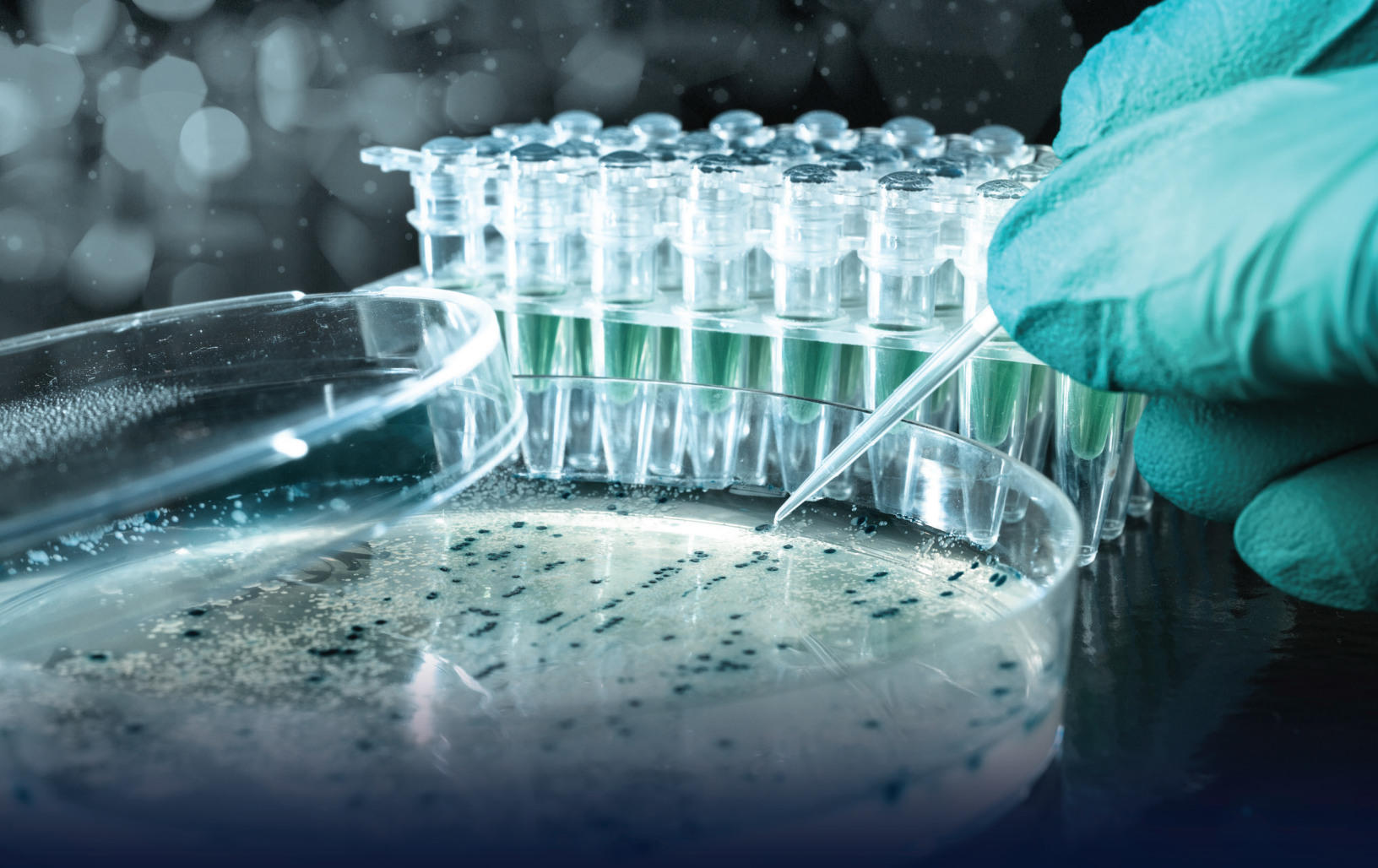

CLINICAL DATA AND DISCLOSURE POLICIES

The European Union, Member States, and International Best Practices

GIPC
Global Intellectual Property Center
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U.S. CHAMBER OF COMMERCE

The U.S. Chamber of Commerce is the world's largest business federation representing the interests of more than 3 million businesses of all sizes, sectors, and regions, as well as state and local chambers and industry associations.

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This report was conducted by Pugatch Consilum, a boutique consultancy that provides evidence-based research, analysis, and intelligence on the fastest growing sectors of the knowledge economy.

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List of Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (DRA, Spain)
AIFA	Agenzia Italiana del Farmaco (DRA, Italy)
BrAPP	British Association of Pharmaceutical Physicians
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (DRA, Germany)
CCI	Commercially Confidential Information
CHMP	Committee for Medicinal Products for Human Use, EU
CSRs	Clinical Study Reports
CTs	Clinical Trials
DRA	Drug Regulatory Authority
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGC	General Court (European Union)
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
HTA	Health Technology Assessment
HMA	Heads of Medicines Agencies
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IP	Intellectual Property
IPRs	Intellectual Property Rights
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Independent HTA agency, Germany)
MAA	Market Authorization Application
MAH	Market Authorization Holder
MHRA	Medicines and Healthcare Products Agency (U.K.)
MPA	Medical Products Agency (Läkemedelsverket, Sweden)
NAFTA	North American Free Trade Agreement
NGO	Nongovernmental Organization
NICE	National Institute for Health and Care Excellence
PhRMA	Pharmaceutical Research and Manufacturers of America
R&D	Research and Development
RDP	Regulatory Data Protection
TLV	Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency, Sweden)
ToU	Terms of Use
TRIPS	Trade-Related Aspects of Intellectual Property Rights
U.K.	United Kingdom
WTO	World Trade Organization

Executive Summary

The purpose of this report is twofold.

First, provide an exhaustive analysis of the clinical data transparency aspects of EU Parliament Regulation 536/2014 on clinical trials and EMA's finalized policies on Publication and Access to Clinical Trials Data.

Second, review the wider policy implications and interface of these central EU-level policies with current data disclosure policies at the EU member state level, looking at five EU countries: Germany, Italy, Spain, Sweden, and the U.K.

Clinical trials represent one of the most important activities carried out by biopharmaceutical companies, scientists, and researchers today. They are fundamental components of the biopharmaceutical research and development process of new medicines and medical technologies. For individual countries and national economies, clinical trials provide direct social and economic benefits. Most obviously, clinical research enables the development of cutting-edge treatments, making novel and innovative medical technologies and products available to patients.

The EU has for a number of years seen a gradual decrease in clinical trial activity. Indeed, across the EU great disparity exists between top and bottom performers. Significantly, both EMA's transparency policy and Regulation 536/2014 seek to stimulate and reverse this trend. It is within this wider context of the state of clinical research in the EU that this report seeks to examine the implications of the new EU regulation on clinical trials and EMA's policy on data disclosure.

Based on this analysis the report highlights three key dimensions of the transparency and data disclosure debate:

1. **Transparency vs. Confidentiality**: Increased transparency of clinical data and research is a laudable goal for all related stakeholders—government, researchers industry, NGOs, and patients. EMA's goals of transparency and public access are both merited and valuable. At the same time, it is also important to balance greater clinical trial transparency with the need to protect proprietary and confidential information. The safeguards built into the EMA policy include a number of important features for market authorization holders, such as recognition by EMA of potential industry CCI, a redaction mechanism, a process of EMA-innovator dialogue prior to publication, and the availability of injunction relief. These are fundamental components of the finalized EMA policy and they need to be implemented and applied in full as the policy moves forward.

2. **Member State Differences**: National transparency and disclosure policies vary greatly between EU member states, with some considerable "gray areas." For instance, legal and regulatory frameworks in place at the member state level can, in some jurisdictions, provides quite broad protection for clinical trial data both in law and in practice. And while it appears that all drug regulatory authorities at the member state level in the five countries sampled are committed to the cause of increased transparency, none of them have a policy of proactively publishing submitted clinical research.

3. **Intragovernmental Differences**: Significant differences exist in disclosure policies between different agencies and governmental bodies within member states. For example, while broadly speaking most institutions and policy bodies (such as drug regulatory authorities, clinical trial ethics committees, and health technology assessment bodies) examined at the member state level support increased disclosure policies, the extent to which they support (through specific policies or in practice) the proactive and specific policies adopted by EMA varies from body to body and country to country.

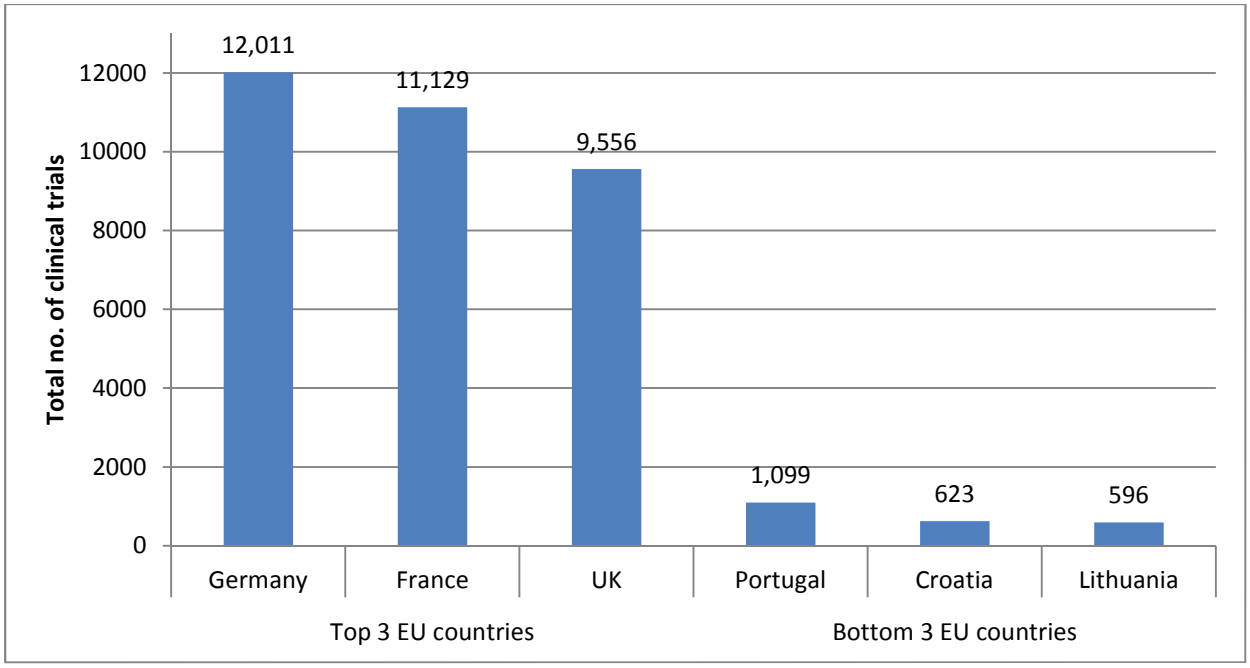
Introduction

This report considers and analyzes the wider policy implications of the clinical data transparency aspects of EU Parliament Regulation 536/2014 and EMA's policy on Publication and Access to Clinical Trials Data, as well as its interface with current data disclosure policies at the EU member state level, looking at five EU countries: Germany, Italy, Spain, Sweden, and the U.K.

