

The Coalition for Affordable T-DM1  
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25th November 2016

The Rt. Hon. Jeremy Hunt MP  
Secretary of State for Health  
Department of Health  
Richmond House  
79 Whitehall London  
SW1A 2NS

Via email: [mb-sofs@dh.gsi.gov.uk](mailto:mb-sofs@dh.gsi.gov.uk)

RE: Request for compulsory licence on patents related to the breast cancer drug T-DM1 sold by Roche under the brand name Kadcyła.

Dear Secretary of State,

This is a request, submitted in follow up to a letter to your department in October 2015 and in advance of a related NICE appraisal hearing on the 29th November 2016, that the Government of the United Kingdom of Great Britain and Northern Ireland (UK) authorise the domestic manufacture and/or importation, use and sale of biosimilar versions of trastuzumab emtansine (T-DM1) used in the treatment of breast cancer, to be supplied to the government for use and sale in the UK.

Our coalition of medical professionals, academics, health activists, IP experts, lawyers and breast cancer patients, are motivated to make this appeal on behalf of women with breast cancer who have or may in the future develop resistance to trastuzumab (Roche brand name Herceptin), and for whom trastuzumab emtansine (T-DM1) is an appropriate and important medicine that can extend and improve lives.

The drug trastuzumab emtansine (T-DM1) is now sold by Roche in the UK using the brand name Kadcyła at a price that is so high that NICE does not consider the drug cost-effective. Roche has been unwilling to offer significant concessions in the price, and as a consequence, women who have breast cancer and who are resistant to trastuzumab alone cannot obtain reimbursements for this drug.

The recent Lancet Commission on Essential Medicines strongly encouraged countries to utilise their legal right to use compulsory licences to secure affordable access to medicines for their citizens. If the UK is willing to invoke its power to grant a compulsory licence on T-DM1 patents, one of two beneficial outcomes will occur. Either (1) Roche will reduce its price enough to avoid the compulsory licence, an event that will have an immediate impact on patients in need of this drug; or, (2) the compulsory licence will be granted and competitors will be allowed to supply a biosimilar version in the UK market, an outcome that will have important economic benefits to the UK Treasury later, and a forward looking government could look to future savings to justify reimbursements for the costly version of the drug in the interim, while the biosimilar products are in development.

Four potential suppliers have held confidential discussions with the petitioners and have indicated an interest and willingness to supply a biosimilar product to patients in the UK. One of the four companies has offered to manufacture the drug in the UK, and we believe other companies may also be willing to do so, if that is a condition of a compulsory licence.

The following issues are addressed in this petition:

1. The Need for Affordable T-DM1 in the UK;
2. Development of biosimilar versions of T-DM1;
3. The legal basis for the non-voluntary authorisations to use T-DM1 patents, and additional strategies to expand access and challenge Roche’s excessive price.

**The Need for Affordable T-DM1 in the UK**

*HER2+ Breast Cancer Rates in the UK*

There are separate registries for the incidence of cancer in Scotland, Wales, Northern Ireland and England.<sup>1</sup> Collectively, there were 55,192 breast cancer cases reported in the UK in 2014.

New cases of breast cancer in 2014	
Scotland (all persons)	4,610
Wales (female)	2,872
N. Ireland (female)	1,293
England (all persons)	46,417
UK	55,192

<sup>1</sup> Information Services Division Scotland. Cancer Information Programme. <http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Breast/>; Welsh Cancer Intelligence and Surveillance Unit. <http://www.wcisu.wales.nhs.uk>; N. Ireland Cancer Registry. [www.qub.ac.uk/nicr](http://www.qub.ac.uk/nicr); Office for National Statistics. Cancer Statistics: Registrations Series MB1. <http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2014> <https://www.gov.uk/government/statistics/cancer-registration-statistics-england-2013>

Since 2001, the number of new cases of breast cancer has been increasing at a rate of 1.9 percent per year, roughly three times the rate of growth in the UK population.

Roughly 20 percent of new breast cancers are diagnosed as HER2+.<sup>2</sup>

Approximately 6-10 percent of new breast cancer cases are diagnosed as stage IV (metastatic) and 20-30 percent of all breast cancer cases will become metastatic.<sup>3</sup>

One reason for the increase in the incidence of the number of cases of breast cancer is that the UK population is getting older. In 2000, 22.9 percent of the UK female population was 60 years or older. In 2015, this had increased to 24.5 percent. By 2030, this is expected to reach 29.3 percent of the population, an increase of 20 percent over the 2015 percentage.

