TRANSPARENCY OF PRE-CLINICAL AND CLINICAL TRIAL DATA IN THE EUI

This document is published by Practical Law and can be found at: uk.practicallaw.com/**w-017-1498**
Get more information on Practical Law and request a free trial at: **www.practicallaw.com**

This note focuses on the transparency of pre-clinical and clinical trial data in the EU. The note identifies relevant legislation and explores guidance documents that relate to the proactive and reactive disclosure of pre-clinical and clinical trial data, including EMA Policies 70 and 43. Key case law is summarised.

by *Jackie Mulryne*, *Arnold & Porter*

RESOURCE INFORMATION

RESOURCE ID

w-017-1498

RESOURCE TYPE

Practice note

CREATED ON

25 January 2019

CONTENTS

SCOPE OF THIS NOTE

This note sets out the current legislation and guidance documents that require disclosure of pre-clinical and clinical trial data in the European Union (EU). It explores the position of the European Medicines Agency (EMA) in relation to disclosure and industry and other stakeholder responses. In particular, it discusses the current initiatives in relation to:

- Proactive disclosure (that is, the information that is released by the EMA and other bodies).
- Reactive disclosure (that is, how the EMA responds to requests for access to documents).

The EMA's policies do not apply to documents held by the national authorities. Many national competent authorities take a different view of disclosure and what should be considered as commercially confidential information and so withheld from disclosure. Those interpretations are not covered by this note.

TRANSPARENCY OF DOCUMENTS

The principle of transparency of documents is enshrined in the fundamental texts of the EU. The Treaty establishing the European Community (and its subsequent versions) notes that the European institutions should conduct their work as openly as possible, and that any citizen of the EU, and any natural or legal person residing or having its registered office in a member state, should have a right of access to documents of the EU's institutions. To implement this, the *Access to Documents Regulation ((EC) 1049/2001)* grants EU citizens and legal entities an express right to access documents held by European institutions.

In relation to medicinal products and the work of the EMA, *Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency* requires that the Access to Documents Regulation should be applied to documents held by the EMA. To implement this, the EMA has chosen to interpret the general right of access very widely, and has stated that one of its key goals is the publication of clinical trial data for a product once the decision-making process on the application is complete. This is because of the perceived importance of establishing trust and confidence in the regulatory system, so the public has a better understanding of regulatory decision-making.

This broad policy of disclosure has been controversial. Many of the documents held by the EMA are documents from third parties, who have submitted data in order to obtain a marketing authorisation for each of their products. This is quite different from legislative or policy documents held by many other EU institutions. A wide interpretation of access does not recognise that the data submitted by companies could contain commercially confidential information. However, there is the perception that companies have, in the past, hidden "unhelpful" data and have not been pro-active in publishing negative data, which may influence how healthcare professionals and regulators view the safety and efficacy of the products. Indeed, in 2015, *The Economist* published an "interactive clinical trial simulator" to demonstrate the potential distortion that may occur if you selectively publish positive results, and supress unfavourable results, for a fictional product (see *The Economist: Clinical trial simulator (29 July 2015)*). As such, many believe companies cannot be trusted to release data about their products.

COMMERCIALLY CONFIDENTIAL INFORMATION

The EMA accepts that "commercially confidential information" should not be disclosed. While there is no definition of "commercially confidential information" in the legislation, the EMA uses the following definition:

> "... 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."
>
> (*EMA: European Medicines Agency policy on access to documents Policy/0043 EMA/729522/2016 (4 October 2018)*. Slightly different wording is used in other EMA documents, but the key elements of the definition are unchanged.)

Under this definition, the relevant information must be both confidential, and harm the economic interests of a company if it were disclosed.

