

Ebola: Company avoids benefit-sharing obligation by using sequences

by Edward Hammond

A US company's new Ebola drug has been developed using the digital sequence information (DSI) of an Ebola virus from the 2014 West African epidemic. This case is sure to draw heavy attention in upcoming intergovernmental discussions at the Convention on Biological Diversity (CBD) and the World Health Organization on access and benefit sharing for pathogens and other genetic resources.

The Ebola sequence was posted online by a European research institute that applies mandatory benefit-sharing obligations to transfers of physical virus samples, but made access to sequences of the same virus available with "no strings attached".

The patented drug is not yet approved by the US Food and Drug Administration but has nevertheless already attracted over \$400 million in development and purchase commitments from the US government. The case concretely demonstrates how DSI can be used to avoid the benefit-

sharing obligations of the CBD and its Nagoya Protocol on Access and Benefit Sharing.

Regeneron Pharmaceuticals, based in New York (US), developed REGN-EB3 using the DSI of a 2014 West African Ebola strain. The strain, named C15, had been isolated in the clinical sample of a 28-year-old Guinean woman by researchers from the Pasteur Institute in Lyon, France, in cooperation with the Nocht Institute in Hamburg, Germany. The Nocht Institute sequenced the C15 virus and posted the result in Genbank, a public "no strings attached" database sponsored by the US government.

While access to the C15 Ebola DSI in Genbank is available without any obligation to anyone with a web browser, when the Nocht Institute transfers a physical virus sample to other laboratories, including laboratories in the United States, it uses a binding material transfer agreement (MTA) that references the CBD and Nagoya Protocol. The MTA requires recipients of the

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C15 Ebola virus to negotiate a benefit-sharing agreement with Guinea, its country of origin, if they use the virus commercially or to generate intellectual property.

But the benefit-sharing requirement does not apply if the virus is accessed as DSI, and this is what Regeneron did. The company downloaded the C15 Ebola virus sequence from Genbank. It then synthesized portions of the virus and used them to create the drug. Because Regeneron accessed DSI from Genbank rather than obtaining a virus sample from Nocht, the obligations of Nocht's MTA are inapplicable – a situation that Nocht and its partners could have prevented and were indisputably aware could emerge when they chose to post the data online without a data access and use agreement.

The financial benefits for Regeneron are huge. To date, the US government has paid the company over \$190 million to develop and begin production of the drug for US biodefence purposes. And the US has further contracted to pay Regeneron \$215.8 million more to buy additional doses for its national biodefence pharmaceutical stockpile. Other governments or private entities might also purchase REGN-EB3, generating more profits for the US company. (Indeed, encouraged by its experience with REGN-EB3, Regeneron has contracted with the US government to create more drugs to treat other biodefence-related infectious diseases.)

REGN-EB3 is being used in small experimental quantities in the current Ebola outbreak in the Democratic Republic of the Congo, but commercial production is so far limited to the US biodefence programme. The precise cost of a course of the drug, a monoclonal antibody combination, has not been publicly revealed but, in line with other similar drugs, is likely to be well over \$10,000 per dose, and potentially multiples of that figure, which is a price far above what the vast majority of African Ebola victims and African governments are able to pay.

There has been no public indication that Regeneron has entered into an agreement with the Guinean government in relation to REGN-EB3, much less a proper Nagoya-compliant access and benefit-sharing agreement with prior informed consent (PIC) and mutually agreed

terms (MAT). Indeed, in the unlikely event Regeneron has secretly done so, such an agreement would be voluntary on the company's part in the eyes of US law, since the Genbank database imposes no benefit-sharing conditions.

The Nocht Institute could have prevented this from happening by using a data access and use agreement for the DSI that is equivalent to the requirements of its MTA. But since Nocht placed the DSI in an "open access" database, in disregard of the interests of Guinea, Regeneron has been able to obtain patents in the United States, Nigeria and South Africa and has applications pending in over 100 more countries – all without any apparent agreement with Guinea to share benefits arising from the utilization of C15.

In short, Nocht's handling of the DSI – which is by no means unique among infectious disease research institutions – has denied Guinea the opportunity to assert its rights under the CBD and Nagoya Protocol. Those rights could, for example, be used to seek affordable access to the drug for itself and other African countries, or to require licensure of the patents to other drugmakers to encourage more affordable production for developing countries.

