research and development policy. Companies have expressed their considerable concerns about the EMA's reactive policy in relation to the uncontrolled use of the data submitted by the data owner, and its declared stance to apply its policy broadly. Some of these concerns have resulted in legal challenges being initiated.

Given the controversy, the EMA stated that its proactive policy is a balanced approach, taking into account the views of various stakeholders—''*This compromise allows access to clinical data but, at the same time, aims to discourage unfair commercial use of the data*.'' The EMA's policy is clearly a compromise between the position of the academics and patient groups on the one hand, and industry on the other. However, given a lack of legislative underpinning, it is unclear whether the adopted policy will satisfy the calls of protagonists for greater transparency. The proactive policy allows the EMA—and arguably the company—to retain some control over the subsequent use of their data and to protect their rights in those data. However, if a person cannot get access to a document as a result of the restrictions under the proactive policy, they could still request that document under the reactive policy, under which there is no control over subsequent use of the documents or protection of the data owner's rights.

Financial Transparency

In order to manage potential conflicts of interest, transparency concerning the interactions between health-care professionals and industry has been considered as necessary. Conflicts of interest can be direct through, for example, financial interests or ownership of a patent, or indirect through, for example, engagement of health-care professionals in clinical development. There is a general agreement that strong, evidence-based practice requires that objective, unbiased research be available to inform individual clinical decisions, systematic reviews, meta-analyses and expert guideline recommendations.

By way of background, two over-arching principles have been established in EU pharmaceutical law and industry codes of practice to manage transfers of value that may influence the behavior related to prescription and supply of medical treatments. They are: (a) the information provided to health professionals should be objective, unbiased, up-to-date, reliable, accessible, transparent, relevant and consistent with the product label; (b) conflicts of interest of health professionals should be declared and addressed. The new EU transparency policy on transfers of value to health-care professionals is a process that seeks to manage potential conflicts of interest through openness. Specifically, the engagement of the health-care professionals should be based on clear, transparent, good governance principles.

Following the lead of their U.S. counterparts, European pharmaceutical companies under the auspices of the European Federation for the Pharmaceutical Industries Association (EFPIA), the European trade body, will be making public the payments they give to doctors and other allied health-care professionals under a voluntary code of practice. Since July 2, 2013, when the EFPIA

[5] Regulation (EU) No 536/2014 of the European Parliament and of the Council of April 16, 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

[6] The Regulation, Articles 36, 37, 94(2).

Disclosure Code[7] was announced, the European pharmaceutical industry has taken on the complex task to set up the necessary internal systems to collect, categorize and prepare for the disclosure of the relevant data. EFPIA's members include national pharmaceutical associations in 33 European countries, including all of the 28 EU member states (except for Luxembourg), plus Norway, Switzerland, Turkey, Serbia, Russia and Ukraine. Companies will start collecting the data on Jan. 1, 2015, and to publish it within the first half of 2016.

Each member company must disclose any transfers of value that it makes to or for the benefit of a health-care professional (or a health-care organization) in Europe. This includes fees for services and consultancy and contributions to costs of events involving these persons. These are services such as speaking at and chairing meetings, participation in advisory boards, sponsorship in relation to attendance at meetings and training services. There is an aggregate-level reporting for research and development.

It is intended that pharmaceutical companies will use a single database to disclose payments. Out of the 33 EFPIA countries, 13 have declared their intention to disclose payments via a central platform; this is the case, for example, for the U.K., the Netherlands, Greece, Croatia and Romania.

In addition to the voluntary pan-European code, many European jurisdictions had pre-existing financial-disclosure requirements set up in their national laws and industry codes of practice. Other countries currently are reviewing their existing disclosure obligations both under their national laws and by adopting new provisions to implement the agreed new industry practice requirements.

There are specific legal issues that should be taken fully into account in the implementation of the agreed policy.

The Protection of Personal Data

The data to be disclosed about individual health-care professionals will include their name, professional address and other identifiers, together with the amount of the payment or the value of the transfer. These data are considered personal data under European data privacy laws. The EU Data Protection Directive (Directive 95/46/EC) currently under review[8] governs processing (such as the collection and use) of personal data. The Directive has been implemented in all EU countries. Other European countries outside of the EU have similar controls. The Directive imposes specific obligations on those who process and control personal data to ensure security, integrity and quality of such data. Processing is very broadly defined to include obtaining, recording, holding, using, disclosing or erasing data. In fact, any activity involving personal data will fall within its scope. One of these obligations is to process any data in such a way that is ''fair and lawful.'' Having individuals' consent to process their personal data generally is viewed as an important ground for legitimate data processing. Health-care professionals will retain the right to refuse to disclose their personal information and to seek correction of mistakes or deletion of their information.

In practice, to the extent that the disclosure obligations are not required by law but voluntarily agreed via self-regulation, the consent of the data subject is needed to process and disclose his personal data.

This is why the EFPIA has recommended that all pharmaceutical companies include consent provisions in their agreements with health-care professionals and review their existing agreements with this particular consideration in mind. The objective is that companies are able to demonstrate that they already have obtained consent at the time the disclosure is made. In principle, companies will not be in breach of their disclosure obligations simply because they work with a health-care professional who withdraws or refuses to give their consent to disclosure. Generally, payment data will be displayed in aggregate if consent is not given. However, this is a point that is still under discussion at the national association level in some countries. This does not exempt the companies from at least trying to obtain the necessary consent.

The differences on the implementation of the EFPIA Disclosure Code among countries and the additional national transparency regimes have presented significant challenges for companies attempting to develop uniformly applied programs across their affiliates in various geographical regions in order to meet these laws and codes of practice.