### *Price is the Primary Barrier to T-DM1 Access in the UK*

T-DM1 is used to treat patients with HER2-positive breast cancer that has spread to other parts of the body and cannot be surgically removed. T-DM1, as a single agent, is approved as a cancer medicine to treat patients who previously received trastuzumab and a taxane, separately or in combination. For most patients, it is the best option.

The National Institute for Health and Care Excellence (NICE) reports that as many as 1,500 women in the U.K. could benefit from T-DM1 every year.<sup>4</sup> For many HER2+ breast cancer patients, T-DM1 is very effective and does not have the negative side-effects associated with chemotherapy.

According to NICE, the list price for T-DM1 is approximately £90,000 per patient per year.<sup>5</sup>

Whilst T-DM1 was viewed by NICE as highly effective, the price charged for it by Roche was so high that it was not deemed cost-effective. In September 2015, it was announced that as of November 4th, 2015, no new patients will be able to receive T-DM1 through the Cancer Drugs Fund because the NHS had removed it and 16 other expensive cancer drugs from its list of covered treatment options.

Thus, patients who could benefit from the treatment will be forced to pay out of their own pocket. The price of £90,000 is more than 3 times the GDP per capita of £28,626,<sup>6</sup> far beyond the reach of most people.

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<sup>2</sup> <http://www.mayoclinic.org/breast-cancer/expert-answers/faq-20058066>

<sup>3</sup> [NCI SEER data analysis 2000-2005] [ACS Breast Cancer Facts & Figures] [O'Shaughnessy, J. "Extending Survival with Chemotherapy in MBC" The Oncologist 2005:10] <http://mbcn.org/education/category/most-commonly-used-statistics-for-mbc>

<sup>4</sup> "Pressure grows on Roche to lower breast cancer drug price." NICE, News and Features. 08 August 2014. <https://www.nice.org.uk/news/article/pressure-grows-on-roche-to-lower-breast-cancer-drug-price> Accessed 28 September 2015.

<sup>5</sup> <https://www.nice.org.uk/news/article/kadcyla-too-costly-for-use-on-the-nhs>

<sup>6</sup> Source: World Bank, 2015 (Local Currency Union).

<http://data.worldbank.org/indicator/NY.GDP.PCAP.CN?locations=GB>

## The Development of Biosimilar T-DM1

### Manufacturing T-DM1

In technical terms, T-DM1 is an antibody-drug conjugate consisting of the monoclonal antibody trastuzumab linked to the cytotoxic agent DM1, a product Roche licenced from ImmunoGen.

The drug acts by seeking out HER2+ cancer cells, and delivering a toxic and lethal payload consisting of DM1, to kill off the cancer cells, while leaving the healthy cells intact.

T-DM1 is made up of 3 components: The antibody, the crosslinker and the cytotoxic molecule.

Like all small molecules, DM1 can be easily synthesised chemically.

Trastuzumab is a humanised monoclonal antibody produced in a mammalian cell line (chinese hamster ovary [CHO] cells). These specific cell lines are well characterised in the laboratory and can be grown in very large incubators called bioreactors. Because we know the genetic sequence of trastuzumab, scientists give the CHO cells specific genetic instructions on how to make the antibodies they want. Getting these cells to accept the instructions requires some optimization, but once the CHO cells produce the antibodies, scientists are able to create clones of these cells and produce a large amount of antibody in the bioreactors. The antibody must then be extracted from the cells and media in series of purification steps. Like all pharmaceutical products, the manufacturing process is tightly controlled and everything from the genetic integrity of the CHO cells to the post-translational modifications on the antibodies must be very closely and continually monitored.

Once one has trastuzumab and DM1, they can be cross-linked or glued together with a succinimidyl trans-4- (maleimidylmethyl)cyclohexane-1-carboxylate (SMCC) reagent in a two step chemical reaction. The SMCC is also crucial for stabilizing the antibody-drug conjugate (ADC) in the body until the antibody can deliver its toxic payload to the cancer cells. To a biochemist, this is not a difficult reaction to accomplish.

### *A Biosimilar of T-DM1 Could Be Available for UK Patients Within 2-3 Years, Perhaps Sooner*

The grant of compulsory licences would induce companies to accelerate the development of a T-DM1 biosimilar. Several reputable companies with the capacity to manufacture biosimilars have already indicated their willingness to assist the UK government in this regard.