To underscore the lack of communication with Guinea in the case, the initial publication describing C15, which appeared in the *New England Journal of Medicine* in 2014, explicitly states that "informed consent was not obtained" for use of the clinical samples. While this is a reference to medical informed consent rather than national prior informed consent in the sense of the Nagoya Protocol, if Nocht and its partners were unable to obtain consent from patients, it is exceedingly unlikely that they obtained PIC from the Guinean government for American companies (or other companies) to use the virus to create proprietary drugs.

It should be emphasized that the Nocht Institute and its partner Pasteur Institute were working to quickly respond to the Ebola outbreak. By isolating and sequencing the virus, and making available early epidemiological and strain information, Nocht's activities were an important part of the international public health response to the outbreak and Nocht should not be criticized for performing them *per se*.

Nor does assertion of the rights of provider countries under the CBD and Nagoya Protocol in the course of epidemic response create any inherent impediment to access to pathogens for public health purposes. To the contrary, sovereign rights of genetic resource providers can be used to improve access to diagnostics and therapeutics in countries and regions where outbreaks occur.

Rather, the problem is Nocht's disregard for African benefit-sharing interests in its handling of the C15 sequence data. Nocht and partners were certainly aware of the possibility that C15 Ebola DSI could be used commercially, including in the generation of synthetic virus and patents. But rather than applying the same benefit-sharing terms to sequences as to virus samples, Nocht distributed the DSI with "no strings attached", enabling companies like Regeneron to utilize African genetic resources without incurring benefit-sharing obligations.

The case is a concrete demonstration of how

DSI can be used to avoid the benefit-sharing obligations of the Nagoya Protocol and CBD. It demonstrates that it is nonsensical to maintain, as some developed countries have, that access to DSI and access to physical genetic resources can be meaningfully separated in the context of benefit-sharing obligations. DSI clearly can be used to avoid benefit-sharing obligations, and DSI utilization, like utilization of physical genetic resources, can result in very substantial monetary and, in this case, potential health benefits.

This case concerns Ebola, but the problem is far from limited to Ebola. It is urgently necessary for the CBD, the World Health Organization and – in agriculture – for the UN Food and Agriculture Organization to address this glaring problem by ensuring proper sharing of benefits arising from the use of genetic resources accessed in the form of DSI.

(NB: See "Excerpt" and "Timeline" for sources.)

Excerpt of binding terms applied by Bernhard Nocht Institute to virus transfers, but not to digital sequence information¹

III. Convention on Biological Diversity:

1. The MATERIAL is considered a genetic resource within the meaning of the Convention on Biological Diversity (CBD). Therefore, PROVIDER and RECIPIENT wish to comply with the terms of the CBD, in particular its regulations on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits as laid out in the Nagoya Protocol. TGK Initial
2. The country of origin of the MATERIAL is Guinea. This Agreement attempts to comply with Article 15 of the CBD, which recognizes the sovereign rights of States over their natural resources. The CBD requires users of genetic resources to share benefits accruing from their use with the country of origin. In the case of subsequent exploitation, suitable and adequate sharing of income must be negotiated by the RECIPIENT with the country concerned. TGK Initial
3. Therefore, in the event of discovery of a potential commercial use for a product or process, or generation of Intellectual Property, which derives from or covers the MATERIAL or MODIFICATIONS, the RECIPIENT shall notify the PROVIDER and the Country of Origin of said discovery. The activity related to said potential use or Intellectual Property shall be suspended. In respect of the circumstances, a new contract containing the relevant legal provisions shall be executed between the RECIPIENT, the PROVIDER, and the Country of Origin. TGK Initial

