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How Pharma And Medtech Should Respond To New EU Rules On R&D On Biological Resources

By Bart Van Vooren, 11 May 2016

The new EU compliance regime implementing the Nagoya Protocol on the use of biological resources imposes extensive track & trace obligations on companies active in pharmaceuticals, medical devices, animal and plant breeding, biocides, and foods and beverages. Although the binding rules are to be expanded with sector-specific guidance documents being drawn up by the European Commission by 2017, companies would be well advised to start work now on implementing procedures to document compliance with the new requirements and also monitor developments at EU member state level, says Bart Van Vooren.

Over the years there have been global news reports of "bio-piracy" by companies accused of illegally profiting from blockbuster drugs derived from developing countries' rich biodiversity. This stimulated the adoption of the 2010 Nagoya Protocol to implement the objective of the 1992 Convention on Biological Diversity: that benefits arising out of R&D on genetic resources should be fairly shared with the country of origin[1].

Since October 2014, strict rules apply in the EU, under Regulation (EU) No 511/2014[2], to enforce compliance with the Nagoya Protocol. However, it would be wrong to assume that the new regulation only encompasses bio-prospecting or ethno-pharmacological R&D. Instead, the EU has purposively set up a broad regime that affects companies developing pharmaceuticals, medical devices, cosmetics, biocides, foods and beverages, as well as plant and animal breeders.

The "ABC" of the Nagoya Protocol

In February 2016, the French Institut de Recherche pour le Développement (IRD) faced a global public relations backlash after it patented an anti-malaria drug without acknowledging the indigenous communities that helped isolate it from *Quassia amara*, a small red-flowered tree native to Central and South America. Critics of IRD argued that its "bio-piracy" was validated by a patent that would prohibit the local population from exploiting their own ancestral remedy, even though their traditional knowledge had led to its discovery.

Subsequently, IRD announced that it had pledged to share benefits with local people and authorities in French Guyana. From facts reported in the journal *Science* it would appear that the Institute was unaware of the new EU compliance regime with the Nagoya Protocol, as discussed in this article. *Quassia amara* also illustrates how many industries may be impacted by the Nagoya protocol: the same plant is also used as a food additive and as an insecticide in biological agriculture.

The 1992 Convention on Biological Diversity (CBD) recognized that countries exercise sovereignty over the biological resources within their jurisdiction. This was the result of growing expectations of the commercial value of biodiversity, and the need to address the mismatch between mostly developing nations' rich biodiversity and their lack of capacity to research and develop these genetic resources into commercial products.

The 2010 Nagoya Protocol thus aims to ensure that the financial and non-financial benefits arising out of R&D conducted on genetic resources will be "fairly and equitably shared" with the country of origin. To achieve this goal, this international agreement consists of three clusters of rules, the so-called "ABC" of the Nagoya Protocol:

Access rules. Since parties exercise sovereignty over their resources, the Nagoya Protocol allows them to require a public permit to acquire a genetic resource and/or related local traditional knowledge. This is known as prior informed consent (PIC). To continue the example of French-Guyana, PIC means that prior to locally ac-

quiring *Quassia amara* for purposes of R&D of a commercial or non-commercial nature, one should check whether public authorization is required, and comply as necessary. There are already 70 parties to the Nagoya Protocol, including Switzerland, the EU and six EU member states. At present, around 50 countries have some form of access legislation. While the US is not a party, that does not mean that US companies remain unaffected by the Nagoya Protocol, especially when they are active in the EU.

Benefit-sharing rules. Aside from PIC, Nagoya parties may require the entity seeking to acquire genetic resources to conclude a contract with local partners as to how benefits from R&D on the genetic resources will be shared. This is referred to as mutually agreed terms (or MAT) and the Nagoya Protocol in annex provides examples of non-financial and financial benefits. In the French-Guyana example, the French IRD committed to full sharing of the research results, awareness-raising with local population, equal sharing of profits from the medicine, and a low price for the medicine in French-Guyana so as to ensure access for the local population.

Compliance with access and benefit-sharing rules. Parties to the Nagoya protocol are not obliged to adopt PIC and MAT obligations, and many choose not to. However, the protocol does require that all parties adopt enforcement rules to ensure that R&D within their own jurisdiction is compliant with applicable access and benefit-sharing legislation of the countries of origin of the genetic resources where these are Nagoya parties.