There are significant differences of opinion on what data within the marketing authorisation dossier, other than manufacturing information, should be kept confidential under this definition. A wide approach to disclosure has been sought by academic researchers and patient groups through their related campaigns. While many pharmaceutical companies agree with disclosure of data for non-commercial purposes, industry has been more cautious about the wholesale disclosure of its data where the data can be accessed by competitors. Further, many companies consider certain information within the authorisation dossier to be confidential, and that disclosure would undermine the protection of their commercial interests (including intellectual property rights).

The EMA previously treated pre-clinical and clinical trial data as confidential, and refused disclosure of such data. However, in 2010, the European Ombudsman, who investigates complaints of maladministration by EU institutions, delivered a number of decisions that were critical of the approach of the EMA, including one relating to clinical study reports (*European Ombudsman: Decision of the European Ombudsman closing his inquiry into complaint 2560/2007/BEH against the European Medicines Agency (24 November 2010)*).

Following these decisions, the EMA has said that it does not consider pre-clinical data or data from clinical trials to be commercially confidential, and it has since released a substantial amount of trial data.

INFORMATION ALREADY RELEASED

Even before considering the *Access to Documents Regulation* and its application to the EMA, competent authorities in the EU already release a large amount of data concerning trials and contained within marketing authorisation dossiers. Once an authorisation has been granted, the relevant data is released. In particular, the publication of each European Public Assessment Report (EPAR) seeks to provide transparency of the basis on which the decision to grant a marketing authorisation has been made, and includes a summary of, and the conclusions reached on, the documentation (both clinical and pre-clinical) submitted by the applicant (Articles 12 and 13 of Regulation 726/2004, or its national equivalent for products subject to national assessment through the decentralised and mutual recognition procedures under Article 21(4) of *Directive 2001/83/EC on the Community code relating to medicinal products for human use*). The EMA also publishes detailed information about the decisions taken by its Committee for Medicinal Products for Human Use and other committees.

In relation to clinical trials specifically, the principle of providing information on clinical trials has been in place since the Declaration of Helsinki in 1968. This is a statement of ethical principles for medical research involving human subjects. As part of this, every research study involving human subjects should be registered in a publicly accessible database before recruitment of the first subject. There are also obligations with regard to the publication and dissemination of the results of research:

> "Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports."
>
> (*World Medical Association: WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (9 July 2018), paragraph 36.*)

In the EU, this broad principle is reflected in the *Clinical Trials Directive (2001/20/EC)*. Member states have an obligation under Article 11 of the Clinical Trials Directive to enter certain information about clinical trials onto the EudraCT database (see eudract.ema.europa.eu) and are required to make some of that information public, in particular in relation to paediatric trials (*Article 57(2) of Regulation 726/2004 and Article 41(1) of the Paediatric Regulation ((EC) 1901/2006)*). The EU Clinical Trials Register (see clinicaltrialsregister.eu) includes publicly available information extracted from the EudraCT database. Companies also have obligations under Articles 41(2), 45(1) and 46(1) of the Paediatric Regulation to supply information to the EMA concerning paediatric studies they have sponsored, or that they are aware are sponsored by others but conducted with their product. The European Commission guidance expands on these obligations and sets out details on the information to be included in the database, and the information to be made public. The guidance states that for all trials (paediatric and non-paediatric), result-related information should be supplied and made public within 12 months of the completion of the trial (not after grant of the marketing authorisation), including a summary of the results and conclusions (*Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC) No 726/2004 (OJ 2008 C 168/02)* and *Commission Guideline on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (OJ 2012 C 302/03)* (October 2012 Commission guidance)).

In addition, self-regulatory codes of practice within the EU require disclosure of clinical trial information (although not covering pre-clinical data). The European Federation of Pharmaceutical Industry Associations (EFPIA), together with the International Federation of Pharmaceutical Manufacturers & Associations, Pharmaceutical Research and Manufacturers of America and Japan Pharmaceutical Manufacturers Association, have issued joint positions on the disclosure of clinical trial information via clinical trial registries and databases and on the publication of clinical trial results in the scientific literature (see *Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (10 November 2008)* and *Joint Position on the Publication of Clinical Trial Results in the Scientific Literature (10 June 2010)*). These provide that:

- Details of ongoing clinical trials should be registered within 21 days of initiation of patient enrolment in a publicly accessible database.