Timeline of the C15 Ebola sequence events discussed here

DATE	LOCATION	EVENT
6 Dec 2013	Guéckédou, Guinea	First death recorded in the 2014 West Africa Ebola epidemic. ²
March 2014	Kissidougou, Guinea	Three siblings in Kissidougou contract Ebola. Two brothers die. A sister, aged 28, survives and is later designated in studies as case “C15”. ³
March 2014	Lyon, France Hamburg, Germany	Clinical samples of 20 patients from Guéckédou, Kissidougou and Macenta, Guinea, arrive at Institut Pasteur in Lyon, France, and Nocht Institute in Hamburg, Germany. These include a sample from C15. ⁴
16 Apr 2014	United States	Pasteur, Nocht and others publish the first epidemiological report on the outbreak in the <i>New England Journal of Medicine</i> . (The final version is released on 19 September.) It describes C15’s case and the virus from her sample. The report states (emphasis added): “This work was performed as part of the public health response to contain the outbreak in Guinea; <i>informed consent was not obtained</i> .” ⁵
30 Jul 2014	Hamburg, Germany	The Bernhard Nocht Institute uploads the genetic sequence of the virus from C15’s clinical sample as Genbank accession KJ660346. ⁶ The virus is now called <i>H.sapiens-wt/GIN/2014/Makona-Kissidougou-C15</i> , sometimes, “Makona strain” or “Makona Ebola”.
26 Jan 2015	Washington DC, USA	Regeneron Pharmaceuticals files a preliminary patent application on a monoclonal antibody drug for Ebola. ⁷ The monoclonal antibodies (MABs) were generated using synthesized pieces of the C15 Ebola genome that Regeneron downloaded from GenBank. ⁸
12 Feb 2015	Hamburg, Germany Galveston, Texas, USA	Nocht researchers send a vial of Guinean Ebola to the University of Texas for inclusion in a US government virus collection. This is quite likely C15. The MTA includes provisions citing the CBD and Nagoya Protocol. Nocht requires that Texas and any subsequent recipient of the virus who uses it commercially and/or generates intellectual property must cease work and negotiate mutually agreed terms with Guinea before proceeding. ⁹
2 Sep 2015	Washington DC, USA	Regeneron is awarded \$45.9 million by the US government to develop REGN-EB3, the Ebola drug created using Nocht-generated DSI from C15. ¹⁰
26 Sep 2017	Washington DC, USA	Regeneron’s first US patent on REGN-EB3 is granted (#9771414). The company is unencumbered by the Nocht MTA because it used Nocht DSI.
30 Sep 2017	Washington DC, USA	Regneron receives a contract worth up to \$362.4 million to produce REGN-EB3 for the US biodefence drug stockpile. \$146.6 million has been paid to date (May 2019). ¹¹
31 May 2018	New York, USA	Regeneron authors publish an article detailing their use of synthesized DSI from the C15 isolate in the creation of REGN-EB3: “...complementary deoxyribonucleic acid (DNA) sequence encoding for EBOV GP (Makona strain; GenBank no. KJ660346) was synthesized and cloned into expression vectors using standard methods...” ¹²
26 Sep 2018	Washington DC, USA	Regeneron’s second US patent on REGN-EB3 is granted (#10081670).
10 Jan 2019	Delhi, India	Regneron files Indian Patent Office Form 3, in relation to its application 01717024283. At this time, Regeneron states that it has obtained patents on REGN-EB3 in the US, Nigeria and South Africa, and that applications are pending in more than 100 other countries. ¹³

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Endnotes

1. Extracted from: Bernhard-Nocht-Institute for Tropical Medicine 2015. Material Transfer Agreement for the Distribution of Biological Material to non-profit recipients. Signed agreement with University of Texas Medical Branch (Galveston). 16 February. Obtained under the Texas Public Information Act. URL: <http://www.pricklyresearch.com/webdump/Ebola2014/NochtUTMBMTA.pdf>
2. Baize S et al. 2014. Emergence of Zaire Ebola Virus Disease in Guinea. *New England Journal of Medicine* 372:1418-25. DOI: 10.1056/NEJMoa1404505
3. Ibid.
4. Ibid.
5. Ibid. This refers to medical informed consent, but it does not appear that PIC under the Nagoya Protocol was obtained either.
6. GenBank (database). Zaire ebolavirus isolate H.sapiens-wt/GIN/2014/Makona-Kissidougou-C15, complete genome (Accession KJ660346).
7. US Patent US9771414, granted 26 Sep 2017. Priority date 26 Jan 2015.
8. Pascal K et al. 2018. Development of Clinical-Stage Human Monoclonal Antibodies That Treat Advanced Ebola Virus Disease in Nonhuman Primates. *The Journal of Infectious Diseases* 2018:218 (Suppl 5). <https://doi.org/10.1093/infdis/jiy285>
9. Bernhard-Nocht-Institute for Tropical Medicine 2015, op. cit.
10. US Department of Health and Human Services Contract HHSO100201500013C.
11. US Department of Health and Human Services Contract HHSO100201700016C.
12. Pascal et al. 2018, op. cit.
13. Regneron 2019. Indian Patent Office Form 3, filed for application 01717024283, 10 January 2019.