Clinical trials represent one of the most important activities carried out by biopharmaceutical companies, scientists, and researchers today. They are fundamental components of the biopharmaceutical research and development process of new medicines and medical technologies. For individual countries and national economies, clinical trials provide direct social and economic benefits. Most obviously, clinical research enables the development and local access to needed cutting-edge treatments, giving patients access to novel and innovative medical technologies and products that normally would be years away. Clinical trials build domestic capacity in biopharmaceutical and clinical research and can over time contribute to containing health care and pharmaceutical costs.

For a number of years the EU has seen a gradual decrease in clinical trial activity.[1] Indeed, across the EU great disparity exists between top and bottom performers. Figure 1 below provides an overview of the top and bottom performers in terms of clinical trial intensity.

Figure 1: Sample of Top and Bottom Performers in the European Union in Terms of Clinical Trial Intensity, 2014[2]



Sources: Pugatch Consilium, Clinicaltrials.gov

The above data show how the top three EU member states host more than 10 times the amount of clinical trials taking place in the bottom three EU member states. Nevertheless, even the European continental leaders of clinical trial activity—Germany, France, and the U.K.—all lag behind countries such as the U.S. and even Singapore on a total and per capita basis.[3]

This drop in research activity and clinical trials conducted in the EU forms the backdrop to both EMA's transparency initiative as well as the new regulation on clinical trials. As will be discussed in this report, both the new regulation and the new policies from EMA seek to increase or, at the very least, not deter investment and clinical research.

The report is structured around the following four sections.

Section 1 provides a brief overview and description of clinical research and poses the question of where control over clinical and research data resides: Does it reside with the public body (whether it be a regulator or evaluator of the data) or with the innovator who invested the time, financial resources, and effort to conduct the research and create the actual data? This section also includes a brief overview of mechanisms, such as biopharmaceutical IPRs, in place to protect and encourage investment and biopharmaceutical innovation.

Section 2 provides an analysis of the proposed and actual transparency initiatives at the central EU level. Specifically, it examines the finalized EMA transparency policy (including safeguards and recourse mechanisms) and the new EU regulation on clinical trials.

Section 3 examines clinical data disclosure and transparency practices by the relevant public bodies in a sample of EU member states. Using case study examples the disclosure and transparency policies and environments in place for clinical research is analyzed in five EU member states: Germany, Italy, Spain, Sweden, and the U.K.

Finally, section 4 provides the main findings of the report on how existing and proposed transparency initiatives should be applied and implemented not only to provide increased levels of data transparency and disclosure but also to maintain and encourage greater levels of biopharmaceutical investment and R&D.

Section 1: Clinical Research Data—Intellectual Property or Public Property?

The past few years have seen drug regulators and policymakers across the developed world zero in on the transparency of clinical data and clinical research. Increasingly, questions are being raised about not only if data collected as part of clinical research and trials should be disclosed, but whether this disclosure should be partial and limited, and carried out in consultation with the sponsor of the clinical trials and research, or if it should be full, and carried out by a regulator or public custodian of the data.

At the center of this debate is a question of where control over clinical and research data resides. Does it reside with the regulator and evaluator of the submitted test data or with the innovator who invested the time, financial resources, and effort to conduct the research and create the actual data? To frame the debate on these issues and the analysis in subsequent sections, this section provides a brief overview of the clinical research and market authorization process as well as the key actors involved.

1.1 Framing the Context—the Biopharmaceutical R&D Process

Developing new biopharmaceutical products and treatments is an expensive, risky, and time-consuming enterprise. While estimates vary, various sources agree on the significant investment and time needed to develop new biopharmaceuticals, with figures ranging from 10 to 15 years and from $1.3 billion to $1.8 billion.[4] Significant resources are invested in basic research and drug discovery as well as the approval, manufacture, and postmarketing monitoring of new drugs. The initial phases involve basic research on disease processes, the discovery of new compounds with potential for treatment, development of the most promising compounds, and analysis of selected compounds, which takes roughly between three and six years. Very few compounds actually make it past this stage to be tested in humans. At the other end of the pipeline, the process of market authorization and manufacturing the drug to scale can take from six months to as much as two years, after which the drug must continue to be monitored and studied as it goes on to medical practice use.

The testing of drug candidates in human volunteers via clinical trials[5] represents the largest investment in the R&D process. The clinical trial process represents an undertaking of six to seven years per drug candidate.[6] One study estimates that the clinical research phase now represents at least 65% of the total cost of the whole R&D process.[7] The process includes complying with a wide range of regulations governing

international best practices related to the quality, safety, and efficacy of drugs, including Good Laboratory Practice guidelines on conducting toxicity studies, Good Manufacturing Practice, and protecting patients through Good Clinical Practice.[8] Despite the huge investment in this process, one recent analysis suggests that only 16% of candidate compounds that are tested in humans are likely to be approved by drug authorities.[9]

1.2 The Rising Cost of Drug Development

The considerable amount of data collected throughout the entire R&D process is thoroughly examined and assembled into an MAA dossier that is entrusted with the DRA for a rigorous and comprehensive evaluation. Crucially this master file, which provides the evidence for the candidate drug's safety, quality, and efficacy, also represents the vast financial and human resources and extensive time needed to acquire and prepare the data for registration and market authorization. It is the sum of all the financial investment, intellectual capital, R&D, and efforts by the innovator to develop a new medicine or medical technology.

The costs and time required for the accumulation and compilation of the data included in a biopharmaceutical registration file has been constantly rising. In the past decade alone, the estimated total costs of drug development have nearly doubled, from an estimated $800 million in 2003 to more than $1.3 billion to $1.8 billion in 2013,[10] with, as mentioned, clinical trials making up the most significant component of the process.

In addition, the complexity and length of the drug development process has also increased. Between 1999 and 2005, the median number of procedures per trial protocol (such as blood tests, X-rays, etc.) increased by 65%; the average length of clinical trials (in days) increased by 70%; and the rate of participants and retention have decreased by 21% and 30%, respectively.[11]

As the number of procedures and time spent on clinical research has increased, so too has the regulatory burden. In most major jurisdictions and drug markets, regulatory requirements have become more stringent and demanding, and, as a result, the length of the evaluation process has increased. For example, the median time for approval of innovative drugs in the EU in 2011 was 447 days,[12] which is more than double than the maximum time limit of 210 days.[13]

1.3 Should Clinical Trial Data be Protected?

Considering the vast financial resources and extensive time needed to acquire and prepare CT data for registration, these data can be viewed as proprietary know-how belonging to biopharmaceutical companies. Indeed, under article 39.3 of the TRIPS agreement, the WTO requires that member states protect these data from "unfair commercial use … [and] against disclosure," two related but distinct concepts.[14]

Introducing Regulatory Data Protection

Recognized internationally for the first time in international agreements by NAFTA and the TRIPS agreement, RDP is a specific type of intellectual property right that prevents third parties (such as generic manufacturers) from relying on these data. In essence RDP is a mechanism in place to ensure that manufacturers of follow-on products that rely on a reference product's submitted MAA cannot obtain marketing approval for their follow-on product for a fixed period of time; that is, for the RDP term.

Unlike patents, RDP does not legally prevent other manufacturers from generating their own registration data. As a rule, RDP legislation in the EU, U.S., Canada, and other major jurisdictions (and in international agreements) does not apply to cases where a second applicant (whether it be a generic or innovator) provides his or her own test data. In such cases the originator may not prevent marketing approval for "new-comers" by invoking RDP. In this sense, as an IP right, RDP is less restrictive and exclusive than, for instance, a patent right.

Layers of Protection

By definition the data included in the registration file of a biopharmaceutical product are disclosed to the health regulatory authorities. Without this data a drug cannot be approved for market use. Generally speaking there are two layers to the responsibility of health regulatory authorities to protect biopharmaceutical registration data against unfair commercial use:

- nondisclosure; and
- protection against unfair commercial use, such as through nonreliance on submitted data.

Nondisclosure aims to ensure that competitors do not gain access to the registration file of the original product.

Nonreliance aims to prevent competitors from relying on and benefiting from an approved registration file in order to compare it to the chemical and toxic levels of the substitute, for example through bioequivalence tests, for a fixed period of time. The concept of nonreliance is for a fixed term which is equivalent to the term of regulatory data protection. As mentioned, this RDP term does not legally prevent other manufacturers from generating their own registration data.

Generally speaking, it has been the layer of reliance that has been the basis for different interpretations and discussions as to what constitutes unfair commercial use of submitted clinical data. This has been the case in developed mature markets as well as emerging and developing countries.[15]

RDP in the EU

RDP legislation in the EU is provided by article 10 of Directive 2004/27/EC (amending 2001/83/EC). This directive was finalized in December 2003 and went into effect in May 2004.[16] Prior to 2003-04 RDP was provided through Directive 2001/83/EC, but legislation was not harmonized between EU members and the term of protection varied between 6 and 10 years. The 2004 amendments harmonized the term of protection according to the 8+2+1 formula. According to this formula new pharmaceutical products are entitled to eight years of data exclusivity, two years of marketing exclusivity (in which generic companies would be allowed to submit bio-equivalence tests), and an additional year of protection for new indications of existing products. This is explained in article 10 of Directive 2001/83/EC.[17] This means that the only clinical trial data a generic company needs to submit in its application for market authorization are from bioequivalence studies. In other words, a generic company can rely on the information generated by the innovator instead of producing its own clinical data. However, the 8+2+1 formula for RDP created by the EU does not allow generic companies to apply this pathway until eight years have passed since the reference product's initial authorization. This period of protection is also provided to biologics.

The EU also provides a separate exclusivity period for orphan drugs. This period is determined based on the characteristics of the product and commercial viability of the product and ranges from 6 to 12 years.[18] An additional period of 2 years exclusivity is available (10+2) for orphan medicines developed for pediatric use through Regulation (EC) No 1901/2006 (Pediatric Regulation).[19]

With regard to the nondisclosure of test data to the public, up until 2010 the nondisclosure element of the EU's RDP regime was clear and undisputed. Guided by Regulation 1049 of 2001 (regarding public access to European Parliament, Council, and Commission documents), EMA did not release to the public documents contained in or as part of a marketing authorization application because these were judged as being of a confidential nature.[20] This changed in 2010 when EMA shifted its position following a ruling by the European Ombudsman and began actively developing new policies and guidelines culminating in the publication of the 2014 policy. This, together with the new clinical trial regulation, is the subject of the next section.

Section 2: Data Disclosure Policies and Transparency Initiatives at the EU Level

2.1 Increasing Transparency and Disclosure of Clinical Trial Data—the EU Reforms its Clinical Trial Laws

Passed by the European Parliament in May 2014, Regulation 536/2014 on clinical trials on medicinal products for human use is the new EU law on clinical trials repealing Directive 2001/20/EC. Although this new law has already entered into force, it will apply only from June 2016.[21]

This legislation is both wide and detailed in its applicability. Fundamentally, the new law changes the manner in which clinical trials are regulated and conducted in the EU. For example, clinical trials conducted in several member states can be applied for and approved through a centralized procedure.[22] Also, regulation will be lighter for trials that are regarded as carrying lower risk. The law also carries with it direct as well as indirect demands for increased transparency of clinical research.