Two key jurisdictions, the U.S. and France, already have conducted a first publication of this financial data. All stakeholders may benefit from the lessons learned from these previous experiences and in particular, companies may use them to inform their global compliance efforts.

The U.S. Experience

The U.S. is the biggest pharmaceutical market where the regulators have significant and broad enforcement and investigative powers to take actions in the event of a regulatory breach. In the U.S., the Physician Payment Sunshine Act, the ''Sunshine Act,''[9] was passed as part of the Patient Protection and Affordable Care Act in 2010. It requires manufacturers of pharmaceutical drugs and devices whose products are paid for by the U.S. Medicare, Medicaid, or Children's Health Insurance Program, as well as group purchasing organizations, to report payments or transfers of value made to U.S. physicians and teaching hospitals. The Sunshine Act requires the Centers for Medicare and Medicaid Services (CMS) to publish these payments and other payment-related information on a public website, now referred to as Open Payments, that may be searched and downloaded. On Sept. 30, 2014, the CMS published a portion of data reported by applicable manufacturers for 2013.

[7] European Federation for Pharmaceutical Industries Association (EFPIA) Code on disclosure of transfers of value from pharmaceutical companies to health-care professionals and health-care organizations.

[8] The EU authorities currently are discussing a new data-protection regime to strengthen online privacy rights and boost Europe's digital economy. The draft data protection legislation may be consulted at http://ec.europa.eu/justice/data-protection/.

[9] Section 6002 of the Patient Protection and Affordable Care Act (PPACA). Medicare, Medicaid, Children's Health Insurance Programs; Transparency Reports and Reporting the Physician Ownership or Investment Interests. 78 Fed. Reg. 9458, 9518 (Feb. 8, 2013).

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The Open Payments database did not start on a good foot. After a number of delays, there have been reports of flaws both in the run-up to the publication of the data and after publication. There are complaints about the utility of the database as it is difficult to search (as different types of payments are listed in separate parts of the database and under different legal entities) and concerns about the accuracy of the data (physicians were having difficulties to register on the system to be able to review the data and request corrections). This ended in one-third of the data submitted by companies having to be withheld by the CMS[10]. The technical challenges encountered are partially explained by the large scale of the U.S. transparency initiative. The obligation to disclose was imposed by law and all U.S. records had to be posted on a single website. In comparison, the scale of the European exercise will be smaller as each country will be using its own platform and in some countries data will be disclosed on each company website.

The French Experience

As a reaction to the Mediator scandal (the diabetes medicine benflurex being widely prescribed off-label as an appetite suppressant), France issued its own Sunshine Act on May 21, 2013. More far reaching than its U.S. counterpart and the EFPIA Code (and with a retroactive effect covering 2012), it covers a broader range of industry sectors, including cosmetics and certain medical devices (regardless of whether the products are reimbursed under the French social security regime), and a wider range of possible beneficiaries, including medical students, professional associations, patient associations, foundations and even media. Companies must disclose details of any contracts to provide services, and any benefits, direct or indirect, cash or in kind transfers of value to a centralized public website[11].

The French EFPIA member association, LEEM, has stated that companies who comply with the existing French disclosure law fulfill their obligations as far as the EFPIA code is concerned, thereby allowing companies to comply with the EFPIA requirements by following the French legal provisions. This does not solve the practical problem of the inconsistencies between the scope of the two disclosure regimes.

The French Sunshine Act has taken an inordinate amount of time to be ready with a number of new orders released to modify the original regulation. This was prompted by the need to simplify the form and the substance of the obligations and to deal with the obstacles posed by the strict French data protection legislation. The deadlines for disclosure have been changed a number of times; however, the information was made publicly available on July 3, 2014, on a website governed by the French Ministry of Health[12]. The French data also present flaws, the company information is not user-friendly; however, a search for media coverage does not reveal many stories criticizing the accuracy of the data.

Conclusion

The new European requirements, through public engagement, seek to manage the relations among all stakeholders who are involved or have an interest in research and development and delivery of health care. The new policies seek to promote mutual trust, which is led by transparency, in order to restore credibility of the research enterprise that is critical to innovation of new treatments and technologies. In this regard, there is no denying that the pharmaceutical sector contributes significantly not only to the health and well-being of patients, but also to economic growth and employment in an increasingly knowledge-based economy. Despite the many achievements, the pharmaceutical sector is confronted with a great number of major health, economic and scientific challenges linked to the need to improve efficiency in research and development, and the timely adoption of new technologies into medical practice.

With these considerations in mind, strategic alliance or collaboration has become a new corporate model that will transform the sector into a fully integrated network of expert collaborators. This involves broader engagement with the relevant stakeholders, including those from academia, patients, regulatory authorities and payers, so that drug development becomes more efficient and effective through better access to innovation, relevant expertise and proper management of costs and risks.

All these efforts have resulted in the current debate focusing on development of good governance and best practices that guide interactions among all stakeholders based on fundamental principles of integrity, mutual respect, responsiveness, accountability, collaboration and transparency. However, a balanced approach should be taken to ensure that the means to achieve transparency and openness are not excessive and that the achievement of such an objective is done in such a way that will not undermine the sector's competitiveness in basic and applied research.

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[10] A total of 199,000 records of payments worth $1.1 billion that were submitted to the CMS were not published in the first release of the database. (https://www.cms.gov/OpenPayments/Downloads/Fact-Sheet-Sept-30-2014-Published-Data.pdf).

[11] French Decree No 2013-414 of March 21, 2013, on the transparency of benefits provided by companies producing or marketing products for human health and cosmetic purposes. Found at: http://legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000027434029&categorieLien=id.

[12] Link to the French Sunshine Act website: https://www.transparence.sante.gouv.fr/flow/main;jsessionid=8069649F0D55B525347E2A3339167BCC.sunshine-public?execution=e1s1.