- Results of clinical trials (irrespective of the outcome) should be posted no later than one year after the medicinal product is first approved and commercially available in any country; for trials completed after this initial approval, results should be posted no later than one year after trial completion.

These provisions are echoed in national codes of practice. For example, in the UK, the Association of the British Pharmaceutical Industry's Code of Practice states that companies must disclose details of clinical trials in accordance with the international Joint Positions (*clauses 7.5 and 13.1, and the supplementary information thereto, Code of Practice for the Pharmaceutical Industry 2019 (1 January 2019)*). Companies are required to publish on the homepage of their websites information on where details of their trials may be found.

A recent BMJ article sought to ascertain the level of compliance with the Commission's requirement that all trials post results within 12 months of completion, and to identify features associated with non-compliance (*BMJ: Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource (12 September 2018)*). The retrospective cohort study found that despite the provisions above, of the 7,274 trials where results were due, only 49.5% reported results, although trials with a commercial sponsor were substantially more likely to post results than those with a non-commercial sponsor (68.1% compared to 11.0%).

The matter has been raised in the UK Parliament. At the end of October 2018, the House of Commons Science and Technology Committee published a report expressing concern that around half of all clinical trials fail to publish their results (*House of Commons: Research integrity: clinical trials transparency, Tenth Report of Session 2017–19 (23 October 2018)*). The report is generally critical of the level of reporting of results of clinical trials, particularly by universities and NHS hospitals. It further notes its concern about "selective non-publication—'or publication bias'—of results" and the risk of the effects of such "bias" on the views of the medicine in clinical practice. The committee specifically recommends that the Health Research Authority (HRA), which manages the ethics committees for clinical trials in the UK:

- Publishes a detailed strategy for achieving full clinical trial transparency, with a clear deadline and milestones.
- Be provided with funding to establish a national programme to audit clinical trial transparency.
- Introduces a system of sanctions to drive improvements in clinical trial transparency, such as withdrawing favourable ethical opinions or preventing further trials from taking place.

The committee also recommends that the UK government consult on whether to provide the HRA with the statutory power to fine sponsors for non-compliance.

PROACTIVE DISCLOSURE

In 2014 the EMA adopted a policy on the proactive publication of clinical data (not pre-clinical data) supporting centralised marketing authorisations, known as "Policy 70" (see *EMA: European Medicines Agency policy on publication of clinical data for medicinal products for human use, Policy/0070 EMA/240810/2013 (2 October 2014)*). This was in response to a call from researchers and academics for greater transparency of clinical data. The policy applies to any new applications for centralised marketing authorisation made after 1 January 2015, and for extension of indication and line extension applications for centralised authorisations made after 1 July 2015. It does not apply to clinical data submitted before these dates, nor to applications made to national authorities.

Under the policy, after the EMA takes its decision, the clinical data within the application dossier (whether the study is conducted within the EU or outside) will be available on the EMA's website (see *EMA: Clinical data*) at the same time as publication of the EPAR. The data will be available in two forms:

- To **view** by all those who register for the website.
- To **download and re-use** by academics and for non-commercial research purposes.

Such disclosure will occur after the EMA's "decision", which includes not only a decision on grant of the authorisation, but also refusal or withdrawal of the application. This has caused some concern for industry, as in many cases, where an application has been withdrawn, the applicant intends to resubmit the data. The policy is stated to cover such data, but there is a question as to whether this may undermine a company's strategy for further research and development, and the re-submission of the data to support an authorisation.