To begin with, one notable change in this new regulation is the establishment of an EU clinical trial database for registration of all clinical trials to be conducted within the EU. Significantly, all the clinical information from these trials is to be stored in an "easily searchable format" so as to "enable citizens of the Union to have access to clinical information about medicinal products."[23] This database, which is to be administered by EMA, will largely replace the existing EudraCT, which until now has been available only to drug regulators and not the general public. All clinical trials conducted within the EU must be registered with this new portal before they begin.[24] According to the new regulation, this database "shall contain the data and information submitted" and defined.[25] Of note is that these transparency requirements include clinical information and data submitted as part of an EU marketing authorization application.

The establishment of a publicly accessible database has obvious implications on the disclosure of information that represents commercial interests. For this reason certain limitations are set on the types of data that can be publicly published. These limitations originate from both the obvious need to protect personal patient data from being publicly disclosed and the understanding that "publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, **while** recognizing the legitimate economic interests of sponsors" [emphasis added].[26]

As discussed in section 1, in the EU, clinical research data have traditionally been viewed as proprietary know-how belonging to biopharmaceutical companies. Protection from "unfair commercial use"[27] has been recognized as a legitimate interest. However, the regulation does not generally consider clinical data as commercially confidential. The regulation states:

> For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorization has been granted, the procedure for granting the marketing authorization has been completed, the application for marketing authorization has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorization of a clinical trial, the decision on the authorization of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.[28]

The regulation later clarifies that information submitted to the clinical research portal will not be published if its confidentiality can be justified. Only on the grounds of an overriding public interest will the said information and data be published:

> The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds … protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure.[29]

At this stage it is difficult to assess the exact impact of the regulation on clinical trial activity and clinical research. It is not clear how and what type of safeguards will be introduced to balance the requirements for increased transparency and publication of clinical research with protecting innovators and commercially confidential information. Nevertheless, the new regulation marks a departure and increase in transparency requirements of clinical research. Coupled with the new policies developed by EMA over the past half-decade, the environment for developing and gaining marketing approval for medicines and medical technologies in the EU has changed.

2.2 New Disclosure Practices within EMA

As mentioned, up until 2010 EMA did not publish any clinical research or data submitted to it as part of a marketing authorization application. Guided by Regulation No. 1049/2001 regarding public access to European Parliament, Council, and Commission documents, EMA did not release to the public documents contained in or as part of a marketing authorization application because these were judged as being of a confidential nature.[30] Article 4 of this regulation permits EU institutions (EMA included) to "refuse access to a document where disclosure would undermine the protection of commercial interests of a natural or legal person, including intellectual property."[31] This changed in 2010 when EMA shifted its position following a ruling by the European Ombudsman and began actively developing new policies and guidelines on how to increase transparency

and data disclosure. Yet neither the legal nor the regulatory framework changed during the time period. As stated in the April 2013 EGC court orders suspending EMA's release of clinical trial data in *AbbVie, Inc.*, *AbbVie Ltd v European Medicines Agency* and *InterMune U.K. Ltd, InterMune, Inc. and InterMune International AG v European Medicines Agency*, the change in EMA policy had not been the result of a change in rules and laws or a judicial ruling. Instead, this change in the agency's position had solely been guided by a change of EMA's interpretation of those relevant rules and laws: "Before the EMA amended its policy on disclosure of clinical study reports, the EMA itself classified those reports as confidential and refused to disclose them to third parties under Regulation No 1049/2001."[32]

In late 2010 EMA published its policy on access to documents (related medicinal products for human and veterinary use).[33] This policy outlined the approach taken by EMA when dealing with requests for access to documents under EMA's possession, and touched on the proactive disclosure of these documents.[34] Following the publication of this policy, the HMA and EMA devised a guidance paper on the identification of CCI in a Marketing Authorisation (MA) dossier after the product approval was granted.[35] The guidance paper's objective was to "facilitate a common and consistent approach across the European Economic Area (EEA) to provide guidance on the identification of commercially confidential information or on personal data that must be protected, provided in the MA dossier after a MA is granted, when dealing with request of access to documents at EEA level."[36]

This guidance (which was formally adopted by EMA in March 2012) identifies CCI as "any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information."[37] The guidance provides a detailed overview of the MA application dossier and determines which part is to be considered confidential (either for commercial reasons or due to personal data protection) or publicly accessible, once the marketing authorization has been granted.[38] However, the document also makes clear that "when it comes to disclosure, the decision lies with the regulatory authorities" and that "in cases of an overriding public health reason, regulatory authorities may disclose information normally classified as Commercially Confidential Information throughout this guidance document if their legislation so provides."[39] Implicitly, this means that disclosure and transparency policies can vary both across EU member states and between member states and central EU institutions such as EMA. (This situation is discussed more fully in the following case study section.)

These policy announcements were accompanied by public pronouncements by senior drug regulators from across the EU. For example, in a 2012 article published in PLOS Medicine, two points were made by these regulators:

1) "clinical data should not be considered commercial confidential information"; and

2) "in an open society, trial sponsors and regulators do not have a monopoly on analyzing and assessing drug trial results."[40]

In June 2013, EMA published *Publication and Access to Clinical-Trial Data*, a draft policy that summed up the agency's work on the issue of transparency and disclosure policies.[41] The draft policy immediately raised considerable discussion from a broad range of stakeholders. Through the remainder of 2013 and into 2014, a number of consultations and meetings were arranged between EMA and affected parties. Many changes to the policy were discussed and suggested during this period, including, for instance, measures to prevent unfair use of published data.[42] Finally, in October 2014, after EMA's management board had unanimously accepted the final revisions to the draft, the agency officially published its new policy: *Publication of Clinical Data for Medicinal Products for Human Use*.

2.3 EMA's Finalized Policy

The stated objective of the 2014 policy is to increase access to data and scrutiny of decisions by EMA without compromising personal privacy or long-term incentives for biopharmaceutical R&D.[43] The policy has two main guiding principles.

The first principle is that increased transparency will lead to greater efficiencies in drug development and medical research. The policy states:

> A high degree of transparency will take regulatory decision-making one step closer to EU citizens, and promote better-informed use of medicines. In addition, the Agency takes the view that access to clinical data will benefit public health in future. The policy has the potential to make medicine development more efficient by establishing a level playing field that allows all medicine developers to learn from past successes and failures. Furthermore, it will enable the wider scientific community to make use of detailed clinical data to develop new knowledge in the interest of public health.[44]

Second, the policy says that greater transparency will bring the agency and its regulatory powers closer to patients: "The Agency also takes the view that a high degree of transparency will take regulatory decision-making one step closer to EU citizens and patients, and promote better-informed use of medicines."[45]

The policy not only provides the agency's position on clinical data transparency, but also exhaustively details its practice regarding the proactive publishing of clinical data held by EMA as of January 1, 2015 (or July 1, 2015, for new indications).

As EMA recognizes, the policy has been shaped in the absence of any clear legal provision mandating EMA to proactively (i.e., in the absence of a specific request under Regulation [EC] 1049/2001 on access to documents) publish documents submitted to the agency by third parties. EMA, therefore, argues it has taken a balanced approach that "takes into account the different stakeholders' competing interests, within the limitations

of the current legal framework."[46] This approach is described as providing a mandate for proactively publishing clinical data under EMA's custody while also applying protection measures for personal and commercially confidential information.

2.4 Defining CCI

EMA's policy includes a significant discussion about clinical data submitted by applicants and CCI. On the one hand, EMA defines CCI as "any information contained in the clinical reports submitted to the Agency by the applicant/MAH that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH."[47] Moreover, EMA states that it "respects and will not divulge CCI."[48] On the other hand, the policy clearly states that "clinical data cannot be considered CCI."[49] Yet as mentioned above, the agency's pre-2010 stance was that all information contained and submitted in a marketing authorization application (including clinical trial data) was confidential and therefore could not be released.

The policy also seeks to ensure future investment in biopharmaceutical research and development:

> Sustained and extensive pharmaceutical research activity is a precondition for future improvements in public health. The policy has no intention to negatively impact on the incentives to invest in future pharmaceutical R&D. It is designed to guard against unintended consequences, e.g. breaches of intellectual property rights that might disincentivise future investment in R&D.[50]

Indeed, as was described in the introduction, the big-picture context in which the EU reformed its laws on clinical trials was the long-term decrease in clinical research and trials activity within the EU. As part of this overall context and policy environment, EMA's policy aims to continue to safeguard protected know-how inasmuch as it is important for incentivizing investment in biopharmaceutical R&D. Specifically, the document states that disclosure will not be allowed "where [it] may undermine the economic and competitive position of the applicant/MAH."[51]

As described for the publication categories, CCI might comprise only specific elements of the studies, mainly details about the product itself; that is, bioanalytical characterizations, in vitro tests, and other studies that do not involve patients.[52] An applicant/MAH will have to provide EMA with justifications for the redaction of certain parts of the clinical data as CCI, and only for the parts which, according to the policy, may contain CCI. These parts and their concomitant justifications are provided in detail in annex 3 of the policy.[53]

Nevertheless, it is interesting to note that the Clinical Trial Advisory Group on Legal Aspects (CTAG5), which was commissioned to advise EMA on its upcoming policy in general and on CCI in particular, concluded its advice by stating that "the Group has not managed to find an agreement about commercially confidential information."[54]

Moreover, the advisory group refers specifically to clinical trial data as partly confidential in nature:

> Some clinical-trial data are commercially confidential and not only in exceptional circumstances, as they contain information such as know-how, intellectual property information regarding the manufacturing, technological approaches and development of innovative medicines proprietary information regarding efficacy and safety measurements and statistical analyses; and the innovator's clinical-trial design and product development strategy as well as the MAH's confidential strategies for managing its clinical development programme. That and other information, which is not in the public domain and for which the author has taken active steps to maintain confidential, would damage the company's commercial interests if made public. This framework reflects the common and well-accepted proposition that Commercially Confidential Information consists of information that a company protects from release because if it were released it could provide competitors a commercial advantage. In this regard, the Commission has recently stated that "keeping valuable information secret is often the only or the most effective way that companies have to protect their intellectual property (such as the results of their research and innovation efforts)."[55]

In addition, while the group's advisory paper outlines in detail the arguments in support of and against a disclosure policy, it nevertheless acknowledges that "a proactive disclosure would require a clear legal basis, which neither Regulation 726/2004 nor Regulation 1049/2001 provide at present."[56]

2.5 Mechanisms and Safeguards for Market Authorization Holders—a Fundamental Part of the New Disclosure Policy

EMA has outlined a process flow to determine what constitutes CCI, what information is to be published, and what safeguards and recourse mechanisms are to be put in place and made available to MAHs. Provided in annex 4 of the policy, this flow begins at the point of submitting an application to EMA, which includes the full Clinical Study Report (CSR[a]). During the appraisal of the dossier, the MAH prepares a second CSR intended for publication, with the redaction of personal data and CCI, in the view of the MAH and in accordance with EMA's principles. If the CHMP's opinion is positive, EMA will review CSR(b) and, if it matches EMA's view, CSR(b) will be published once the decision has been published.[57]

However, if EMA does not approve CSR(b), EMA will initiate a consultation process with the MAH, in which EMA will prepare the CSR intended for publication in EMA's view (CSR(c)) and will send it to the MAH for its approval.[58] While this back-and-forth process must be completed during the appraisal process timelines, in cases where EMA and the MAH cannot reach an agreement on the extent of the redaction, EMA shall have the final say, and it will notify the MAH on the form of the CSR intended for publication.[59]

In cases where the MAH disagrees with EMA's final version of the CSR intended for publication, EMA's policy grants the MAH 10 business days to seek an interim injunction

from the EU General Court.[60] During this time, EMA will publish only the undisputed part of the CSR. However, the application for an interim injunction must be made concomitantly with an application for the annulment of EMA's decision.[61] In cases where the General Court has ruled against granting injunction, the MAH may appeal the General Court's decision within two months.[62]

The introduction of the redaction mechanism, the consultation period between EMA and MAHs, and the availability of injunctive relief and an appeal mechanism are important parts of the finalized EMA policy. It gives MAHs and EMA a formal mechanism and path under which disagreements can be managed, discussed, and resolved. Full implementation and application of these procedures and mechanisms will be an important part of the policy moving forward.