A biosimilar of trastuzumab is currently available in South Korea and India. Companies are manufacturing and testing trastuzumab biosimilars for marketing approval in the EU. This is a major advantage since it means biosimilar trastuzumab candidates already exist for the antibody portion of T-DM1. DM1 can be bought from a supplier or made in-house and linked

to a trastuzumab biosimilar. Altogether, the development phase and pre-clinical testing can take up to 2 years.

Biosimilar marketing approval in the EU (and UK) requires preclinical testing that can take up to 2 years if animal testing is required. Depending on the pre-clinical and physiochemical tests, the European Medicines Agency's (EMA) Committee for Human Medicinal Products (CHMP) requires a number of clinical trials to be performed. Based on current biosimilars that are available, and the burden of proof needed to show safety and biosimilarity the minimum requirements can be a phase 1 and phase 2 clinical trials. Phase 1 clinical trials can take up to 1 year depending on the endpoint and analysis, and Phase 2 can take up to 2 years. Some patients will have access to a biosimilar or the originator biologic drug in the clinical trials.

As discussed below, there are options available to overcome exclusive rights in test data exclusivity rule, to avoid or mitigate barriers that prolong the development and approval of biosimilar products.

We have also discussed with biosimilar manufacturers the option of working with the UK government to put UK patients on trials, financed by the UK government, in return for concessionary prices and/or an equity position in the biosimilar product for sales outside the UK. This would have the dual benefits of accelerating access to the biosimilar product, before formal regulatory approval, and ensuring a low price for the drug.

The fact that several companies are in late stage development of biosimilar versions of trastuzumab, and emtansine (DM1) is a relatively easy product to manufacture, are factors that favor successful development of the biosimilar product.

### **Legal Basis for Compulsory Licensing**

One legal foundation for granting a compulsory licence is the UK Patents Act 1977 (as amended) Sections 55-59 on "Crown Use," European Regulation 1257/2012, and the TRIPS Agreement.

#### Crown Use

Section 55 on "Crown Use" provides broad authority for "any government department and any person authorised in writing by a government department" to make use of a patent "for the services of the Crown" without the patent holder's consent. Use under Section 55 does not require any specific grounds, as appears, for example in Section 48.

Section 55(1)(a)(i) allows the Crown to "make, use, import or keep the [patented] product, or offer to sell it where to do so would be incidental or ancillary to making, using, importing or keeping it," and additionally, under (a)(ii), to "sell or offer to sell it ... for the production or supply of specified drugs and medicines." The Section has additional relevant language relating to specified drugs and medicines, adding in (1)(c) that the Crown, "without prejudice to the foregoing, where the invention or any product obtained directly by means of the

invention is a specified drug or medicine, may sell or offer to sell the drug or medicine,” and in (1)(d) that the Crown “may supply or offer to supply to any person any of the means, relating to an essential element of the invention, for putting the invention into effect.”

“For the services of the Crown” is defined in Section 56(2) and includes, under 56(2)(b), “the production or supply of specified drugs and medicines.”

Crown Use has been used by the UK, including specifically for pharmaceuticals, through the 1960’s and 1970’s. In the case of *Pfizer v. Ministry of Health* (1965), for example, the UK used these provisions in order to authorise the purchase of generic antibiotics (tetracycline) from Italy for use in NHS hospitals.

In 1991, the UK government authorised the supply of machines known as lithotriptors, for treating kidney stones, under the Crown Use provisions of the Patent Act 1977 (*Dory v Sheffield HA* [1991] FSR 221).

In the 1990’s, amidst lengthy litigation between Murex Diagnostics and Chiron regarding patents on hepatitis C (HCV) diagnostic tests, the British Ministry of Health’s threat of utilizing Crown Use provisions was instrumental in getting Chiron to licence its patents. Chiron’s 10-K filing to the SEC for fiscal year 1995 explicitly acknowledged the pressure this placed on the company to “grant a license it would not otherwise have granted.”<sup>7</sup>

In one of the interim judgments in the Chiron litigation, Hoffmann J referred to the pricing negotiations between the NHS and the patent holder as “a poker game” (*Chiron Corp & Ors v Organon Teknika Ltd & Anor* [1992] FSR 512).