All use is subject to the EMA's terms of use, whereby the use of the data must be for non-commercial purposes only. Commercial purposes include using the data to support an application to obtain a marketing authorisation, and any extensions or variations thereof for a product anywhere in the world, or selling, trading or supplying the data to a third party that has not agreed to the terms of use.

Commercially confidential information (using the EMA definition above) will be redacted. Examples of what is, in principle, accepted as commercially confidential information appear in Annex 3 to the policy. However, the policy contains the assertion that "in general", data within an application is not commercially confidential. Where redaction of commercially confidential information is proposed by the applicant, the EMA will conduct a consultation with the applicant, and the EMA will decide if the information should be redacted.

The EMA's terms of use for Policy 70 are for the benefit of any and all applicants or authorisation holders and, accordingly, each applicant or authorisation holder may, in its own right, enforce the terms of use directly. How this might operate in practice if an authorisation holder believes its data has been used in breach of the terms of use is unclear. The EMA also states that "[c]ourts may require the EMA to disclose the identity of the users who do not comply with the [terms of use] to the marketing authorisation holders/applicants" (see *EMA: Questions and answers on the European Medicines Agency policy on publication of clinical data for medicinal products for human use EMA/357536/2014 (8 June 2015)*). The terms of use are stated to be subject to English law but it is unclear whether the EMA considers that any challenge under the policy would be brought in the English courts, or in the European General Court. It is also unclear if these terms of use will be updated after the relocation of the EMA from London to Amsterdam.

The number of accounts and registered views/downloads has been steadily increasing since the introduction of Policy 70 (see EMA: EMA Clinical Data Publication (CDP), Joint meeting between the EMA's Patients' and Consumers' Working Party and the Healthcare Professionals' HCPs Working Party (18 April 2018)). Fifty-four sets of documents (comprising 36 initial marketing authorisation applications and 18 extension applications) have been published since 2016, comprising a total of 3,279 documents. This is compared to the 92 medicines that the EMA recommended for marketing authorisation, and 51 recommendations for extensions to the indications of authorised products, in 2017 alone. In terms of redactions, commercially confidential information was accepted in only 1.46% of documents (from the 4.4% proposed by marketing authorisation holders).

As part of its Brexit business continuity plan, the EMA is temporarily suspending the publication of clinical data under Policy 70 (see *EMA: Press release, Brexit preparedness: EMA to further temporarily scale back and suspend activities (1 August 2018)*). Data packages submitted before the end of July 2018 will be processed and published on the website, but new procedures submitted after 1 August 2018 will not.

CLINICAL TRIALS REGULATION

Consistent with the EU-wide policy towards increased transparency, the *Clinical Trials Regulation ((EU) 536/2014)* also contains provisions in relation to increased transparency of clinical data (although not pre-clinical data). The Clinical Trials Regulation states that the sponsor of a trial conducted in the EU under the Regulation should submit a summary of the clinical results to the EU database within a year of the end of the trial. In addition, where the trial was intended to be used for obtaining a marketing authorisation (whether through the centralised procedure or via the national authorities), the applicant should submit the clinical study report 30 days after the marketing authorisation has been granted (or refused or withdrawn) (*Articles 36 and 37, Clinical Trials Regulation*).

Although the recitals state that "in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted ..." (emphasis added) (*recital 68*), the

Clinical Trials Regulation states that the EU database shall be publicly accessible unless, among other things, confidentiality is justified on the grounds of:

> "... 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"
>
> (*Article 81(4)(b)*).

The Regulation contains no definition of commercially confidential information, and it is likely that in practice, the definition used by the EMA will be used in the context of the Regulation.

The Regulation, and data posting requirement, do not come into operation until the clinical trials portal and database has been set up and independently audited, and only six months after notification of the successful audit is published by the Commission. The operation of this database has been delayed a number of times, as the development of a system to cover so many aspects of the new Regulation is taking longer than expected. In October 2018, the EMA Management Board reported that the development of the auditable version of the portal and database is complete, and that its development has entered an "intensive phase of pre-testing". However, the formal audit will take place once the EMA has relocated to Amsterdam. As such, the current estimation is that the portal will be able to "go live" in 2020 (*EMA: EMA Management Board: highlights of October 2018 meeting (5 October 2018)*).