A few stakeholders (including the European Ombudsman) have raised questions on the redaction mechanism, specific redactions made, and the interpretation of what constitutes CCI.[63] While the practical definition and application of what constitutes CCI and what can be agreed to be redacted between MAHs and EMA is ongoing and will develop over time, it is of key importance to recognize that this mechanism and the accompanying consultation period and additional recourse mechanisms offered to MAHs is a critical part of the finalized EMA transparency policy. The continued application and implementation of this part of the policy is an essential component of the overall data disclosure framework.

There is also the issue of potential market authorization delay as a result of disagreement between EMA and the MAH. Lengthy discussions and court proceedings could end up delaying market approval and ultimately patient access to the new product.

2.6 Available Recourse Mechanisms within EMA's Disclosure Policy for Improper Use of Published Clinical Trials

Aiming at allowing access to clinical data, while at the same time discouraging potential unfair commercial use of these data, EMA has incorporated a ToU as a protective measure to be applied for general purposes and for academic and noncommercial use. While users registered for general purpose use are to be able to view published data in "view-on-screen-only" mode after a simple registration process, identified users (who provide EMA with identification details and organization affiliation) can also download and print the data, and are also permitted to refer to them in publications.[64] In addition, a watermark is to be applied to the published information "to emphasize the prohibition of its use for commercial purposes."[65]

The ToU is incorporated in a way that provides EMA with a legal basis for its practice. Specifically, the purpose of the ToU is to exclude the agency from "all representations, warranties, obligations and liabilities in relation to the *Clinical Reports* as made

accessible to the *Users* to the maximum extent permitted by law."[66] In addition, the policy relieves EMA of any responsibility "for the *User's* compliance with the terms" [emphasis in the original].[67] Thus, any use of the published data that exceeds the scope provided in the ToU will be the user's responsibility.

However, cases of legal disputes or claims of improper use arising from the use of published data and the ToU must be settled through a legal channel. Given that EMA is a pan-European agency and potential users of the published clinical research can be situated in any member state, there is a question as to under which legal jurisdiction any disputes or claims would be settled. Therefore, the policy states that any such cases "shall be governed by and construed in accordance with the law of England and Wales."[68] The reason for applying English and Welsh law is that "since the EMA is based in the United Kingdom and the disclosure of documents will take place in that country, the ToU are governed by U.K. law."[69]

While overall a positive step, a number of potential hurdles and scenarios exist whereby an MAH may find that the ToU does not protect the improper use of its published data. To illustrate the potential hurdles and complexities in applying the ToU, the following pages provide a brief scenario analysis. Before outlining the scenario an important caveat must be noted: EMA's policy has only just been adopted and is still at the very beginning of the process of its implementation and full use. Consequently, the purpose of this scenario is not to give a detailed delineation of exactly what will transpire under EMA's new policy. Rather, the purpose is to give a sense of some of the potential hurdles and challenges MAHs, EMA, and other relevant stakeholders could face when dealing with a scenario of improper use of accessed data.

Protecting Against Improper Use of Data—a Scenario Analysis

As mentioned, EMA has stipulated in its policy the terms of use that will apply for anyone who wishes to use the published data. EMA has attempted to be as categorical as possible about the intended use of the published research, emphasizing its noncommercial nature. A few excerpts illustrate this: "the *User* may use the *Clinical Reports* solely for academic and non-commercial research purposes," EMA states, and "the *User* may not use the *Clinical Reports* to support an application to obtain a marketing authorisation and any extensions or variations thereof for a product anywhere in the world" or "make any unfair commercial use of the *Clinical Reports.*"[70] Furthermore, the ToU is governed by U.K. law, which grants the courts of England and Wales a "non-exclusive jurisdiction to settle any dispute or claim arising out of or in connection with these *Terms*."[71]

Although the ToU is an essential part of any legally binding contract,[72] reliance on it as the prime measure against unfair commercial use is potentially difficult for three primary reasons.

First, in some jurisdictions, once information is published within a public domain, it can no longer be regarded as confidential. For example, the Australian Therapeutic Goods

Administration states that "information that is already in the public domain is not considered as commercially confidential. **For example, the prior publication of an evaluation outcome from an overseas regulator would be considered information already in the public domain**" [emphasis added].[73]

Second, the current constellation of legal framework provided by the ToU does not completely address potential violations of the ToU by persons or bodies that act outside the EU or by third parties. For example, consider an entity or institution from a non-EU country that may acquire CT information through a contact within the EU, and then use the information for commercial purposes in his non-EU country. While the ToU strictly forbids such improper use, and would also hold the violator's EU contact liable for his violation,[74] it is not clear how action can be taken against a third party. Legal analysis suggests that while an MAH could use the ToU to take direct action, it would need to identify the specific user of the EMA data to take action against; that is, a direct link would need to established between the breach of the ToU and a specific entity or person.[75] In case of a third party, improper data use would be difficult to trace if the data were sold or transferred to said third party.

The third gap arises as it concerns the possibilities of enforcing ToU violations, as illustrated in the above scenario. Simply put: How would compliance with EMA's ToU be enforced on an entity in a non-EU country? Any potential violations of the ToU are liable to legal action under the law of England and Wales.[76] It is fair to ask whether a successful legal action taken in an English court can be enforced in a jurisdiction outside the U.K. or the EU. This is particularly the case in countries where legal recourse mechanisms are less developed than in the EU. The risk here is that any improper data use occurring outside the U.K. or EU is likely to lead to lengthy litigation and court proceedings. Under this scenario it is difficult to see a practically effective recourse mechanism in place for the enforcement of the EMA ToU. Especially since it is clear that the onus for any potential legal action against improper data use is on an MA holder, not EMA.[77] On this point EMA refers to enforcement in the context of U.K. law. It states: "The Contracts (Rights of Third Parties) Act 1999 opens an opportunity to applicants and MAHs to operate and enforce the ToU directly, even if the EMA were not to enforce them."[78] Thus, it is highly plausible that a ToU violation for commercial purposes outside the EU might lead to legal battles that are fought primarily by MAHs.

2.7 Private Sector Disclosure Policies

Other stakeholders have played an active part in the debate for greater transparency and data disclosure. As is discussed in section 3 for each member state, the AllTrials initiative has been actively supported by a number of bodies, including HTA bodies such as NICE in the U.K.

In addition to these bodies the biopharmaceutical industry has also introduced policies that aim to increase levels of transparency and the availability and dissemination of

clinical research. In 2009, a "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" was published by the innovative pharmaceutical industry's main trade organizations: PhRMA (U.S.), EFPIA (Europe), JPMA (Japan), and IFPMA.[79] This joint position states that "results of all clinical trials should be publicly disclosed, regardless of outcome." Nevertheless, "in all cases disclosure will be undertaken in a manner consistent with applicable national laws and rules governing protection of intellectual property."[80]

More recent is the position statement published by EFPIA and PhRMA in mid-2013 that is now in force and in practice. The *Principles for Responsible Clinical Trial Data Sharing* (*Principles*) outlines a balanced approach between greater transparency and maintaining incentives for further investment in clinical research.[81] Indeed, as noted in a joint BrAPP-ABPI master class, held at the Royal College of Pathologists on March 25, 2014, these principles provide a baseline of minimum requirements for increased transparency, where companies may, and some already have, gone beyond those requirements.[82]

The first element of the industry's principles is the publication of all CT results, whether favorable or unfavorable. As stated in the commitment: "All company-sponsored clinical trials should be considered for publication in the scientific literature irrespective of whether the results of the sponsors' clinical trials are positive or negative. At a minimum, results from all phase 3 clinical trials and any clinical trial results of significant medical importance should be submitted for publication."[83]

The second element concerns the requests for clinical trial data. PhRMA and EFPIA member companies were required under this commitment to "implement a system to receive and review research proposals" and to "establish a scientific review board which will participate in the review of data requests to determine whether they meet the criteria … regarding the qualifications of the requestor and the legitimacy of the research purpose."[84] The criteria are set to ensure the quality of the secondary research, and the researchers are "encouraged and expected to publish the result of their analyses."[85] However, *Principles* also state that "researchers must agree not to transfer the shared data or information to parties not identified in the research proposal, use the data for purposes not contained in the research proposal, or seek to re-identify research participants."[86]

The third element concerns the publication of CSRs. According to *Principles*, "biopharmaceutical companies will make publicly available, at a minimum, the synopses of clinical study reports (CSRs) for clinical trials in patients submitted to the FDA, EMA, or national competent authorities of EU Member States." While personal data and CCI will be redacted from the CSRs, the full versions will be disclosed upon request, per the given criteria.[87] In addition, "biopharmaceutical companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants."[88]

The industry *Principles* provide for a significant opening and increase in transparency while at the same time ensuring stronger mechanisms and measures of protection for individual companies and data. It remains to be seen what the implementation of EMA's policy and the new clinical trial regulation will mean in practice at the EU level as well as at the member state level. But the PhRMA-EFPIA *Principles for Responsible Clinical Trial Data Sharing* are increasing transparency and disclosure of data while maintaining an adequate degree of flexibility and protection for the innovators and creators of this data.

Having provided an overview of the data disclosure policies and legislation at the EU level, the paper now moves to examine the current practices relating to transparency and disclosure of CT data in five EU member states: Germany, Italy, Spain, Sweden, and the U.K.

Section 3: Data Disclosure Practices in the Local Context—a Case Study of Five EU Member States

Having discussed the transparency policies and initiatives that have been launched at the central EU institution level, the purpose of this section is to examine those policies that exist at the member state level.

It is important to reiterate that while EMA has tremendous indirect influence on shaping transparency and disclosure policies at the member state level (as well as more widely internationally), legally its remit extends only to those data and MAA submissions made through the EU's centralized procedure. As cited above (and pointed out by EMA and the HMA in 2012): "When it comes to disclosure, the decision lies with the regulatory authorities."[89] Indeed, disclosure and transparency requirements at the member state level vary among the 27 EU countries. It depends on the background and tradition of, on the one hand, broader issues of political and social transparency and, more specifically, what type of clinical data transparency initiatives have been in place. Overall, national drug regulatory agencies continue to play an important role through both national applications as well as the decentralized procedure and the mutual recognition procedure; the latter two which are both formalized legal procedures for gaining market authorization for medicinal products in more than one EU country.[90]

In addition to drug regulators at the member state level, there are other important actors, such as clinical research ethics committees, P&R authorities, and other health authorities as well as NGOs, patient groups, and other related stakeholders. These groups all independently and jointly shape the transparency debate and ultimately influence disclosure policies. For example, in the U.K. the Health Research Authority (which, through its Research Ethics Committees, reviews and approves applications for clinical research and trials in the U.K.) has publicly declared its intention of increasing transparency as well as the publication of clinical data as part of the ethical review process.[91] The agency is also a signatory to the AllTrials campaign.[92]
Using case study examples, the disclosure and transparency policies and environments in place for clinical research is analyzed in the below subsections in five EU member states: Germany, Italy, Spain, Sweden, and the U.K. Together these five countries provide a good mix of relatively dynamic, innovation-based, and growing economies with economies that face long-term structural challenges as well as immediate economic difficulties caused by the ongoing euro crisis. Furthermore, of particular importance in

this context is that these countries are also relative high versus low clinical trial research performers.