In August of 1996, Chiron agreed to licence the relevant patents to Murex.<sup>8</sup>

### *E.U. Regulations and TRIPS Flexibilities Permitting Compulsory Licences*

The United Kingdom’s authority for issuing a compulsory licence is supported by (1) European Regulation 1257/2012<sup>9</sup>, paragraph 10, which states that, “Compulsory licences for European patents with unitary effect should be governed by the laws of the participating Member States as regards their respective territories;” and (2) Article 31 of the Agreement

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<sup>7</sup> In 1995, Chiron stated in its 10-K submission to the United States Securities and Exchange Commission that, “Most countries limit the enforceability of patents against government agencies or government agencies or government contractors. Generally, the patent owner may be limited to monetary relief and may be unable to enjoin the infringement. This can be of particular importance in countries where a major customer of Chiron or its licensees is a governmental agency. The inability to enjoin such infringement and the necessity of relying exclusively on monetary compensation could materially diminish the value of a particular patent. Furthermore, many countries (including European countries) have compulsory licensing laws under which third parties may compel the grant of non-exclusive licences under certain circumstances (for example, failure to ‘work’ the invention in the country, patenting of improvements by a third party or failure to supply a product related to health and safety). The mere existence of such limits on injunctive relief and compulsory licensing systems could force Chiron to grant a license it would not have otherwise granted.” See Chiron’s SEC filing here: <http://www.sec.gov/Archives/edgar/containers/fix013/706539/0000912057-96-005452.txt>.

<sup>8</sup>

<http://www.thefreelibrary.com/Chiron,+Ortho+Diagnostic+Systems+and+International+Murex+Reach...-a018623523>

<sup>9</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:361:0001:0008:en:PDF>

on Trade Related Aspects of Intellectual Property Rights (TRIPS), which permits use of a patent without authorisation of the rights holder “where the law of the Member allows...” TRIPS Article 31(b) furthermore waives a notification requirement in cases of public noncommercial use, as would be the case with Crown Use.

This particular provision of the TRIPS Agreement was further clarified by the Doha Declaration on TRIPS and Public Health, paragraph 5(b), which states that, “Each member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.” Paragraph 4 of the same declaration notes that the TRIPS Agreement “can and should be interpreted and implemented in a manner supportive of WTO members’ right to protect public health and, in particular, to promote access to medicines for all.”

### **Challenges in Registering Biosimilar Products: Data Exclusivity**

One of the challenges facing biosimilar suppliers will be registration of the drug. This will be easier if the UK can take steps toward waiving the exclusive rights in test data that establish the safety and efficacy of products, and permit the biosimilar suppliers to proceed with registration based upon bioequivalence to products already registered. The European Commission has issued a series of Directives which create obligations on the Government of the United Kingdom to recognize certain time-limited rights in test data which may be relevant, including Directive 2001/83 on the Community code relating to medicinal products for human use. However, language in European Union regulations as well as other globally referenced ethical norms would prohibit the unethical repetition of clinical trials on human subjects.

#### *Regulatory Prohibitions and Global Norms Regarding the Unethical Repetition of Clinical Trials on Human Subjects*

In the event that registration based on bioequivalence to already-registered products is not possible, it may be necessary to conduct expensive new clinical trials, replicating evidence already provided to government regulators. This will lead to delays, and the outlays on the clinical trials are wasteful, thereby limiting the benefits of competition and creating a conflict with regulations and global norms on ethics.

Directive 2001/83 does provide for possible exceptions regarding registration of products, if the testing on human subjects “would be contrary to generally accepted principles of medical ethics to collect such information,”<sup>10</sup> a circumstance that appears relevant in the case of duplicative clinical trials for breast cancer medicine.

Likewise, Directive 2001/20/EC<sup>11</sup> contains prohibitions on repetitive testing, and consideration of the serious risks involved:

(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries.

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<sup>10</sup> Directive 2001/83/EC, Part 4(G).

<sup>11</sup> Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

[...]

### Article 3

2. A clinical trial may be undertaken only if, in particular: (a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored[.]

Being required to perform new clinical trials would also be in conflict with the Declaration of Helsinki on the Ethical Principles for Medical Research Involving Human Subjects. Here we note that the World Health Assembly Global strategy on public health, innovation and intellectual property (WHA61.21), Element 6.2(f), calls upon national and regional regulatory agencies to:

“promote ethical principles for clinical trials involving human beings as a requirement of registration of medicines and health-related technologies, with reference to the Declaration of Helsinki, and other appropriate texts, on ethical principles for medical research involving human subjects, including good clinical practice guidelines”

This principle is echoed in the EMA’s Committee for Medicinal Products for Human Use (CHMP) updated biosimilar guidelines, which includes among its stated aims “facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials.”<sup>12</sup>