Note that in terms of Brexit, the UK government has stated that it intends to align UK transparency provisions with those currently in operation in the EU, and intends to implement the Clinical Trials Regulation as far as possible (*Department of Health and Social Care: How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal (3 January 2019)*). For more information on the implementation, see *Legislation Tracker, Brexit: EU legislation expected to apply or be implemented in UK pre-Brexit and during transition: tracker.*

REACTIVE DISCLOSURE

Despite the existence of *Policy 70*, and the adoption of the *Clinical Trials Regulation*, documents concerning relatively few products have so far been released, and future disclosures are currently stalled. In the meantime, the EMA will release documents, including pre-clinical and clinical data, in response to requests made directly to it. This is the area that has, so far, caused the biggest controversy, and has led to litigation.

The *Access to Documents Regulation* grants EU citizens and legal entities an express right to access documents held by European institutions (see Transparency of documents). Article 4 contains exemptions to the right of disclosure, in particular where disclosure would undermine the protection of the commercial interests of a natural or legal person, including intellectual property rights, unless there is an overriding public interest in disclosure. Further, where third party documents are proposed to be disclosed in response to a request, the institution should consult with the third party in order to agree any necessary redactions. The timelines for responding to requests are short, as the Access to Documents Regulation states that an initial response should be provided within 15 working days, although this can be extended to 30 working days in exceptional circumstances.

This general right of access to documents applies to documents held by the EMA (Article 73, *Regulation 726/2004*), and the EMA has published a number of policy and guidance documents on how this right of access to documents will operate. In particular, in 2010, the EMA published a policy defining how it would respond to requests for access to documents related to medicinal products for human and veterinary use, known as "Policy 43". A revised version of Policy 43 came into effect on 4 October 2018, which has a broader scope as it also applies to documents that are not related to medicinal products for human or veterinary use (*EMA: European Medicines Agency policy on access to documents Policy/0043 EMA/729522/2016 (4 October 2018)*). The policy states that the EMA will ensure the widest possible access to EMA documents concerning any matter related to the policies, activities and decisions falling within the EMA's remit and responsibilities. Access to a document will be denied only if one of the exceptions applies, and the exclusions set out in the Access to Documents Regulation are repeated, in line with the EMA's definition of commercially confidential information.

The EMA also published guidance on the application of Policy 43 to particular categories of documents and types of information held by the EMA (see *EMA: Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use EMA/127362/2006 (4 October 2018) and Output of the European Medicines Agency policy on access to documents non-related to medicinal products for human and veterinary use EMA/183710/2016 (4 October 2018)*; see also *HMA/EMA Working Group on Transparency: HMA/EMA guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation application - release of information after the granting of a marketing authorisation (14 March 2012)*). In relation to the documents within an application for a marketing authorisation (although the guidance does not specifically refer to pre-clinical or clinical trial data), it is said that such documents will be considered as "non-releasable" prior to the final decision (approval, refusal, or withdrawal). However, once the relevant decision has been made, the documents will be considered as "releasable", and will be disclosed, subject to appropriate redactions.

The policy is well used. The EMA Annual Report 2017 indicated that the number of requests for access to documents received by the EMA had increased from 377 in 2014 to 844 in 2017, with 2,807 documents being released in 2017 (see *EMA: Annual report 2017 (2 May 2018)*). Note that the EMA has recently stated that, due to the high volume of requests resulting in an excessive workload for the EMA, it will no longer process requests from outside the EU (see *EMA: Access to documents*).