The following table provides some examples of these countries' activity within the clinical trial arena:

Table 1: Clinical Trial Activity within the Five Selected EU Member States

Country	Gross no. of CTs	Standardized no. of CTs per capita	CT activity (2013)	% of phase I+II trials from 2013 activity
Germany	12,230	148.8	733	53%
U.K.	9,770	149.1	694	56%
Italy	7,259	117.2	527	42%
Spain	6,776	141.9	557	41%
Sweden	3,709	375.8	208	39%

Sources: Pugatch Consilium analysis, Clinicaltrials.gov

These data suggest that Germany and the U.K. lead in terms of CT activity, but also in terms of more early stage trials, which typically involve the newest health technologies, but are also the most complex and riskiest to conduct.

Each country discussion below includes three distinct areas of analysis:

- a general overview of the protection of clinical data and relevant public bodies/custodians;
- the specific data protection framework in place with a discussion of trade secret protection; and
- the current national debate/state of play in light of the wider transparency debate and policies put forward by EMA and new clinical trial regulation.

3.1 Germany

General Overview

In Germany the protection and publication of clinical trial data is regulated under the German Medicines Act (Arzneimittelgesetz)[93] and the Act against Unfair Competition (Gesetz gegen den Unlauteren Wettbewerb).[94]

The relevant bodies in the market authorization process in Germany are the German DRA (BfArM), which is an independent body under the supervision of the German Ministry of Health (Bundesministerium fuer Gesundheit), the Joint Federal Committee (G-BA), and

the HTA body, IQWiG. BfArM (an independent federal authority within the portfolio of the Ministry of Health) assesses MAAs of new drugs that were submitted through the decentralized or the mutual recognition processes and grants marketing authorizations based on safety, quality, and efficacy criteria. BfArM is also the national body responsible for pharmacovigilance.[95] The Joint Federal Committee commissions IQWiG to perform clinical assessments of newly marketed drugs. IQWiG's recommendations provide the basis for reimbursement decisions and binding guidelines.[96] As the German official HTA body, IQWiG relies greatly on clinical trial data, provided mainly by BfArM and also by manufacturers per IQWiG's requests.

Data Protection Framework

Data Protection

The protection and publication of clinical trial data is regulated by The Medicines Act[97] and the Act against Unfair Competition.[98] Section 42b of the Medicines Act requires that results from clinical trials, whether favorable or unfavorable, be submitted in the form of a report to the competent authority and entered into a designated database under the responsibility of the German Institute for Medical Documentation and Information.[99]

However, information that concerns the marketing authorization process, the public assessment report, and pharmacovigilance, and is considered to be a trade secret, will be deleted and shall not be disclosed; see section 34 [1a]).[100] In addition, the compliance with the terms of the EU's RDP framework are also provided in the Medicines Act under sections 24a and 24b, which states that requests for marketing authorization information can be complied with only after 10 years have passed since the drug's marketing approval.[101]

Trade Secrets

While no law is dedicated to trade secrets, the protection of trade secrets is regulated under section 17 of the Act against Unfair Competition (Gesetz gegen den Unlauteren Wettbewerb),[102] and under section 6 of the Freedom of Information Act (Informationsfreiheitsgesetz).[103]

According to the definition of the Federal Constitutional Court of Germany (order dated March 14, 2006),[104] information qualifies as a trade secret

- first, if it is related to a particular business enterprise;
- second, if it is kept confidential for the purposes of safeguarding economic interests; and
- third, if the enterprise has an apparent and legitimate interest in keeping the information confidential.

Thus, under the German legislation, commercial know-how qualifies as a trade secret.[105] Section 17 of the Act against Unfair Competition forbids any unauthorized use of information that qualifies as a trade secret for the purposes of competition or for the

benefit of a third party. The Freedom of Information Act also grants similar protection: Section 6 of the act states that "no entitlement to access to information shall apply where such access compromises the protection of intellectual property. Access to business or trade secrets may only be granted subject to the data subject's consent."[106]

Current State of Play in Light of EMA's New Policy

The subject of proactively publishing clinical trial data has gained much interest in Germany, both professionally and from the public, in part due to the unique structure and flow of the drug authorization process. As described, the German HTA body—IQWiG—is an independent body whose clinical benefit assessments are commissioned by the Joint Federal Committee for the purposes of reimbursement decisions and prescription guidelines. Since the beginning of EMA's consultations concerning its proposed new transparency policy, IQWiG has become a key player, because its assessments rely almost wholly on clinical trial data. IQWiG, which receives the information required for its assessments from BfArM, is a strong supporter of EMA's policy for proactively publishing clinical trial data. IQWiG had heavily criticized EMA for accessibility changes that were proposed during the consultation process, claiming that "these conditions make any scientific analysis of clinical trial data, for example as a part of a benefit assessment, absolutely impossible."[107] In IQWiG's comments on EMA's proposed policy, IQWiG made clear its support for the publication of clinical trial data and specifically that these data should not be considered commercially confidential:

> IQWiG strongly supports the statement that clinical trial data cannot be considered CCI and that the interests of public health outweigh consideration of CCI for clinical trial data. IQWiG also supports the classification of documents with regard to CCI in Annexes I and II of the policy.[108]

In addition, IQWiG also stated that "patient-level data should be made available," and that "EMA [should make] available all clinical study reports available at the agency from past or future submissions for any drug approved in Europe."[109] From its perspective, upon receiving what it deems as insufficient information from a manufacturer, IQWiG can decide to withhold its recommendations concerning the drug candidate, thus delaying reimbursement.[110]

NGOs and other nongovernmental actors have also called for increased disclosure of clinical trials. In 2012, the "Berlin Declaration" was launched, which calls for unrestricted access and publication of all clinical trial data. The declaration has been signed by almost 4,000 institutions and persons including the Drug Commission of the German Medical Association, the German Society of Epidemiology and Public Health, and the President of the Berlin Chamber of Physicians.[111] The German Heart Foundation, an additional supporter, has issued a press release with a similar narrative.[112]

However, official governmental bodies, such as the MoH and BfArM, have offered a more muted and balanced approach. For example, BfArM stated in its 2012-13 annual

report that “access to clinical trial information cannot be granted unconditionally, due to the owner’s rights and the potential conflict between the publication of the data and the protection of trade secrets.”[113] Other policymakers have also voiced their concerns over demands for full publication and transparency. In response to the Berlin Declaration, Dr. Peter Liese (a German member of the European Parliament) answered that he does not support the inclusive publication of “raw” data from all clinical trials, on grounds of potential unwarranted access to personal data and the need to protect intellectual property rights.[114]

BfArM’s reluctance to disclose inclusive “raw” data can also be viewed within the complexity of the legal requirements on data protection in Germany. For example, in a 2013 survey of European national drug regulators on existing policies and legislation in place for data protection that was conducted by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, BfArM emphasized that “any response to [request for nonurgent information] exceeding a high-level compilation of information would be extremely burdensome due to the complexity of Data Protection in Germany.”[115]

Table 2: CCI Disclosure Policies in Germany

Can clinical trial data be considered as CCI?	Clinical trial data, which qualify in part as commercial know-how under German law, are considered as a trade secret. As such, certain parts of the information that concerns the marketing authorization process, the public assessment report, and pharmacovigilance will be deleted and shall not be disclosed. However, results of clinical trials, which are registered within the German-designated database, will be published whether favorable or unfavorable.
Are there any classifications/specifications on the disclosure of clinical trial data?	The HTA process is performed by the independent IQWiG, which publishes its preliminary recommendations on its website prior to the publication and implementation of the G-BA guidelines on the drug. IQWiG is a firm supporter of EMA's policy, and has stated that the interests of public health cannot outweigh consideration of CCI for clinical trial data.
Do national HTA agencies, health bodies, NGOs, or patient groups support EMA's policy?	Over 4,000 health authorities and professionals, NGOs, and concerned individuals both from Germany and from other countries have signed the "Berlin Declaration" of 2012, which calls for unrestricted access and publication of all clinical trial data. BfArM's stance on this issue is that access to clinical trial information cannot be granted unconditionally, due to the owner's rights and the potential conflict between the publication of the data and the protection of trade secrets.

3.2 Italy

General Overview

The protection and publication of clinical trial data in Italy is regulated under the Personal Data Protection Code (Codice in materia di protezione dei dati personali)[116] of 2004 and the Industrial Property Code (Codice della proprietà industriale)[117] of 2005. As of 2004, all clinical trials conducted in Italy must be registered within the OsSC database, under the responsibility of the Italian DRA, AIFA.[118]

AIFA is the competent authority responsible for approving drugs for marketing. AIFA bases its decisions on recommendations from two advisory committees: the Technical and Scientific Commission (Commissione Tecnico Scientifica) and the Pricing and Reimbursement Committee (Comitato Prezzi e Rimborso).

The Technical and Scientific Commission (part of the Italian Society of Health Technology Assessment) provides the clinical assessment of the drug candidate's dossier. The authorization process's progress is visible online in a designated website accessible only by pharmaceutical companies.[119]

Data Protection Framework

Data Protection

The Personal Data Protection Code defines personal data that are garnered by public bodies for scientific purposes as substantially within the public interest. The dissemination of research and study data is permitted (provided that personal data have been de-identified, and other related restrictions) "in order to promote and support research and collaboration in science and technology public bodies, including universities and research institutions," with the exception of sensitive data, or data under legal protection, such as trade secrets.[120]

Trade Secrets

Italy is one of few EU countries that have a clear legal definition of trade secrets.[121] Article 98 of the Industrial Property Code states:

> The business information and the technical-industrial expertise, including the commercial ones, subject to the owner's legitimate control, are protected as long as: a) they are secret, in the sense that they are not … generally well-known or easily accessible for experts and operators in the field; b) they have an economic value, and c) they are subjected … to measures which may be deemed reasonably adequate to keep them secret.[122]

The rights that follow on and which are granted to the owner of the trade secret is enunciated in the following article, which states that the: "legitimate owner of the business information and expertise set forth in Article 98 is entitled to prohibit third

parties, absent his consent, from acquiring, disclosing to others or using, unlawfully, such information and expertise, except for cases where they have been achieved autonomously by the third party in question."[123]

Furthermore, a 2013 policy reorganizing the rules concerning the obligations of publicity, transparency, and dissemination of information by public authorities clearly states that "transparency, **in accordance with the provisions of state secrets, of secrecy, statistical confidentiality and protection of personal data**, contributes to the implementation of the principle of democracy and the constitutional principles of equality, fairness, good performance, accountability, effective and efficient use of public resources, integrity and loyalty in service to the nation" [emphasis added].[124]