We have attached to this document a statement signed by Dr. Sarah Edwards, a medical ethics expert in the UK, stating that duplicative clinical trials for generics and biosimilars, made necessary under data exclusivity regulations, are a violation of established principles of medical ethics. Specifically, the statement makes reference to the aforementioned World Medical Association (WMA) Declaration of Helsinki on the Ethical Principles for Medical Research Involving Human Subjects (the “Helsinki Declaration”), as amended most recently at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013<sup>13</sup>, which states, in part, that:

16. ... Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

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<sup>12</sup> Guideline on similar biological medicinal products. CHMP/437/04 Rev 1. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/10/WC500176768.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf)

<sup>13</sup> Available at <http://www.wma.net/en/30publications/10policies/b3/>

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

*The UK Government Has Paid For Clinical Trials Before, and Should Do So with T-DM1*

If clinical trials must be performed, the UK Government should fund them as it has done in the past on various occasions, including four clinical trials relating to bevacizumab (trade name Avastin), an eyedrop medication first approved in 2004 for colorectal cancer also used for the treatment of eye diseases such as macular degeneration: the BOLT 2010 study<sup>14</sup>, funded by the National Institute of Health Research (NIHR); the IVAN randomized 2012 study<sup>15</sup>, funded by NIHR and the Health Technology Assessment Programme; the LUCIDATE study<sup>16</sup>, funded by NIHR Moorfields Biomedical Research Centre (Novartis also provided funding); and the “ABC” study<sup>17</sup>, funded by NIHR and the National Eye Research Centre.

*Alternative: Compulsory Licence to Rely Upon Test Data*

If the Government cannot fund clinical trials, it could grant a compulsory licence to rely upon test data, subject to payment of a royalty or a contribution toward the costs of the originator’s clinical tests. We recommend that the cost-sharing contribution be based upon a pro-rata share of documented trial costs, adjusted for the risks of success by stage of the trial. The pro-rata share should be based upon the percent of revenue generated by the sales of the drugs in the United Kingdom, compared to the global revenues for the drugs.<sup>18</sup>

The compulsory licence of data has precedent as a remedy for anti-competitive practice, including in cases such as *NDC Health/IMS Health* (the “IMS Decision”)<sup>19</sup>, the *Magill TV Guide* case<sup>20</sup>, and the 2004 Microsoft decision<sup>21</sup>. In *Magill*, the European Court of Justice affirmed an order of the compulsory licence of data comprising daily television listings where

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<sup>14</sup> Sivaprasad S, Crosby-Nwaobi R, Esposti S, Peto T, Rajendram R, Michaelides M, et al. Structural and functional measures of efficacy in response to bevacizumab monotherapy in diabetic macular oedema: exploratory analyses of the BOLT Study (Report 4). *PLoS ONE* 2013;8 (8):e72755.

<sup>15</sup> Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 2012;119(7):1399–411.

<sup>16</sup> Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W, et al. A randomized trial to assess functional and structural effects of ranibizumab versus laser in diabetic macular edema (the LUCIDATE study). *American Journal of Ophthalmology* 2014; Vol. 157, issue 5:960–70.

<sup>17</sup> Keane PA, Heussen FM, Ouyang Y, Mokwa N, Walsh AC, Tufail A, et al. Assessment of differential pharmacodynamics effects using optical coherence tomography in neovascular age-related macular degeneration. *Investigative Ophthalmology and Visual Science* 2012;53(3):1152–61.

<sup>18</sup> This approach is similar to that required by the European Commission to avoid duplicative testing on vertebrate animals, in cases where duplication of tests creates conflicts regarding ethics.

<sup>19</sup> *NDC Health/IMS Health*, Decision (interim measures) of 3 July 2001, OJ 2002 L 59, 18.

<sup>20</sup> *Magill TV Guide* [1989] O.J.L78/43, aff’d by the CFI in Case T-69/89 *RTE v. European Commission* [1991] E.C.R. II-485, [1991] 4 C.M.L.R. 586; Case T-76/89 *ITP v. European Commission* [1991] E.C.R. II-575, [1991] 4 C.M.L.R. 475; Case T-70/89 *BBC v. European Commission*. [1991] E.C.R. II-535, [1991] 4-C.M.L.R. 669; aff’d by the ECJ in Joined Cases C 241 & 242/91 *P RTE and ITP v. European Commission* [1995] E.C.R. I-743, [1995] 4 C.M.L.R. 718.

