

TTIP as a Platform for Progress in Pharma and Medtech Regulations

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I. Introduction

Opponents of the transatlantic trade and investment partnership treaty (TTIP) fear that the EU might lose the capacity to protect public health as it deems appropriate.¹ The freedom to regulate would be jeopardized because TTIP would bind the EU to the United States' regulatory interests, which are expressly or implicitly assumed to live up to a 'lower' standard than those in the EU. The 'TTIP-leaks' provide a good opportunity to examine the potential impact of the agreement on EU public health regulation. This brief contribution uses as its starting point the document "Tactical State of Play of the TTIP negotiations" (hereafter "Tactical Document") of March 2016,² and focuses on pharmaceuticals and medical devices. In light of the statements in this document, we query what would change for the EU consumer, and what would be the impact on the EU regulators' role in protecting public health.

II. Mutual Recognition of Good Manufacturing Practices for Pharmaceuticals

1. Introduction

The Tactical Document states that a significant step forward was made on the mutual recognition of Good Manufacturing Practices (GMP) for pharmaceuticals. In the following paragraphs we shall explain that, in our view, such mutual recognition could indeed be a step forward for all stakeholders on both sides of the Atlantic: the consumer would benefit from increased safety of pharmaceutical products with shorter lead-times to market, the regulator could re-focus inspections where needed the most, and pharmaceutical companies would benefit from reduced cost by eliminating double inspections. Finally, it is only in the context of TTIP that the EU and the USA are progressing rapidly towards mutual recognition, after two decades of efforts in that direction.

2. Good Manufacturing Practices in the European Union

Under EU law, manufacturers of pharmaceuticals must respect GMP. In order to obtain a marketing authorization for a medicinal product, the applicant must prove that manufacturing complies with the principles and guidelines of GMP.³ Similarly, holders of a manufacturing authorization must "comply with the principles and guidelines of GMP for medicinal products and use only active substances which have been manufactured in accordance with GMP."⁴

The GMP Directive 2003/94/EC defines GMP as "the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use."⁵ In substance, GMP includes effective quality assurance, employing qualified personnel, maintaining suitable manufacturing premises and equipment, establishing appropriate documentation procedures, maintaining quality control, and so on. According to Article 3 of the GMP Directive, the supervisory authorities of the EU Member States are responsible for conducting audits of manufacturers. This is because the European Medicines Agency (EMA) does not have inspectors of its own. Instead, the role of the EMA is coordination and support, and the national authorities must take account

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1 Editorial, *Warning: TTIP could be hazardous to your health*, *Journal of Public Health*, Vol 37 No 3, pp 367-369.

2 Author not specified, *Note - Tactical State of Play of TTIP Negotiations - March 2016*. This negotiation document was leaked in March 2016. It is accessible via <https://www.ttipp-leaks.org/> (consulted 27 May 2016).

3 Article 8(ha) of Directive 2001/83/EC.

4 Article 46(f) of Directive 2001/83/EC.

5 Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

of the compilation of Community procedures on inspections and exchange of information, drawn up by the Commission with support from the EMA.

3. Mutual Recognition of GMP

The EU currently has active mutual recognition agreements (MRAs) for GMP of pharmaceuticals with the following countries: Australia, Canada, Israel, Japan, New Zealand and Switzerland. The agreement between the EU and Canada appropriately explains their purpose. The text expressly states that the underlying idea behind the MRA for GMP compliance certification, is that both Canada and the EU Member States have 'equivalent' GMP compliance programmes. Therefore, the issuance of a certificate by an authority of one Party certifying that a facility is in compliance with GMPs, should suffice so that the other party accepts that facility as GMP-compliant.⁶ The EU-Canada MRA explicitly states that "*It should be understood that equivalent does not mean identical but it does mean leading to the same result.*"⁷ To achieve their objective, the success of MRAs is significantly dependent on the successful completion of a confidence building exercise and subsequent evaluation of its results. This is a process integrated in all of the EU's MRAs.

That last point is where the EU and the USA have failed in the past. Article 5 of the EU-USA MRA of 1999 established a three-year transition period, and article 9 established that equivalence would be determined by having in place regulatory systems respecting a pre-defined set of pre- and post- approval quality criteria. The transitional period lapsed in November 2001 largely because the FDA had concerns that GMP practices on the EU Member States' side were not sufficiently harmonized, and that overall divergence with the USA was too significant. Of course, fifteen years ago, the European Medicines Agency had not yet attained its current mature role in coordinating principles of GMP.