Under this policy the government may restrict access to certain information in cases where "the documents relate to the privacy or confidentiality of individuals, legal persons, groups, undertakings and associations, with particular reference to the interests of the correspondence, medical, professional, financial, industrial and commercial property owners."[125] Furthermore, "certain information … may be omitted if the information would … prejudice the legitimate commercial interests of economic operators, public or private, or might prejudice fair competition between them."[126]

Current State of Play in Light of EMA's New Policy

In Italy the entire process of the evaluation and assessment of a new drug marketing application is performed by AIFA. The agency is responsible for a wide range of pharmaceutical policy including market authorization, P&R policy, regulation of clinical trials, pharmacovigilance, and manufacturing inspections and certification.[127]

AIFA supports greater transparency. AIFA's position can be viewed in the words of the head of the agency: "The principle of transparency is a fundamental value and a milestone for the Italian Medicines Agency [which]…believes that the overriding pursuit of ever greater levels of transparency and also access to information about clinical trials of drugs … I believe that transparency is not an option but an obligation for those who work in sensitive areas such as public health and it is this belief that we have worked and gained the recognition of directors more transparent and we intend to continue in this path."[128]

However, while promoting transparency in general, AIFA nevertheless places restraints on the type of data that can be made publicly accessible. The public assessment reports of drugs that were authorized under the decentralized or the mutual recognition procedures are being published on AIFA's website, yet only after the deletion of information of a commercially confidential nature.[129] The legislative decree of 2006, which regulates the implementation of EU Directive 2001/83/EC, regulates the current practice on data transparency. Article 32 of this legislation states: "The AIFA shall promptly make available to the public via the website, the evaluation report, together with its reasoned decisions, **after deletion of any information of a commercially confidential nature**" [emphasis added].[130]

The same practice applies for the network of the Regional Ethics Committees: *The Guidelines for the Establishment, Organization and Operation of Ethics Committees for Clinical Trials*, published in 2013, states that "the protocol of the trial must [guarantee] the right to disseminate and publish the results by the investigators who conducted the study in accordance with the provisions in force concerning the confidentiality of sensitive data and patent protection."[131] The published information will be made visible free of charge for health care institutions, yet only "for internal use and by taking all necessary precautions to ensure the confidentiality [of the information]. ... They cannot, however, make it the subject of publications, or other form of scientific communication, without prior permission of the promoter."[132]

In addition, the early recommendations of AIFA's advisory board on the appraisal of market authorization applications—the Technical and Scientific Commission (Commissione Tecnico Scientifica [CTS])—concerning a drug candidate authorization process are visible only to pharmaceutical companies through a designated website.[133] The CTS conducts its assessments with the aid of experts from the National Institute of Health (Istituto Superiore di Sanità). As part of its general policy framework, the institute promotes transparency as one of its administrative goals (and follows the general 2013 regulation outlined above). Neither AIFA nor representatives of the CTS or the National Institute responded to EMA's request for comment on its policy, which was sent to competent authorities of all EU countries in 2013 as part of its consultation process.

Instead, EMA's request was responded to by 13 representatives of numerous patient groups, consumer associations, and lay members of regional ethic committees. In these responses the group of representatives focused on two aspects of the policy, which they considered critical:

1) the need for a clearer definition on what is considered CCI, with emphasis on the publishing of negative CT results; and
2) that the open access and controlled data should be made available to the public along with the submission of the MA application, without waiting for EMA's decision.[134]

Currently, numerous patient groups in Italy are actively involved in the discussion over transparency of clinical trial data. The PartecipaSalute Project (headed by the Mario Negri Institute for Pharmacological Research and the Italian Cochrane Center) is a cooperation and collaboration project that groups together many of these patient groups (such as the Gruppo GRAL and the Gruppo Accademia del cittadino Regione Toscana), experts from various fields (such as pharmacology, medicine, and law), and independent research bodies.

Table 3: CCI Disclosure Policies in Italy

Can clinical trial data be considered as CCI?	Clinical trial data can be considered, in part, as CCI. The legislative framework provides that the government may restrict access to certain information, in cases where the information would prejudice the legitimate commercial interests of economic operators, public or private, or might prejudice fair competition between them.
Are there any classifications/specifications on the disclosure of clinical trial data?	AIFA supports increased transparency, and aims for implementation of greater transparency practices. Nevertheless, the legislative framework provides that certain parts, such as the evaluation report together with its reasoned decisions, will be published only after deletion of any information of a commercially confidential nature. This practice is also shared by the ethics committees.
Do national HTA agencies, health bodies, NGOs, or patient groups support EMA's policy?	The PartecipaSalute Project, which amalgamates several health bodies, NGOs, and patient groups, is a firm supporter of the policy, whose stance is that "the authors and proponents of the research who fail to publish their results" are considered "the worst offenders."

3.3 Spain

General Overview

The protection and publication of clinical trial data in Spain is regulated under three main laws: the Personal Data Protection Law (Ley Orgánica de Protección de Datos de Carácter Personal de España)[135] of 1999, the Unfair Competition Law (Ley de Competencia Desleal)[136] of 1991, and the Clinical Trials Decree (Real Decreto 223/2004 por el que se regulan los ensayos clínicos con medicamentos)[137] of 2004.

The Spanish market authorization authority AEMPS is the competent DRA in Spain. Although the Spanish health care system is highly decentralized, the drug authorization process is performed in whole under the responsibility of AEMPS, which is also responsible for the clinical assessment of the drug candidate master file, clinical trial data included.[138]

AEMPS operates a publicly accessible database (AEMPS Medicines Online Information Center)[139] of all marketed drugs in Spain, in which the marketed drugs' authorization status (authorized, suspended, or revoked) is available as is a summary of characteristics. However, the reasons for revoking a drug are not available on the database, nor are clinical trial data.

Data Protection Framework

Data Protection

The main legislation concerning data protection in Spain is the Personal Data Protection Law (Ley Orgánica de Protección de Datos de Carácter Personal de España)[140] of 1999. This is the primary law that applies to data collected during clinical trials.[141]

In terms of clinical trial-specific regulations, a number of regulations have been enacted relatively recently. In 2004, a new decree regulating clinical trials entered into force. Under this decree a sponsor must "agree with the researcher's obligations regarding data processing, reporting and publication of results."[142] Furthermore, the sponsor of the trial is also "required to publish the results, both positive and negative, of authorized clinical trials in scientific journals."[143] In 2007, further provisions to the Personal Data Protection Law of 1999 were introduced through decree 1720/2007, thus permitting the disclosure of clinical trial data only for the interest of public health.[144] Its enforcement is carried out by the Spanish Data Protection Agency (Agencia Española de Protección de Datos).

Clinical trials in Spain must be registered within the EUDRACT database, as well as within a new designated database established in 2013 by the Spanish MoH. The competent authorities of the autonomous communities have access to clinical trials that are conducted within their territory through the new database. However, under the 2004 Clinical Trials Decree, AEMPS will make publicly available only the trials' sites, pathology, and population tested, given no objections are set by the sponsor.[145] This position is illustrated in legislation from 2006, which regulates the rational use of drugs. Article 16 of this legislation states that "the Spanish Agency for Medicines and Health Products ensures public access to its decisions regarding drug approvals, modifications, suspensions and revocations … and a summary of the product features. … The evaluation report will also be publicly accessible, [yet only] after deletion of any information of a commercially confidential nature."[146]

Trade Secrets

Spain does not have a clear definition of trade secrets. The Unfair Competition Law (Ley de Competencia Desleal)[147] of 1991 provides the legislative framework for the protection of trade secrets. However, it also limits the scope of trade secrets to the information that a company has reasonable and objective interest to keep confidential, in accordance with an objective criterion.[148]

Under this decree, an unauthorized disclosure of a trade or business secret is unfair, if it was "made with the intention of taking advantage … or impair the owner of the secret."

However, intention of gaining advantage over the owner of the trade secret or causing him damage by the disclosure is a necessity.[149]

On the other hand, the decree also provides protection from abuse of dominant position by the owner of the confidential information. Article 7 of the decree states that the concealment of information that is necessary to the recipient's economic decision making (or the provision of unclear, unintelligible, ambiguous information or in a delayed manner) is also considered to be unfair.[150]

Current State of Play in Light of EMA's New Policy

AEMPS is responsible for the drug marketing authorization process in Spain. AEMPS is not responsible for P&R policy or HTA. P&R policy is primarily set at the central level through the Spanish Ministry of Health and other related government agencies. Indeed, since health care in Spain is highly decentralized, some autonomous communities operate their own HTA agencies (e.g., AESTA in Andalusia, and Avalia-t in Galicia). These agencies, however, are not independent bodies, and they all operate under regional health departments and in close collaboration with the national HTA agency, Instituto de Salud Carlos III.[151]

With regard to clinical trials and protection of submitted data, AEMPS has until now been relatively clear in its public stance and actual policy. The current legislative framework and interpretation of it by the Spanish authorities provides a high level of data protection. In addition to the EU-wide 10-year period of RDP, Royal Decree 1345/2007 (which regulates the marketing authorization and registration of drugs) provides complete confidentiality for the entire documentation, which composes the drug candidate's application dossier and the experts' reports on its clinical benefit analysis. Article 15 of this decree is composed of one explicit sentence: "The documentation of the application for authorization and the expert reports shall remain confidential."[152] Similarly, while AEMPS will publish the public assessment report of a product after its approval, publication will only take place after deleting any information deemed to be CCI.[153]

In terms of the new Spanish clinical trial database, while one of its goals, according to the Minister of Health Ana Mato, is transparency, which "guarantees the protection of people and the quality of the results," actual practice suggests that this does not entail full disclosure.[154] This is because the registration of clinical trials in the Spanish database follows the guidelines that were provided by the European Commission in 2009, which "does not contain results-related information on clinical trials."[155] While AEMPS has stated that it will publish both positive and negative results of the trials, public access to the data will be limited "to the relevant parts of the trials."[156] While AEMPS does not elaborate on this issue, the regulatory framework provided in the AEMPS manual for registration of clinical trials suggests that the publication of the EPAR will take place only after deleting any information deemed to be CCI.[157]

In relation to EMA's request for comments on its new policy, AEMPS did not publish any official response. The national HTA agency, Instituto de Salud Carlos III, however, along with the Basque, Andalusian, and the Galician agencies, have all explicitly supported the EUnetHTA position regarding EMA's new policy, which does not consider clinical trial data as CCI, except for the parts classified by EMA as potential CCI (sections 2.7.1, 5.3.1, and 5.3.2 of Annex I of the policy).[158] Currently, both the national and the regional HTA agencies rely on data submitted to them by AEMPS for their clinical benefit assessments.[159] However, these agencies operate under legislation and codes of conduct that forbid the dissemination of information classified as confidential.[160] For example, the Instituto De Salud Carlos III follows the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers, which also refers to the protection of IPRs.[161]

In terms of NGOs and other nongovernmental actors, the Spanish Working Group on Health, Drugs, and Innovation, which is composed of several groups of consumers and of health care professionals (such as the Spanish Organization of Consumers and Users, Pharmacists Without Borders, and Doctors of the World), in June 2014 published a letter to the head of AEMPS. The letter outlines the group's concerns regarding the changes in accessibility (mainly the "view-on-screen-only" mode that was suggested) and urged AEMPS to oppose them.[162]

Table 4: CCI disclosure policies in Spain

Can clinical trial data be considered as CCI?	Clinical trial data are considered, in part, as CCI. The legislative framework provides that "the documentation of the application for authorization and the expert reports shall remain confidential." In addition, AEMPS has stated that it will publish both positive and negative results of clinical trials, which will be registered in the Spanish-designated database, yet public access to the data will be limited only "to the relevant parts of the trials."
Are there any classifications/specifications on the disclosure of clinical trial data?	The legislative framework provides that the publication of the EPAR will occur only after any information deemed to be CCI has been deleted. The confidentiality of CCI is acknowledged in the AEMPS manual for registration of clinical trials and in the national HTA agency's code of conduct.
Do national HTA agencies, health bodies, NGOs, or patient groups support EMA's policy?	The national and regional HTA agencies support full publication of clinical trial information (in accordance with the EUnetHTA's position). This position is also embraced by NGOs including the Spanish Working Group on Health, Drugs, and Innovation.