The implementation of this "ABC" of the protocol within the EU is divided between the national and Union level. The member states are competent to adopt rules on access and benefit-sharing (AB) since they have sovereignty over their genetic resources. The EU has adopted the compliance rules across the entire EU internal market (C), but civil and criminal sanctions and enforcement procedures are again adopted at the member state level.

The EU compliance regime consists of two legal instruments: First, Regulation 511/2014 of 16 April 2014 "on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union". This basic regulation has been supplemented with an implementing regulation of Oct. 13, 2015 with, among other aspects, rules on how compliance will be monitored by national authorities. Between 2016 and 2017, the European Commission will also publish a general and several sector-specific guidance documents for pharmaceutical and medical device companies, plant breeders, chemicals companies and others on how to comply the new regime.

Establishing Whether The Company Falls Under EU Rules

The scope of Regulation 511/2014 is defined in sweeping terms. Companies, universities, gene banks, botanical gardens or natural history museums may all be captured by the EU rules when they conduct research and development on "any material of plant, animal, microbial or other origin containing functional units of heredity". This could include honeybush, viruses, pineapples, intestinal bacteria, mice, eukaryotic and prokaryotic cells, and so on.

The Nagoya regime also intends to include derivatives, such as enzymes derived from pineapple, essential oils, snake venom, proteins or flower fragrances. Commercial and non-commercial entities conducting R&D on these genetic resources are called "users". As a first step, such users will need to know whether their activities are at all covered by the EU's Nagoya compliance regulation. In what follows, we provide a brief example of how to conduct that exercise.

Unfortunately, there is significant legal uncertainty, mainly because the EU rules were adopted without sufficient attention being given to the diverse sectoral R&D processes it regulates. We briefly highlight a few basic conditions for the regime to apply, using as a hypothetical example the development of a vaccine against the Zika virus. The summary is not comprehensive and the following conditions are cumulative.

- First, any natural or legal person who conducts R&D on genetic resources within the EU is subject to the Nagoya compliance regulation. The location of R&D within one of the 28 EU member states is the geographic anchor-point. This means that if a US-owned pharmaceutical company conducts research on Zika in a research facility in an EU member state, it will be captured by the compliance obligations in the regulation. Conversely, R&D entirely outside the EU, even when the resulting product is ultimately marketed within the EU, would not be captured by the compliance regime.

- Second, the regulation applies to genetic resources accessed after Oct. 12, 2014. This is the day on which the Nagoya Protocol entered into force in the EU. If the company conducts R&D on a Zika strain acquired after that day, the EU regulation will apply. Conversely, if the virus was acquired before that date, and held in storage by that company, the R&D activities after Oct, 12, 2014 would in principle fall outside the EU compliance regime.

- Third, the acquisition of the genetic resource must have occurred in a party to the Nagoya Protocol. The first Zika infection of the recent epidemic was confirmed in May 2015 in Brazil. Since that country is currently not a party to the Nagoya Protocol, R&D on a strain acquired locally would not trigger the EU regime. Of course, when subjected to a compliance check under the EU regime, the company will need to have evidence that the Zika strain originated from Brazil at the time it was not a Nagoya party.

- Fourth, it may seem obvious that developing a Zika vaccine constitutes "research and development", so that the EU rules apply. However, since R&D is not defined in the EU regulation, various questions can arise. For example, is it R&D to merely sequence the DNA of the virus? Is receiving purely digital information on Zika considered to constitute "access" to a genetic resource, and is *in silico* research also covered? In the general guidance document of 2016, the commission intends to provide clarification. An advanced draft states that users should assess whether the R&D "creates new insight" into the genetic and/or biochemical characteristics of the resource. Commodity trade in genetic resources would thus not be captured, but most other activities would easily fall within that definition. Basic research without the intention to develop a product would likely also be captured by the EU compliance rules.