It is against that background that we should read pages 12 and 13 of the Tactical Document. On mutual recognition, it confirms that both the EMA and the FDA intend to establish an MRA under TTIP that includes all 28 EU Member States, provided that the FDA receives reports of the audits conducted under the Joint Audit Program (JAP). The JAP is essentially a peer review system covering all GMP inspectorates of the European Economic Area (EEA) to ensure harmonised inspection standards and interpretation of GMP requirements. The Tactical Document states that the FDA now accepts to receive these JAP audit reports, together with some additional information, and that it will take a decision on mutual recognition within three months of receiving the JAP report. The Tactical Document adds that "*in comparison with the process followed for the other MRAs on GMP, it is remarkable that the FDA would essentially rely on the JAP since it is an EU MS internal system of audits*". The Tactical Document thereafter confirms that the Commission wishes to accelerate the program so that all audits of all Member States are completed before the signature of TTIP.

These developments have clear benefits for patients, regulators and the industry.

The point of cost-reduction for EU and US pharmaceutical companies is the most obvious. An MRA reduces the need for double GMP inspections, eliminating fees and waiting times. This argument often seems to ring hollow to critics of TTIP, and it is certainly not the only reason to have an MRA.

For the regulator, MRAs have significant benefits too. Indeed, GMP inspections do not only occur in manufacturing plants in the EU or the USA, but throughout the world. Many Asian companies manufacture finished drugs and Active Pharmaceutical Ingredients (APIs), which all need to comply with GMPs. Since the EMA and FDA are by far the most active in conducting GMP inspections,⁸ an MRA will allow both agencies to collaborate towards leveraging inspection resources on a global scale. The main benefit here is not cost-reduction, but greater efficacy through joint EU and US identification of the highest risks in urgent need of inspection, as well as an overall increase in inspections of manufacturers around the globe. That, in turn, increases the safety of medicinal products brought to the USA and EU markets.

Finally, an MRA is not about 'lowering' the good manufacturing practices of EU pharmaceutical com-

6 Agreement on mutual recognition between the European Community and Canada, OJ 16 October 1998 L280/3, chapter 6 on good manufacturing practices, points 3.1, 3.2 and 3.3 general considerations.

7 Idem.

8 S. Milmo, *Collaborating on GMP inspections*, Pharmaceutical Technology, Volume 39, Issue 9, September 2015.

panies to the detriment of the consumer. Substantively, on the EU side the so-called ‘Qualified Person’ will still have to certify that each batch of finished product has been manufactured in line with the marketing authorization. On the USA side, the ‘Quality Unit’ of the marketing application holder remains similarly responsible to determine compliance. Thus, the MRA is about recognizing the equivalent substantive outcomes of systems, which may vary in structure or format. It is also telling that several MRAs are already in place with countries that have advanced inspectorates and pharmaceutical industries. In this area, TTIP is about tried-and-tested rapprochement between partners with equivalent regulatory challenges and solutions, even if the benefit is difficult to quantify.

4. Do we Need TTIP to Get these Benefits?

It could be argued that TTIP is not necessary in order to achieve mutual recognition of GMP between the EU and the USA. This argument is not without merit. Past efforts towards mutual recognition between 1998 and 2001 failed. An MRA is now possible in part because of global regulatory convergence in GMP, as for example promoted by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). According to the Tactical Document, TTIP negotiations, if anything, created momentum and time-pressure to complete the work that had been on-going for two decades. The Tactical Document expressly states that it “*is of the utmost importance that member states deliver JAP audit reports within a shorter time frame, so that the 28 audits can be completed by the time of signature of TTIP*”. Additionally, the Tactical Document shows that the GMP MRA does not exist in isolation, and is linked to negotiations over TTIP as a legal basis for the exchange of confidential and trade secret information. Thus, an MRA can certainly function as a standalone legal instrument. However, in our reading the Tactical Document shows that TTIP provided the platform and momentum needed to finalize a process which had been on-going for 20 years. Given the interconnectedness of TTIP negotiations, it is not guaranteed that the MRA could be salvaged in case TTIP as a package-deal would fail.

III. Medical Devices

1. Introduction

The Tactical Document shows that negotiations on medical devices are progressing, but that US authorities are requesting further measures in relation to some of the three main priorities for the medical devices sector under TTIP. These priority areas are the single audit system, the unique device identification (‘UDI’) system, and the regulated product submission. The following paragraphs address these three topics and explain that while these are “light” measures that are unlikely to compromise patient health (on the contrary), they may still create significant benefits for industry and regulators alike.