3.4 Sweden

General Overview

The protection and publication of clinical trial data in Sweden is regulated under the Personal Data Act (Personuppgiftslag) of 1998[163] and the Publicity and Secrecy Act (Offentlighets—och sekretesslag) of 2009.[164] The Medical Products Agency (Läkemedelsverket) is the national competent authority, responsible for the regulation of drug manufacturing and marketing in Sweden.

The primary clinical benefit assessment of drug candidates is performed by the Dental and Pharmaceutical Benefits Agency (TLV), a government agency that makes national pricing and reimbursement decisions for all newly licensed pharmaceuticals in Sweden. In order for a newly marketed drug to be reimbursed within the pharmaceutical benefit scheme, the manufacturer must submit a request for the assessment of its drug candidate

by the TLV through the Swedish DRA.[165] The TLV assessments are based mainly on systematic reviews of the scientific literature.[166]

The Swedish Council on Technology Assessment in Health Care (Statens beredning för medicinsk utvärdering) is an independent HTA agency that may also conduct clinical benefit assessments of drugs for the purposes of producing guidelines and disseminating information for health care professionals; its reports have no bearing on reimbursement decisions.[167]

Data Protection Framework

Data Protection

The publication of clinical trial data is regulated under several laws. The Personal Data Act permits the collection of clinical trial data (regarded as sensitive personal data) for research purposes, if the research has been approved by the ethical board and the research's public benefit outweighs the intrusion of privacy.[168]

In addition, in 2003 the MPA published its "provisions and guidelines on clinical trials of medicinal products for human use," which also relates to the subject of confidentiality. Under these provisions, research investigators and sponsors are required to submit to the MPA "any information required for the Agency to perform its supervision of clinical trials and for the Agency to be able to enter data in the common EU databases."[169] However, with regard to the disclosure of this information, the MPA can provide relevant information, but "only to the parties concerned, and with consideration to confidentiality legislation in force."[170]

Sweden does not operate a designated database for the registration and monitoring of clinical trials conducted within its territory. Instead, clinical trials are registered by the institute in which they are conducted, in addition to their registration within the EudraCT database. For example, the Karolinska Clinical Trials Registry is a Swedish online register of clinical trials being undertaken at the Karolinska University Hospital and other hospitals in Stockholm and the surrounding area.[171]

Trade Secrets

Within the Act on Protection of Trade Secrets of 1990,[172] a trade secret is defined under Swedish law as "information on business relations or operating conditions of a business which is kept secret and of which the disclosure is aimed at causing damage to the business proprietor from a competition point of view."[173] This act, however, is not exhaustive, and does not contain any reference to the subject of competing interests in relation to disclosure of CCI.

In 2009 the Public Access to Information and Secrecy Act entered into force.[174] This act provides that government agencies must consider the right of access to public documents that is granted under the Freedom of the Press Act, and will particularly ensure that individuals are given the opportunity to seek public documents.[175] However, a stipulation

of maintaining confidentiality does exist, and classified information shall not be disclosed to individuals or other authorities unless where specified by the act. In addition, the act also states that a government agency that is provided with confidential information is compelled to keep it confidential under law. Significantly, in cases of conflict between secrecy provisions, where one permits the disclosure of specific information, this provision prevails.[176]

Current State of Play in Light of EMA's New Policy

The Swedish MPA supports increased transparency initiatives, yet is compelled under current legislation not to disclose CCI. In its website, the Swedish MPA states that "The MPA, like all government agencies, follows the basic rules to ensure open government. According to Freedom of the Press Act, the documents of the administration requested by the public shall be disclosed promptly. However the MPA is also has under obligation to follow the rules contained in the Official Secrets Act."[177] The provisions set within the Secrecy Act are comprehensive and straightforward, and legally binding for all public and private agencies, such as the TLV.

The Swedish Medical Association (Läkarförbundet) explicitly supports the AllTrials campaign and its call for increased data transparency.[178] In addition, the Swedish Higher Education and Research Council is a signatory of the aforementioned Berlin Declaration of 2012, which calls for unrestricted access and publication of all clinical trial data.[179]

However, EMA's request for comments on its new 2013 policy was met only with the SBU's explicit support in the EUnetHTA position.[180] However, as mentioned, the SBU is an independent body that produces assessments that are based on systematic literature reviews of published research on the topic at hand.[181] Its reports have no bearing on reimbursement decisions.[182]

Table 5: CCI Disclosure Policies in Sweden

Can clinical trial data be considered as CCI?	The Swedish legislative framework does not contain any reference to the subject of competing interests in relation to disclosure of CCI. However, under this framework, clinical trial data can be considered, in part, as a trade secret, thus compelling the MPA to disclose such information "only to the parties concerned, and with consideration to confidentiality legislation in force."
Are there any classifications/specifications on the disclosure of clinical trial data?	The MPA has to date not provided a detailed list of clinical trial data that constitute a trade secret. In addition, while several health authorities and NGOs showed explicit support in EMA's policy, official positions by the MPA emphasize the overarching legal framework, which restricts the disclosure of confidential information
Do national HTA agencies, health bodies, NGOs, or patient groups support EMA's policy?	The SBU supports the EUnetHTA position, which does not consider clinical trial data as CCI, except for the parts classified by EMA as potential CCI.

3.5 United Kingdom

General Overview

The protection and publication of clinical trial data in the U.K. is regulated under the Freedom of Information Act of 2000 (which modified the Data Protection Act for public bodies and authorities)[183] and the Common Law Duty on Confidentiality.[184]

The MHRA is the national DRA, which is responsible for the entire MA process of a drug candidate, including its clinical benefit assessment, and the registration of clinical trials in the U.K. The MHRA makes its Public Assessment Reports publicly available, albeit with personal data and CCI removed.[185]

NICE, a nondepartmental public body, conducts clinical and economic drug assessments based on a set of criteria related to the authorized drug's use. Its recommendations serve as the basis for the scope of a drug candidate's inclusion within the National Health Service.[186] NICE makes its recommendations publicly available through its website, in full or in a summarized version[187]; yet personal data and CCI is disclosed only in cases where the interest of the public in disclosing the information outweighs the interest of the public in withholding it.[188]

Since 2014, clinical trials designated to be conducted within the U.K. must be registered in a publicly available database operated by the Health Research Authority, a national organization aimed at streamlining research regulation in the U.K.[189] While the registration is not mandatory, it is a condition for a favorable opinion of the Research Ethics Committee, and noncompliance is considered a breach of established regulations under Good Research Practice.[190]

Data Protection Framework

Data Protection

The publication of clinical data in the U.K. is regulated under several laws and codes of practice, yet the primary law is the Freedom of Information Act.[191] The Freedom of Information Act 2000 provides public access to information held by public authorities by compelling them to publish certain information about their activities, and by allowing members of the public to request information from public authorities.[192]

The Freedom of Information Act provides exemptions that require a public interest test that permits the disclosure of exempt information in cases where the interest of the public in disclosing the information outweighs the interest of the public in withholding it.[193] Section 43 of the act states that "information is exempt information if it constitutes a trade secret, or if its disclosure under this Act would, or would be likely to, prejudice the commercial interests of any person (including the public authority holding it)."[194]

In the Guidance on the Disclosure of Types of Human and Veterinary Medicines Information prepared by the MHRA in discussion with the ABPI and others, the MHRA details the types of information that are exempt from public disclosure, such as "information provided in confidence" and information that represents a "commercial interest."[195] However, the Freedom of Information Act differs between "absolute exemptions," which automatically reject requests to access such information, and "qualified exemptions," which necessitate a public interest test. In these instances the MHRA will consider whether the interest of the public in disclosing the information outweighs the interest of the public in withholding it.[196]

The MHRA treats each request for information on a case-by-case basis, and may consult with the owner of the information prior to its submission upon request.[197] Although the owner's refusal to permit the disclosure of said information is not binding, the MHRA will not submit information that is exempt under the Freedom of Information Act.[198]

The information that is routinely published, or disclosed upon request, is detailed in the aforementioned guidelines prepared by the MHRA, and consists of (among others)

- remote access for companies to view confidential information about their own marketing authorizations;
- reasons leading to the suspension or revocation of marketing authorization; and
- decisions about designation of borderline/unauthorized products.[199]

Trade Secrets

The U.K. does not have designated or specific trade secret legislation in place. Currently, trade secrets are protected in the U.K. under common law, on a case-by-case basis.[200] This means that the scope of protection on trade secrets and its limitations are provided by court decisions and precedents.

In order to qualify as a trade secret, the information must have the "necessary quality of confidence" about it; that is, confidential circumstances must exist in order to create an obligation to keep the information confidential, such as commercial interests.[201]

In terms of the MHRA and clinical data, the aforementioned guidelines prepared by the MHRA provide a detailed list of the types of information that will be routinely published and hold no exemptions, and information considered as qualified exemptions will be subjected to a public interest test prior to its disclosure upon request by third parties.[202] For example, the detailed information on a drug's development and manufacturing process, marketing authorization applications, and the disclosure of clinical trial data after grant of marketing authorization are considered as qualified exemptions, and are therefore liable to the public interest test.[203] The guidance acknowledges the competing interests in these cases:

> This type of information represents a considerable investment by the company submitting the dossier. It could, if disclosed, harm their commercial interests and offer commercial advantage to competitors. … Release of such information could affect decisions by pharmaceutical companies to market medicines in the U.K. to the detriment of patient and animal welfare. Any request for information that we suspect may have commercial sensitivity would be tested for public interest with the third party before disclosure.[204]

Current State of Play in Light of EMA's New Policy

The unique infrastructure of a new drug's marketing authorization process in the U.K., which involves the national competent authority (MHRA) as well as a nondepartmental HTA body (NICE) and additional national organizations (such as the HRA), bears a potential for conflicts between different policy points.