<sup>21</sup> *Microsoft/Windows 2000* Case No. COMP.37,792, March 24, 2004.

broadcasters denied newspapers “access to the basic information which is the raw material indispensable for the compilation of such a [television] guide.”<sup>22</sup>

In the *IMS* Decision, IMS, a pharmaceutical information services provider, refused to licence its copyright in an aggregation of regional sales report data to NDC, a competitor in the German market. The Commission ordered a compulsory licence of this aggregation to NDC, on reasonable and nondiscriminatory terms, where IMS’s refusal would have eliminated competition on the German market for regional sales reports.<sup>23</sup>

And in 2004, Microsoft was ordered to licence interoperability data on reasonable and nondiscriminatory terms, where the Commission found that the company refused to licence code and interface information to rivals while designing better interoperability between the Windows product and Microsoft’s own software.

We have included extensive discussion of relevant competition law principles, *infra*.

### **Competition Law: Investigation of Roche for Abuse of Dominant Position**

The Department of Health could request that the Competition and Markets Authority initiate a thorough investigation into Roche for abuse of dominant position via excessive pricing of T-DM1 and/or the failure to licence its patents on the drug. A finding of abuse of dominant position would bring with it the legal authority to levy potentially significant deterrent fines on Roche.

There is sufficient basis to justify a thorough investigation into an abuse of dominant position by Roche for excessive pricing of Kadcyła. In addition to the unique medical indication for Kadcyła, making it the only medicine available for certain breast cancer patients, Roche is afforded substantial market power by virtue of the monopoly powers afforded it by the patent system, as well as EU regulations on marketing authorisation and data exclusivity that prevent the entry of biosimilars into competition. Through this monopoly power, Roche prices Kadcyła well above competitive levels, charging unaffordable prices for its medicine far beyond what is reasonable or feasible for UK government reimbursement or for UK patients and consumers. And Roche has done so while refusing efforts to grant a licence in exchange for reasonable royalties, which creates a separate basis for allegations of anti-competitive behaviour.

In August 2014, KEI Europe requested that Roche issue a voluntary licence for T-DM1 in exchange for reasonable royalties, and Roche denied this request on 12 September, 2014. The request, and Roche’s rejection, are enclosed.

#### *Legal Authority for Inquiry*

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<sup>22</sup> Joined Cases C 241 & 242/91 P *RTE and ITP*, para. 56.

<sup>23</sup> The subsequent case history of the *IMS* Decision is lengthy and complex, but the European Court of Justice ultimately asserted, in Case C-418/01 *IMS Health GmbH & Co OHG v. NDC Health GmbH & Co KG* [2004] 4 C.M.L.R. 28, that a compulsory licence could be granted on such data where 1) the product or service protected by copyright must be indispensable for carrying on a particular business; 2) The refusal prevents the emergence of a new product for which there is potential consumer demand; 3) The refusal is not objectively justified; 4) The refusal is such as to exclude all competition on the secondary market.

The Competition and Markets Authority is authorised by the Competition Act 1998 (the “Act”) and EC Regulation 1/2003 (the “Modernization Regulation”) to enforce and apply laws prohibiting the abuse of a dominant position, including Article 102 of the Treaty of the Functioning of the European Union (“Article 102”), and Section 18(1) (the “Chapter II Prohibition”) of the Act. Both Article 102 and the Chapter II Prohibition are implicated in the context of Roche’s excessive pricing for Kadcyła. Under the Modernization Regulation, the CMA is obligated to enforce and apply Articles 101 and 102 when national competition law is applied to abuse prohibited by Article 102.

Additional authority is provided by Section 134 of the Enterprise Act 2002, providing for investigations into a “detrimental effect on customers in the form of ... higher prices ... or less choice of goods or services in any market in the United Kingdom....”<sup>24</sup>

Article 102 provides that, “Any abuse by one or more undertakings of a dominant position within the common market or in substantial part of it shall be prohibited as incompatible with the common market in so far as it may affect trade between Member States.”

Similarly, the Chapter II Prohibition provides that, “...any conduct on the part of one or more undertakings which amounts to the abuse of a dominant position in a market is prohibited if it may affect trade within the United Kingdom.”

Both Article 102 and the Chapter II Prohibition thus require (1) that the undertaking be dominant in a relevant market; and (2) that the undertaking is abusing that dominance.