2. Medical Devices in the European Union

The current EU regime on medical devices comprises three directives.⁹ This contribution focuses on the Medical Devices Directive 93/42 (“the Directive”). The regime is currently undergoing revision, in an effort to address some of its shortcomings. The new Medical Devices Regulation is still being negotiated, and its adoption is expected around mid or late 2016.¹⁰ It will start applying three years after its adoption. Below we briefly outline the rules of the Directive (and the new Regulation) that are relevant to the TTIP negotiations.

First, medical devices in the EU are not subject to a pre-marketing authorization. Instead, the system is based on a combination of self-certification by the manufacturers, and a conformity assessment procedure conducted by a so-called “notified body”. Notified bodies are entities that have been accredited by the competent authority of an EU Member State to assess the conformity of products with the relevant legislation. Their legal status varies from public bodies to associations and commercial undertakings.

9 The Active Implantable Medical Devices Directive 90/385/EEC, the Medical Devices Directive 93/42/EEC, and the In Vitro Diagnostic Medical Devices Directive 98/79/EC.

10 The future legislative package on medical devices consists of the new Medical Devices Regulation and the new Regulation on In Vitro Diagnostic Medical Devices. Once adopted, the new rules on medical devices will enter into force three years later; those on in vitro medical devices five years later.

The applicable conformity assessment procedure depends on the risk presented by the product class. For low-risk devices, manufacturers may self-certify compliance with the requirements of the Directive. Higher risk devices are subject to inspections by the notified bodies. The new Regulation tightens the rules on notified bodies, but essentially keeps the principle of self-certification or notified body involvement depending on class.

The USA use a very different system, where all new devices require prior approval from the FDA. Hence, the EU and US regimes impose different substantive requirements *and* apply different inspection procedures. Currently, when a US company wants to market a medical device in the EU or vice versa, a given manufacturing facility is audited by both the FDA and (if applicable) by EU notified bodies. This is one area where TTIP is trying to increase convergence (see below, point 3).

Second, traceability of medical devices is currently not required at EU-level, although there is a Commission Recommendation on the use of a unique device identification (UDI) system.¹¹ This Recommendation calls for the inclusion of unique identifiers in the database of the EU country where the device is marketed, facilitating device safety monitoring and reporting, recalls and other field safety corrective actions. While the Recommendation was a step in the right direction, it is non-binding and certainly did not create an EU-wide system for tracing medical devices. The new Regulation does include specific traceability provisions and envisages a mandatory internationally compatible UDI system for the EU.

3. The TTIP Agenda for Medical Devices: a Threat to Public Health?

TTIP critics often voice concerns that the treaty would lower the EU's capacity to protect public health in that it would "lower the standard". In our view, how-

ever, the proposed medical devices measures could strengthen cooperation, encourage the sharing of best practices, increase traceability and reduce red-tape.

The TTIP agenda for medical devices essentially consists of three points.

(i) *Quality Management System Audits*: manufacturing facilities for the EU and US markets are subject to audits by both US and EU inspectors. Under TTIP, parties are discussing the creation of a "single audit" system. The single audit system already exists at international level. The Medical Devices Single Audit Programme (MDSAP) is currently being tested within the framework of the International Medical Device Regulators Forum (IMDRF). At the moment, the EU is merely an observer to the IMDRF and is therefore not fully participating in the MDSAP. Instead, three European Commission experts and experts from three Member States (UK, Ireland and - more recently - Poland) are observing the MSDAP Pilot. Despite repeated US requests to formally join the MSDAP, the European Commission indicated it would not decide on further steps until at least the end of 2016. Because of the central role of notified bodies, EU Member States are closely involved in this debate, and the European Commission will discuss further involvement in the MSDAP with the EU Notified Body Operations Group (NBOG).

Significantly, the aim of a single audit is not to harmonise EU and US QMS regulatory requirements. It is not a mutual recognition mechanism either. Instead, the aim is to put in place a single audit whereby auditors can check compliance with the requirements of several jurisdictions at the same time.¹²

In our view, a single audit system could put an end to double auditing and reduce the burden on manufacturers and regulators. The proposed mechanism is not likely to lower the EU standard. On the contrary. One single audit would test compliance with both regimes, leaving the applicable requirements as they are, but streamlining and increasing efficiency of the inspections. Furthermore, for certain devices the FDA pre-marketing authorization system imposes stricter audits – and higher standards, as civil society is keen to remind us of¹³ – than the self-certification and/or notified body checks in the EU. A single audit system involving experts from both sides of the pond may very well become a platform for the FDA to share best practices with EU notified body inspectors.