As discussed earlier, the MHRA has published guidelines that provide a detailed outline of the types of information that are considered as potentially CCI, and are therefore liable to the public interest case, in which the MHRA will consider whether the interest of the public in disclosing the information outweighs the interest of the public in withholding it.[205] Although the list is not exhaustive, it can potentially be stricter than EMA's definitions in terms of the scope of what is considered as confidential information, as detailed in its policy's annex.[206] For example, the guidance makes it clear that "any information prior to granting or refusing a marketing application" and "some of the information post grant" is considered in the MHRA guidelines as trade secrets and know-

how that represent commercial interests, and therefore is liable to the public interest test with the information's owner prior to its disclosure.[207]
On its website, the MHRA states that it is "committed to ensuring transparency in the area of clinical trial data"; however, the emphasis is being placed on the "greater transparency of clinical trial results to be achieved via the development of the European Union clinical trials register," while the subject of EMA's proactive publishing of "raw data" of CTs receives no reference.[208]

NICE (one of the early signatories of the AllTrials Campaign) holds a more favorable view of the proactive publishing of CT data. In one of its official statements on its website, NICE states that it "strongly believes that all clinical trial data should be made available so that those with responsibility for developing guidance and making treatment decisions have all the necessary information at hand to help them do so safely and efficiently. … However, NICE will only approach the European regulatory authorities if the pharmaceutical companies have not provided the necessary clinical data."[209]

NICE's publication scheme is outlined in detail within its technology appraisal guide. The CT data upon which NICE bases its appraisals are attained either directly from the manufacturer or through the MHRA,[210] and are subject to a confidentiality agreement that is signed between NICE and the manufacturer, and that is binding for NICE's consultants and commentators as well.[211] In places where the information provided to NICE is considered CCI, "it is the responsibility of the submitter to provide 2 versions: a version for NICE to share with the Appraisal Committee and consultants and commentators (including the confidential information marked as per the instructions provided by NICE), and another for release into the public domain (with the confidential information redacted)."[212]

In its publication scheme, NICE recognizes the need to strike a balance between the potentially conflicting commercial and public interests:

> If NICE wishes to publish or share data regarded by the data owner as academic or commercial in confidence, both NICE and the data owner will negotiate to find a mutually acceptable solution, recognising the need for NICE to support its recommendations with evidence and the data owner's right to publication. However, the data owner retains the right to make a final decision about the release of confidential information to consultees and commentators and into the public domain.[213]

However, while NICE acknowledges the data owner's "right to make a final decision about the release of confidential information … into the public domain," it nevertheless requires justification for such decisions. In its publication scheme NICE states that "if NICE is challenged that confidential information it has received should be released in the interests of fairness during an appraisal, at appeal, through judicial review or otherwise, the information's owner must submit evidence justifying the reasons for NICE

maintaining that confidentiality. Without such evidence, NICE is entitled to conclude that the information is no longer confidential."[214]

In a recent hearing within the House of Commons Health Select Committee on NICE, Prof. David Haslam, NICE chair, stated:

> My personal view on this is I can see no reason whatsoever not to publish all the data, and I think there's a moral imperative from the point of view of the patients who've been part of the trials that their time, their effort shouldn't be ignored. I think everything should be in the public domain and I've always felt that way very strongly.[215]

Other groups, whether they be professional bodies or NGOs, have also expressed support. For example, a recent survey conducted within the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians found that 80% to 90% of respondents believe that increased publication of clinical trial results (including negative results) and increased access to clinical trial data will ultimately lead to better medicines and better health care for patients, while 10% to 18% believe that increased access to a publication and dissemination of clinical trial results will harm the commercial environment in which companies operate.[216] Based on these findings, the faculty has provided numerous recommendations, such as that "summary-level results of clinical trials [will be] submitted for publication soon after trial completion," and that "the pharmaceutical industry [should] revisit its policy of publication … and adopt the more generally accepted policy of publication based on trial completion date."[217]

And, of course, the AllTrials campaign began in the U.K., launched in 2013. Its website states that the campaign is an initiative of "Bad Science, BMJ [British Medical Journal], Centre for Evidence-based Medicine, Cochrane Collaboration, James Lind Initiative, PLOS and Sense About Science and is being led in the US by Dartmouth's Geisel School of Medicine and the Dartmouth Institute for Health Policy & Clinical Practice."[218]

Table 6: CCI Disclosure Policies in the U.K.

Can clinical trial data be considered as CCI?	Clinical trial data can, in part, be considered as CCI. Their disclosure will be considered by the MHRA on a case-by-case basis and upon a public interest test, which considers whether the interest of the public in disclosing the information outweighs the interest of the public in withholding it.
Are there any classifications/specifications on the disclosure of clinical trial data?	The MHRA has published guidance that provides a detailed list of the types of information that will be routinely published, disclosed upon request, and information that will be subjected to the public interest test prior to its disclosure upon request.
Do national HTA agencies, health bodies, NGOs, or patient groups support EMA's policy?	NICE has been a long-standing supporter of the publication of clinical trial data. The AllTrials initiative started in the U.K.

Section 4: Conclusions

The purpose of this report has been twofold.

First, provide an exhaustive analysis of EU Parliament Regulation 536/2014 on clinical trials and EMA's finalized policies on Publication and Access to Clinical Trials Data.

Second, review the wider policy implications and interface of these central EU-level policies with current data disclosure policies at the EU member state level, looking at five EU countries: Germany, Italy, Spain, Sweden, and the U.K.

Based on this analysis the report highlights three key dimensions of the transparency and data disclosure debate:

1. **Transparency vs. Confidentiality**: Increased transparency of clinical data and research is a laudable goal for all related stakeholders—government, researchers industry, NGOs, and patients. EMA's goal of transparency and public access is both merited and valuable. At the same time, it is also important to balance greater clinical trial transparency with the need to protect proprietary and confidential information. The safeguards built into the finalized EMA policy includes a number of important features for market authorization holders, such as the availability of injunctive relief, a redaction mechanism, a recognition by EMA of CCI, and a process of EMA-innovator dialogue prior to publication. These are fundamental components of the finalized EMA policy and they need to be implemented and applied in full as the policy moves forward.
2. **Member State Differences**: National transparency and disclosure policies vary greatly between EU member states with some considerable "gray areas." For instance, legal and regulatory frameworks in place at the member state level can, in some jurisdictions, provide quite broad protection for clinical trial data both in law and in practice. And while it appears that all drug regulatory authorities at the member state level in the five countries sampled are committed to the cause of increased transparency, none of them have a policy of proactively publishing submitted clinical research.
3. **Intragovernmental Differences**: Significant differences exist in disclosure policies between different agencies and governmental bodies within member states. For example, while broadly speaking most institutions and policy bodies (such as drug regulatory authorities, clinical trial ethics committees, and health technology assessment bodies) examined at the member state level support increased disclosure policies, the extent to which they support (through specific policies or in practice) the proactive and specific policies adopted by EMA varies from body to body and country to country.

The increase of clinical data disclosure through the new regulation on clinical trials and EMA's finalized policies marks a change in the manner in which clinical test data are treated in the EU. Prior to 2010, EMA did not release or proactively publish any such data on the grounds of confidentiality and the protection of confidential information. Through a long process of consultation and discussion, a number of important safeguards and mechanisms to protect confidential information have been introduced into the finalized EMA policy. These include the availability of injunctive relief, a redaction mechanism, a recognition by EMA of CCI, and a process of EMA-innovator dialogue prior to publication. And while potential challenges in practical application exist, a ToU is also in place to protect the improper use of accessed data for, for example, commercial purposes.

Together these mechanisms provide MAHs with a clearer process on how to appeal and resolve differences between EMA and MAHs on what constitutes CCI and what information should be made publicly available. Yet while the policy is now in place and finalized, the next challenge is to ensure that the application and implementation of the finalized policy includes and fully makes available these mechanisms and safeguards.

Notes

[1] See Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, p. 2; and D. Cressey. (2014). "Overhaul Complete for EU Clinical Trials," *Nature*, June 4, 2014.

[2] Based on number of registered clinical trials within the clinicaltrials.gov database as of 2014.

[3] Pugatch Consilium. (2014). *Scaling up Global Clinical Trial Activity: Key Trends and Policy Lessons*, October 2014, http://www.pugatch-consilium.com/?p=1967.

[4] Mestre-Ferrandiz, J., Sussex, J. & Towse, A. (2012). *The R&D Cost of a New Medicine*, Office of Health Economics, p. 1.

[5] The World Health Organization defines clinical trials as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." See WHO. "Health Topics: Clinical Trials," http://www.who.int/topics/clinical_trials/en/.

[6] Mestre-Ferrandiz, J., Sussex, J. & Towse, A. (2012). *The R&D Cost...*, p. 24.

[7] DiMasi, J. & Grabowski, H. (2007). "The Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, Vol. 28, Issue 4-5, p. 472.

[8] International Conference on Harmonisation of Technical Requirements for Registration of Biopharmaceuticals for Human Use (ICH), "ICH Guidelines," http://www.ich.org/products/guidelines.html.

[9] DiMasi, J., Feldman, L., Seckler, A. & Wilson, A. (2010). "Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs," *Clinical Pharmacology and Therapeutics*, Vol. 87, No. 3, pp. 272-277.

[10] See DiMasi, J. A. et al. (2003). "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, Vol. 22.2, p. 151-185; see also Mestre-Ferrandiz, D. et al. (2012). "The R&D Cost of a New Medicine," London: Office of Health Economics, p. v.

[11] PhRMA. (2013). *The Biopharmaceutical Research Industry Profile, 2013*, Washington, D.C., p. 37, http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf.

[12] Wang, T. & McAuslane, N. (2012). *New Drug Approvals in ICH Countries: 2002-2011*, Centre for Innovation in Regulatory Science (CIRS), p. 1, http://cirsci.org/sites/default/files/New%20drug%20approvals%20in%20ICH%20countries%2002-11%20for%20release.pdf.

[13] EMA. (2013). *Applying for EU Marketing Authorisation for Medicinal Products for Human Use*, http://www.ema.europa.eu/docs/en_GB/document_library/Brochure/2011/03/WC500104233.pdf.

[14] WTO, TRIPS Agreement, part II—Standards concerning the availability, scope, and use of intellectual property rights, section 7: protection of undisclosed information, article 39(3). The full article reads: "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."

[15] For example, up until 2006, the Canadian biopharmaceutical regulations provided little actual protection for clinical data submitted during the market approval process. Russia is another example, being one of the most recent high-profile countries to commit to the introduction of a six-year RDP term as part of its accession to the WTO. The growth in the number of markets introducing an RDP framework is a reflection of the value of offering protection for submitted clinical test data and how offering RDP encourages biopharmaceutical investment and the introduction of new products.

[16] *Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 Amending Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use*, Official Journal of the European Communities, April 30, 2004, L 136/34. For the previous legislation, see also *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use*, Official Journal of the European Communities, November 28, 2001, L 311/67.

[17] Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. The article reads:

By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-

clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorized together with the full composition of the reference product and if necessary other relevant documentation. The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

[18] See Hathaway, C. et al. (2009). "Exclusivity Strategies in the United States and European Union," *Food and Drug Law Institute*, May/June, pp. 37-38.

[19] See Regulation (EC) No. 1901/2006 of the European Parliament and of the Council and DG Health and Consumers, "Medicines for Children," accessed March 2014, http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm.

[20] For full details of the relevant guiding regulations and interpretation, see "Order of the President of the General Court," Case T‑44/13 R, AbbVie, Inc., AbbVie Ltd v European Medicines Agency (EMA), European Court of Justice, April 25, 2013.

[21] See Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, OJ L 158, May 27, 2014, article 99, p. 53.

[22] D. Cressey. (2014). "Overhaul Complete for EU Clinical Trials," *Nature*, June 4.

[23] Ibid., article 81, §2, p. 48.

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