The term “undertaking” is not defined in the Act or the TFEU, but has been interpreted by case law to cover businesses such as Roche. As pointed out in footnote 3 of OFT402, the term “undertaking” is not a defined term, but has come to be widely understood as covering “any natural or legal person engaged in economic activity, regardless of its legal status and the way in which it is financed...[including] companies, partnerships, firms, businesses, individuals operating as sole traders, agricultural cooperatives, associations of undertakings (e.g. trade associations), non-profit making organisations and...public entities that offer goods or services on a given market.” This interpretation is echoed in footnote 11 of the CMA8, *Competition Act 1998: Guidance on the CMA's investigation procedures in Competition Act 1998 cases*, which defines “undertakings” as “any natural or legal person carrying on commercial or economic activities relating to goods or services, irrespective of legal status” (citing previous OFT manuals and case law such as C-205/03 P FENIN [2006] ECR I-6295).<sup>25</sup>

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<sup>24</sup> Enterprise Act 2002, Section 134(5).

<sup>25</sup> See *also* OFT 401, stating that, “The term undertaking is not defined in the EC Treaty or the Act but its meaning has been set out in Community law. It covers any natural or legal person engaged in economic activity, regardless of its legal status and the way in which it is financed. It includes companies, firms, businesses, partnerships, individuals operating as sole traders, agricultural co-operatives, associations of undertakings (e.g. trade associations), non profit-making organisations and (in some circumstances) public entities that offer goods or services on a given market.” *Agreements and Concerted Practices: Understanding Competition Law*, OFT 401, December 2004. Available at [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/284396/oft401.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/284396/oft401.pdf) (Citing

*Kadcyla Has the Dominant Position as a Medication for HER2+ Patients Who Have Progressed on Herceptin*

The European Court has defined a dominant market position as: "...a position of economic strength enjoyed by an undertaking which enables it to prevent effective competition being maintained on the relevant market by affording it the power to behave to an appreciable extent independently of its competitors, customers and ultimately of its consumers."<sup>26</sup>

With regard to Article 102, the European Commission has provided Guidance explaining that market power is a function of market position, expansion or entry, and countervailing buying power.<sup>27</sup> These factors are additionally among those considered in the Chapter II Prohibition.

Roche's Kadcyla occupies the dominant position for medicines available to HER2-positive patients that have progressed on trastuzumab and taxane chemotherapy, in the geographic market of the United Kingdom, because for many HER2-positive patients who have developed resistance to Herceptin it is the only medicine available. Following results of the June 2014 EMILIA clinical trial, first author Ian Krop, MD, PhD assistant professor in the Department of Medicine at Harvard Medical School and director of breast cancer research at the Dana-Farber Cancer Institute in Boston said of T-DM1 that, "These data suggest that T-DM1 should be considered a standard of care for patients with metastatic breast cancer who have progressed on trastuzumab and lapatinib."<sup>28</sup> Other HER2 medicines, such as Roche's Perjeta (pertuzumab), are distinguishable in that they require that no other treatment have been given previously.<sup>29</sup>

According to data provided by the NHS, between April 2014 and March 2015, 778 patients received Kadcyla from the Cancer Drugs Fund.<sup>30</sup> As stated *supra*, NICE has estimated that 1,500 women per year in the UK could benefit from T-DM1.<sup>31</sup>

*Roche's Unaffordable Price for Kadcyla Constitutes Abuse of the Dominant Position*

Article 102 and Section 18(2) of the Chapter II Prohibition provide that, *inter alia*, conduct may constitute abuse of a dominant position if it consists of directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions.

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*Höfner and Elser v Macrotron* [1991] ECR I-1979, [1993] 4 CMLR 306 and Case T-319/99 *Fenin v Commission*, [2003] ECR IT-357.)

<sup>26</sup> Case 27/76 *United Brands v Commission* [1978] ECR 207, [1978] 1 CMLR 429.

<sup>27</sup> 2009/C 45/02.

<sup>28</sup> See Veronica Hackethal, "T-DM1 Now Preferred for Progressive HER2 Breast Cancer," Medscape, June 27, 2014. Available at: <http://www.medscape.com/viewarticle/827507>

<sup>29</sup> See, e.g., the National Cancer Drugs Fund List approved criteria. National Cancer Drugs Fund List Ver4.2, May 22, 2015. Available at:

<http://www.england.nhs.uk/wp-content/uploads/2015/05/ncdf-list-may15-upd.pdf>

<sup>30</sup> See quarterly figures available at <http://www.england.nhs.uk/ourwork/pe/cdf/>

<sup>31</sup> *Supra* at note 4.

(<https://www.nice.org.uk/news/article/pressure-grows-on-roche-to-lower-breast-cancer-drug-price>).