Furthermore, it is clear that the European Commission is not willing to rush this, as it is holding off

11 European Commission, Recommendation (2013/172/EU) of 5 April 2013 on a common framework for a unique device identification system of medical devices in the Union.

12 See, for example, European Commission, *EU Position Paper on Medical Devices*, 15 April 2015, which states that "there is no intention to use TTIP to harmonise EU and US QMS regulatory requirements."

13 See, for example, BEUC, *How will TTIP affect the health of Europeans?*, 21 September 2014.

on becoming a full member to the MDSAP. From an EU law perspective, formalizing a single audit also requires the establishment of a legal basis, a process which in and of itself will require further debate and consideration. This cautious approach suggests that the parties are weary about repeating mistakes from the past. Indeed, the 1999 MRA between the USA and the EU meant to put in place a system of mutual recognition of inspections, but instead led to distrust and more, not less, inspections.

(ii) *Unique Device Identification (UDI)*: As explained above, the new Medical Devices Regulation will create a mandatory UDI system. While the USA UDI system has been operational since 2014, the EU mechanism will only start to apply in a few years-time (*i.e.*, not before the new Regulation enters into force). The Tactical Document confirms that European Commission experts are reviewing the US UDI database and are making the technical preparations for integrating the (future) EU UDI system in that database. The aim is that both systems are “*aligned and interoperable*”, allowing data exchanges. Hence, if and when the EU-wide UDI system becomes operational, TTIP negotiations will have contributed to technical compatibility of this system with the existing USA databases. Interoperability of both systems is crucial for the protection of public health: it can play a key role in the fight against counterfeit goods, and traceability is a fundamental pharmacovigilance component.

(iii) *Regulated Product Submission*: Negotiators are discussing the use of a common template for regulatory submissions. That template is being tested and developed at international level, under the auspices of the IMDRF. The EU and USA experts are currently testing the table of contents agreed within the IMDRF, which shows that the project is taken one step at a time and is subject to multiple test phases. In our view, the regulated product submission is not merely *presented* as a “harmless measure to reduce red-tape”,¹⁴ but actually aims to reduce red-tape, nothing more, nothing less.

IV. Conclusion: The Fallacy of Splendid Isolation

The TTIP negotiations on pharmaceuticals and medical devices do not suggest that public health in the EU is threatened. In both areas, negotiations focus

on relatively technical-procedural issues where benefits are clearly mutual. Discussions over ‘lowering standards’ may not be that relevant after all. On pharmaceuticals, the benefits of mutual recognition for GMP exist for consumers, regulators and business alike. Such mutual recognition necessarily draws on an element of trust between regulators, which is currently being built up between the EMA and the FDA during the TTIP negotiations. In our view the facts on GMP mutual recognition speak for themselves: regulators can more efficiently leverage resources to the benefit of public health, and medicines can be brought to the market more efficiently. This can only be the result of trans-Atlantic regulatory trust, and any criticism thereof tends to result from either an aversion for globalisation, or a (latent) anti-Americanism, or both.

The same conclusion can be drawn from our analysis of the negotiations on medical devices. Traceability of medical devices should necessarily be seen in the context of a global menace of smuggling and counterfeiting. Falsification of sunglasses or handbags is often dismissed as a *fait-divers*, but counterfeiting also occurs in the medical sector. Since counterfeit goods originate both inside and outside the EU or the USA, it is crucial that both parties set up a compatible and interoperable system to track and trace genuine products. Cooperation supports public health protection, it does not detract from it.

Admittedly, both examples are very specific, and it can be argued that these benefits can be reaped on an individual basis. Therefore, TTIP is allegedly not necessary and cherry-picking the benefits should suffice. However, in our view such argument misses the point of TTIP. Take the example of GATT, which progressed in a piecemeal fashion for several decades. However, by the end of the 1980’s times had changed, and the regime of global trade required a qualitative leap forward - the World Trade Organization, gathering negotiation momentum linking multiple issues towards a holistic deal that ties them together on a new legal foundation. In our view, TTIP negotiations are no different from the Uruguay round in terms of historical significance. Continuing the WTO comparison, the debate surrounding TTIP similarly reflects the ideological rift that was the basis for the 1999 ‘Bat-

¹⁴ Some non-governmental associations warn that TTIP measures may be presented as harmless while in fact harming patient health.

tle of Seattle' during the WTO Ministerial Conference. This obviously does not bode well for the future of TTIP. However, when we look back at the ex-

periences of the 20th century, splendid isolation and a retreat from international trade have only worsened global problems, not resolved them.