In October 2016, the European Medicines Agency (EMA) started publishing clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure. By actively publishing clinical data, the EMA wants to build public trust and confidence in their decision-making processes, and to improve scientific discussion in the field of regulatory science, by allowing reassessment of the data in academia, and avoiding unnecessary clinical trials. This report overviews the development of regulatory transparency in Europe, including issues and concerns around the new EMA policy.

INTRODUCTION
Traditionally, research and development (R&D) in the life sciences takes place under strict confidentiality. One of its most important incentives is the exclusive use of intellectual property to market products at an attractive price. In such an environment, transparency does not occur naturally. This is the same for the regulatory approval processes – marketing authorization applications—that convey valuable data to regulatory authorities. Those authorities preserve this data confidentiality and add their own motives for doing so: Regulators require a safe environment to express their views on the submitted data. Furthermore, individual regulatory authority members prefer not to be specifically connected with regulatory decisions, in case these turn out to be wrong.

ACTIVE TRANSPARENCY: EPAR
Since 1995, this “life sciences black box” has been moving in the direction of more transparency. The first sign was the introduction of the European Public Assessment Report (EPAR), a form of “active transparency.” The European legislator believed that patients, health care professionals and the general public should have access to certain information about medicinal product regulatory decisions. The chosen method was to provide the official assessment report without including commercially confidential information and personal data.

PASSIVE TRANSPARENCY: FREEDOM OF INFORMATION ACT
The second development occurred when the EMA became subject to the “EU Freedom of Information Act” on 1 May 2004. This was the basis for “passive transparency.” Internal rules for implementation of this regulation provide that public access to a document should be refused if disclosure would undermine the commercial interests, including intellectual property, of a natural and legal person.

COMMERCIALLY CONFIDENTIAL INFORMATION
The EPARs and information requests have delivered huge amounts of valuable information about regulatory decisions for patients, physicians and academia, but also for lawyers and competitors within the industry. The road to the EU’s current level of transparency was not without obstacles. Initially, the EMA deleted all
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(clinical and preclinical) data submitted by applicants with their application, based on their interpretation of the Trade-Related Aspects of Intellectual Property Rights (TRIPs) agreement.

In May 2010, the European Ombudsman released his opinion about the EMA’s refusal of a scientific institute’s request for access to information about specific medicinal products. The EMA had refused access to the clinical study report submitted with the application; the Ombudsman concluded that the EMA should balance the general interest of transparency with the commercial interests of the applicant. Based on this opinion, the EMA drafted guidelines stating that information encompassing clinical and non-clinical development of a medicinal product is not per se commercially confidential. Data included in clinical trial reports is regarded as data that can be disclosed. Non-clinical studies are intended, inter alia, to identify the pharmacological properties and to understand the toxicological profile of the medicinal product, while clinical trials intend to discover or verify the effects of one or more investigational medicines. Regulation of these trials aims to ensure that the rights, safety, and well-being of trial subjects are protected and the results of clinical trials are credible. These disclosure rules had been previously challenged before the European Court of Justice, but this was the first successful challenge.

CLINICAL DATA PUBLICATION
The latest step towards transparency is the EMA policy to actively publish the clinical data that are submitted by pharmaceutical companies to support their request for marketing authorization and are assessed by the Committee for Human Medicinal Products (CHMP). Clinical data normally include:

- Clinical overview: Critical analysis of the clinical data in the submission package, including the conclusions and implications of the clinical data
- Clinical summary: Detailed factual summarization of all the clinical information submitted
- Individual clinical study reports
- Three clinical study report appendices: The study protocol, the sample case report form used to record information on an individual patient, and documentation of the statistical methods used to analyze the data.

These documents correspond respectively to modules 2.5, 2.7 and 5.3 of the Common Technical Document (CTD). The policy applies to clinical data submitted to the Agency for Marketing Authorization Applications submitted from 1 January 2015 onward, regardless of the regulatory outcome. This policy also covers clinical data submitted from 1 July 2015 onward in support of a new indication or a line extension for an existing centralized marketing authorization.

CLINICAL DATA THAT WILL NOT BE PUBLISHED
The publication of clinical data is restricted to documents that are related to applications submitted to the EMA. Therefore, clinical data submitted to national competent authorities (e.g., in the framework of a decentralized procedure) will not be published. In practice, the impact of this restriction will be limited as most national marketing authorizations concern older and generic medicinal products. Clinical data about nationally authorized medicinal products submitted to the EMA (e.g., in the framework of an arbitration procedure or pharmacovigilance) will also not be published. Clinical data submitted before 2015 will not be published,
although the EMA will give access to them through the current information request procedure.

EMA CLINICAL DATA WEBSITE
Clinical data are being published at the EMA Clinical data website and can be accessed by using an EMA username and password. All documents will not be available at once, as the EMA continues to populate this database.

PRACTICAL ISSUES
Each application dossier should provide clinical data formatted so that EMA can publish them after the regulatory procedure has been concluded. This means that the applicant must not include commercially confidential information in the dossier. If data considered commercially confidential must be included, the applicant can mark this text and explain to the EMA why it should be deleted from the published documents. All personal data (e.g., data from which trial subjects could be identified) must also be removed from the clinical data in accordance with European privacy legislation. The EMA published an external guidance document for pharmaceutical and biotech companies about preparing regulatory submissions while considering future publication.

THE CLINICAL TRIAL REGULATION
Improved transparency in respect of clinical research was an important aim of the EU legislator when adopting the new clinical trials legislation. The Clinical Trial Regulation, effective in December 2017, requires that the sponsor must submit a summary of clinical trial results to the EU-database within one year from the end of a trial in all concerned EU member states, unless otherwise provided in the approved protocol. This summary shall be accompanied by a layperson summary. Moreover, if the results of a clinical trial are submitted in support of a marketing authorization, the applicant is obliged to publish the clinical study report in the database within 30 days after the granting of the marketing authorization.

CONCLUSIONS
The EMA has made significant steps to enhance transparency. Although there will now be extra vigilance and work required whenever a regulatory submission is made, there are also benefits. As the EMA points out, transparency could eliminate unnecessary clinical trial duplication, because clinical data submitted to the EMA will be available to everyone. This also allows health care professionals and their patients to become acquainted with clinical data, and give scientists the basis for new research.

The most important aspect could be that these steps in the field of transparency may help industry and regulators battle the distrust apparent from books and articles with titles like The Truth about the Drug Companies: How they deceive us and what to do about it and Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients and even the movie The Constant Gardener. One may hope that increased transparency can convince these and other critics of the integrity of the regulatory system and the quality of regulatory science.

References available upon request.