There are a number of questions relating to Policy 43. For example, unlike Policy 70, there are no terms of use associated with the policy, and the same rights of access are provided to everyone, including competitors. There are no restrictions or conditions on use, and the third party requestor is free to use the data worldwide as they wish, without being subject to confidentiality provisions. More practically, the timelines imposed on companies to review and redact the documents the EMA proposes to release are very short, and the process generally requires input from a number of business stakeholders.

In response to the broad scope of Policy 43, industry bodies such as EFPIA developed their own principles for sharing data, although the policy specifically excludes pre-clinical data (see *EFPIA: Principles for Responsible Clinical Trial Data Sharing: Our Commitment to Patients and Researchers (18 July 2013)*). These principles go beyond the legislative requirements, but allow marketing authorisation holders to retain some control over how their data is used by third parties when disclosed under these principles, rather than when the data is disclosed by the EMA under Policy 43. Under these principles, pharmaceutical companies will release, on request, anonymised patient- and study-level clinical trial data, along with full clinical study reports and protocols for US and EU approved medicines to "qualified scientific and medical researchers". Such release is subject to patient privacy and confidential commercial information protections. Data requestors are required to provide a rationale for their proposed research, along with their analysis, publication and posting plans; any potential conflicts of interest, including potential competitive use of the data; and the source of any research funding. Companies can therefore retain some control over the release, and ensure that confidential information is not provided to competitors, while also allowing wide access to data to academics and healthcare professionals.

COURT CASES RELATING TO WHAT IS DISCLOSED AND WHAT IS EXEMPT FROM DISCLOSURE

As a result of the difference in opinion on which data should be considered as commercially confidential information and therefore withheld from disclosure, the EMA has been subject to a number of challenges to its *Policy 43*.

The first wave of these cases was brought by InterMune and AbbVie (*AbbVie Inc and another v EMA (Case T-44/13R) EU:T:2013:221; AbbVie Inc. and another v EMA (Case T-29/13) EU:T:2014:695* and *InterMune UK Ltd and others v EMA (Case T-73/13R) EU:T:2013:222*). In these cases, the companies applied to the European General Court for annulment of the EMA's decisions that it would disclose the research-related documents contained in the marketing authorisation dossier, and applied for interim orders preventing the EMA from disclosing that information pending the court's decision. Several EU and US pharmaceutical trade associations and intellectual property rights associations sought to intervene to support the applicants. However, these cases did not proceed to judgment as they were resolved out of court, and the cases were withdrawn.

Since these cases were withdrawn, a series of others have been filed. On 5 February 2018, the General Court delivered three judgments concerning the application of the *Access to Documents Regulation* to documents held by the EMA (*Pari Pharma GmbH v EMA (Case T-235/15R) EU:T:2018:65; MSD Animal Health Innovation GmbH v EMA (Case T-729/15) EU:T:2018:67* and *PTC Therapeutics International Ltd v EMA (Case T-718/15) EU:T:2018:66)*. A further decision was delivered on 25 September 2018 (*Amicus Therapeutics UK Ltd and another v EMA (Case T-33/17) EU:T:2018:595*). In all cases, which concern both clinical and pre-clinical data, the General Court upheld the EMA's approach to disclosure, and rejected the arguments of the companies as to the confidential nature of the documents. In summary:

- The General Court rejected the arguments of the parties that there was a general presumption of confidentiality over certain documents. The provisions on access apply to all documents held by the EMA.

- As a result, each document, and all the information within it, needs to be considered on an individual basis to assess whether it can be withheld from disclosure under one of the exemptions. The General Court stated that information can be withheld from disclosure on the ground that it constitutes commercially confidential information in only limited situations where "specific" and "actual" evidence is provided to show how disclosure would seriously undermine a company's commercial interests.

- The concern that a wide interpretation of access could undermine the EMA's decision-making, and lead to companies altering the amount of information provided to the EMA, was dismissed as invalid.