- Finally, the example of Zika illustrates that the EU compliance regime contains special rules for international pathogens such as Ebola or Zika. On Feb. 1, 2016, the World Health Organization declared Zika a public health emergency of international concern. In that case, the EU regulation states that R&D may start without first having secured PIC and negotiated MAT in accordance with the Nagoya Protocol. However, strict deadlines apply for complying afterwards. In addition, in case of non-compliance with EU rules, the sanction is that the company cannot claim any exclusive rights to the developments made via the R&D on the pathogen of international concern.

The Obligations Under EU Rules

Once the company has established that the EU regulation applies to its activities, it imposes an obligation to "exercise due diligence" to ascertain that users conduct R&D in accordance with PIC and MAT obligations. The reference to due diligence can be misleading, because the failure to comply can result in strict sanctions. These include an obligation to discontinue R&D on the genetic resource, which could have an impact on the commercialization of the resulting product.

To comply with the due diligence obligation, users must "seek, keep and transfer to subsequent users" information and documentation on the genetic resources on which they conduct R&D. This is essentially a "track and trace" obligation, which means that users must:

- Exercise a sufficient level of care and effort so as to (a) ascertain whether the Nagoya party has access (PIC) and benefit-sharing (MAT) rules, (b) ensure that prior informed consent is obtained where necessary, and (c) negotiate mutually agreed terms if required.

- Set up a database containing the information and documentation previously obtained, covering the entire time period of the R&D, and keep this data for 20 years after the R&D ends.

- Provide this documentation and information to subsequent users to ensure a "chain of compliance" from one user to the next. Issues of commercial confidentiality under this obligation have not been addressed in the EU regulation.

Thereafter, the user conducting R&D must also make a "compliance declaration" at two points in time. This will allow national competent authorities to monitor user compliance with the Nagoya Protocol. A central EU web-portal is being developed where users will have to upload their compliance declarations. The timepoints for the declarations are:

- When a public or private grant is received to carry out R&D on the genetic resource or associated traditional knowledge.
- At the stage of final development of a product developed through R&D on the genetic resource or associated traditional knowledge.

The second checkpoint is likely the most significant. Prior to seeking market approval, placing the product on the market, or even selling the result of R&D outside the EU, the user must declare and prove compliance with the EU obligations under the Nagoya Protocol. Parts of the declarations will be publicly accessible. Although not an EU member state, in Switzerland a new application for authorization of a medicinal product whose development is based on the utilization of genetic resources must include the registration number from the Federal Office for the Environment. In this way, an explicit link is made between the marketing authorization and compliance with the obligations under the Nagoya Protocol.

The EU regulation requires that its compliance obligations are supported by national civil and criminal enforcement rules in all member states. For instance, in the UK, the National Measurement & Regulation Office has been appointed as the national competent authority. It acts in accordance with the Statutory Instrument 2015 No. 821 of March 2015. The rules foresee civil sanctions for failure to exercise due diligence, failure to track and trace information, and failure to make the declaration. Civil sanctions include compliance notices, variable monetary penalties, and also stop notices on commercialization of products where PIC and MAT have not been complied with. Failure to comply with civil sanctions is subject to criminal sanctions.

Conclusion

The EU compliance regime is still in its infancy and many aspects require clarification. The commission intends to publish in the coming months a general guidance document clarifying the scope of application of EU rules. It will subsequently work on sector-specific guidance documents covering pharmaceuticals, medical devices, plant breeding, animal breeding, food and beverage, biocides, and other relevant sectors. These documents will focus on sector-specific R&D processes on genetic resources, and should be finalized in 2017.

Trade associations based in Brussels are actively engaged in this drafting process, but individual companies are strongly advised to monitor and participate when needed. Similarly, it is crucial to monitor developments at national level. For example, the final adoption of the new French biodiversity law linked to the Nagoya Protocol is expected this summer. The newly founded French Biodiversity Agency is expected to be operational on Jan. 1, 2017.

Although the Nagoya legal regime is still a moving target, in order to avoid problems with commercialization in a few years' time, it is important that companies now put in place procedures that implement, adequately document and declare due diligence. These procedures can then be updated when guidance documents from the commission are available, and in line with national enforcement practice by member state authorities. It is also likely that the Court of Justice of the EU will ultimately have to interpret specific aspects of the regime.

References

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2. *Regulation (EU) No 511/2014 of 16 April 2014 on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union, OJ, May 20, 2014, L150/59, http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32014R0511&from=EN*

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