- The EMA's application of its Policy is not in breach of the World Trade Organization's (WTO) Agreement on Trade-related aspects of Intellectual Property Rights (TRIPS) (*WTO: Agreement on Trade-Related Aspects of Intellectual Property Rights*). Under TRIPS, where test results or data for new chemical entities must be submitted to authorities to gain an authorisation, the data must be protected from unfair commercial use, and member countries (including the EU) must protect such data from disclosure, except where necessary to protect the public. The applicants in these cases claimed that as TRIPS only applies to information that is secret, the EMA was breaching its obligations by disclosing the data. However, the court stated that the EMA's interpretation of what constitutes commercially confidential information is in line with the relevant legal provisions, and is consistent with TRIPS.

- The EMA is not under an obligation to show that there is an overriding public interest justifying disclosure of the documents, unless the EMA takes the view that the documents are protected by an exception.

For more information, see Legal update, General Court confirms EMA approach to transparency (EU).

MSD Animal Health and Intervet International, and PTC Therapeutics, have appealed the General Court's findings to the Court of Justice (*MSD Animal Health Innovation and Intervet International v EMA (Case C-178/18P)* and *PTC Therapeutics International v EMA (Case C-175/18P)*). In addition, ongoing cases that raise similar issues are pending before the General Court (*Intercept Pharmaceuticals v EMA (Case T-377/18)*). It is therefore likely that further guidance from the court will be available in due course.

SUMMARY TABLE OF DISCLOSURE REGIMES APPLICABLE TO DATA HELD BY THE EMA

See table overleaf

SANCTIONS

In relation to the proactive policies, which place obligations on marketing authorisation holders to disclose information about their clinical studies, penalties may be imposed on companies for not providing the results of paediatric clinical trials, under:

- The *Penalties Regulation ((EU) No 658/2007)*, which sets out financial penalties for infringement of certain obligations in relation to centralised marketing authorisations, and the obligations in the Paediatric Regulation; the penalty should not exceed 5% of the marketing authorisation holder's annual turnover in the EU, although daily penalties can be imposed if the infringement is ongoing.

Summary table of disclosure regimes applicable to data held by the EMA				
	Law and Guidance	**EMA's Proactive Policy 70**	**Clinical Trials Regulation (Regulation)**	**EMA's Reactive Policy 43**
Data covered by the policy	Data relating to all trials (paediatric and non-paediatric) conducted under the Clinical Trials Directive.	Data within dossiers for products approved under centralised procedure.	Data relating to all products (centralised, decentralised procedure, mutual recognition procedure, national) that includes trials conducted under the Regulation.	Data within dossiers for products approved under centralised procedure.
Location of trial	Trials with at least one site in the EU/EEA; where the trial forms part of a paediatric investigation plan, obligations also include studies outside the EU.	Data submitted to the EMA and contained in the marketing authorisation dossier, regardless of trial site location.	Trials with at least one site in the EU conducted under the Regulation.	Clinical data contained in the marketing authorisation dossier, regardless of trial site location.
Data that should be disclosed	General information about the trial; a summary of positive or negative results.	Clinical data (including clinical overview, summary of results, clinical study reports and individual patient data).	General information about the trial; summary of results; clinical study reports.	Any data held by the EMA.
Timing	Within six months of completion of the trial for paediatric trials, and otherwise, within one year of the end of the trial. Information should be posted earlier, if already published in scientific journals.	After decision on authorisation (or withdrawal/ refusal), at the same time as publication of the EPAR.	Summary results: within a year of the end of the trial, unless scientific reasons justify a longer period of time. Full results: within 30 days of the marketing authorisation being granted (or refused or withdrawn).	In response to a request, usually within 30 days.
Position on commercially confidential information (CCI)	Only a summary is provided, so issue does not arise.	"In general ... most of the information in clinical reports would not be considered CCI"; EMA applies standard definition, but interpretation has not yet been tested.	"... in general the data included in a clinical study report should not be CCI"; likely that the EMA's definition will be used to determine CCI, and this has not yet been tested.	EMA considers that clinical data are not CCI, and the interpretation is subject to ongoing court cases.
Application	Trials regulated by the Clinical Trials Directive, which took effect, at the latest, on 1 May 2004. If past paediatric trials are included in a paediatric investigation plan, or submitted under the Paediatric Regulation, they should also be included.	1 Jan 2015 for new applications. 1 July 2015 for line extensions. (Policy suspended for submissions after 1 August 2018	Trials approved from approximately 2020 onwards.	Any data held by the EMA.

From 28 January 2019 onwards, the "core elements" of the Penalties Regulation will now be set out in new Article 84a and Annex II of *Regulation (EC) 726/2004* (as amended by Article 1(38) of *Regulation (EU) 2019/5*). For clarity however, Article 4(1) of the new Regulation specifies that the provisions of the Penalties Regulation will continue to apply unless and until repealed. Regulation (EU) 2019/5 also introduces new provisions regarding financial penalties, including the ability to impose penalties on entities other than marketing authorisation holders provided they form "part of the same economic entity" as the authorisation holder in question and: "(a) exerted a decisive influence over the authorisation holder"; or "(b) were involved in, or could have addressed, such failure to comply with the obligation by the authorisation holder" (Article 1(38), Regulation (EU) 2019/5).

- National legislation (see for example, in the UK, *regulations 91 to 93* of the *Human Medicines Regulation 2012 (SI 2012/1916)*).

The *Clinical Trials Directive* and Commission guidance do not contain sanctions for non-compliance where this relates to non-paediatric trials. However, the publication of clinical trial data is becoming an increasingly "hot topic" with the EMA and national competent authorities, and it is likely that authorities will increasingly rely on this guidance to "force" disclosure. For example, the fact that transparency and disclosure obligations are included in national codes of practice means that member companies who fail to comply may be subject to sanctions (including adverse publicity) in accordance with self-regulatory provisions under the relevant code (see, for example, the decision of the Prescription Medicines Code of Practice Authority in *Director v Roche, Cases AUTH/2898/11/16 and AUTH/2901/11/16*). The PMCPA has made similar enquires of companies following the September 2018 BMJ article.

In addition, under the *October 2012 Commission guidance*, where results are not posted within nine months of the end of a trial for paediatric trials, or 15 months for other trials, these trials will be "flagged" on the database.

Under the *Clinical Trials Regulation*, member states are required to put in place penalties to cover non-compliance with the transparency provisions (Article 94(2)). Such rules on penalties have not yet been implemented in member state implementing legislation.

PRACTICAL TIPS

Transparency of pre-clinical and clinical data is generally increasing, with stakeholders expecting greater amounts of data to be released. Companies are advised to:

- Ensure reporting of information about clinical trials is up-to-date, and the company has standard operating procedures on how, what and when information and data should be published.

- If your company receives notice from the EMA of a request for access to documents under *Policy 43*, and the company wishes to seek redactions of commercially confidential information within the document, you should seek to explain to the EMA why disclosure could damage your commercial interests. Any reasons should be as specific as possible, including details of the expected harm the company would suffer if the information was released. Keep any requested redactions to a minimum; following the General Court's decisions, a position that entire documents are confidential is unlikely to be accepted by the EMA.

- Make sure all regulatory submissions to the EMA are reviewed with the expectation that the document will be released to competitors. To the extent possible, ensure all commercially confidential information is removed, and all patent applications are made before submission.

- Know what information is already available about the company's products, in public documents or published literature. It is unlikely that the EMA will accept that anything that is in the public domain can be redacted, even if the information in the relevant submission is not in the same form as the public information.

- Determine the company's position on controlled access (such as under EFPIA's *Principles for Responsible Clinical Trial Data Sharing*). If competitors can obtain data directly from the company, they will not need to use the EMA's Policy 43.