In OFT402, the Office for Fair Trading explained that “...the way in which an IPR is exercised may give rise to concern if it goes beyond the legitimate exploitation of the IPR.” See *Sirena v. Eda*, 1971 ECR 69, (high price of an intellectual property licence may, ‘if unjustified by any objective criteria and if it is particularly high, be a determining factor’ in finding an abuse of dominance).

Various cases, in the UK and internationally, provide guidance as to abuse of a dominant position.

In the UK, the 2002 case of *Director General of Fair Trading v. Napp Pharmaceutical Holdings Limited* the Competition Commission Appeal Tribunal fined Napp £3.21 million for abuses of dominant position in using a “virtual monopolist” position (not subject to competitive pressure) to price certain drugs at, on average, over ten times higher than the competitive price.<sup>32</sup> The Tribunal asked first whether prices were higher than would be expected in a competitive market, and second, whether there were substantial barriers to entry that would limit competitive market pressure:

The Director considers that a price is excessive and an abuse if it is above that which would exist in a competitive market and where it is clear that high profits will not stimulate successful new entry within a reasonable period. Therefore, to show that prices are excessive, it must be demonstrated that (i) prices are higher than would be expected in a competitive market, and (ii) there is no effective competitive pressure to bring them down to competitive levels, nor is there likely to be.<sup>33</sup>

Similarly, in Decision of Director General of Fair Trading, No. CA98/3/03, Exclusionary Behaviour by Genzyme Limited, 27 March 2003 (Case CP/0488-01), the Office of Fair Trading fined Genzyme £6.8 million for violations of the Chapter II Prohibition where the company “abused its dominant position by making the NHS pay a price which includes home delivery of Cerezyme [a medicine for Gaucher disease] and provision of homecare services if the NHS wishes to purchase Cerezyme, and by adopting a pricing policy for Cerezyme which results in a margin squeeze.”<sup>34</sup>

In the European Court of Justice, cases such as *United Brands Company v. Commission*, 1978 ECR 207, are additionally instructive.<sup>35</sup> In *United Brands*, the Court created a two-part test for abuse of a dominant position: (1) the existence of an excessive profit margin as measured by the difference between price and costs of production; (2) the profit margin must be unfair either in isolation or in comparison with prices of competing products.<sup>36</sup> The Court

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<sup>32</sup> Case No. 1001/1/1/01, Decision CA98/2/2001. Available at <http://www.catribunal.org.uk/238-565/1001-1-1-01-Napp-Pharmaceutical-Holdings-Limited-and-Subsidiaries.html>

<sup>33</sup> *Id.*, paragraph 203.

<sup>34</sup> Available at

<http://webarchive.nationalarchives.gov.uk/20140402142426/http://www.offt.gov.uk/OFTwork/competition-act-and-cartels/ca98/decisions/genzyme>

<sup>35</sup> Available at <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:61976CJ0027&from=EN>

<sup>36</sup> *Id.*

there disapproved of profit margins of 100%. See also *British Leyland Public Limited Company v. Commission* (disapproving 100% profit margin in case where differential fees for left-handed cars were “fixed at a level which was clearly disproportionate to the economic value of the service provided and that the practice constituted an abuse by BL of the monopoly it held by virtue of the British rules.”);<sup>37</sup> C.f. *Tournier*, 4 C.M.L.R. 248 (prices of music royalties found excessive based upon objective price comparison; *United Brands* approach was not possible because it was not possible to determine costs).

South Africa has considered a different test for excessive pricing that is particularly useful in the context of patented pharmaceuticals. In the case of *Hazel Tau et al. v. GlaxoSmithKline, Boehringer Ingelheim, et al.*, James Love of KEI (then of Consumer Project on Technology) put forth a framework for considering excessive pricing in which essential intellectual property goods, such as the HIV medicines at issue, unaffordable prices are presumed excessive unless one of three conditions hold: (1) the owner licenced the IP to competitors on a non-discriminatory basis in exchange for a reasonable royalty; (2) If competitive provision of the good is not economically feasible, prices are reasonable in light of cost of making the good available; or 3) the given prices are necessary to generate the income needed for the development of the good, where there is no substantial market.<sup>38</sup>

The application of the test in that case demonstrated evidence of excessive pricing in that HIV medicines were unaffordable to most HIV patients in South Africa, competition was feasible via generic manufacturing, there was a substantial market for the medicines, and the patent holders refused to issue non-discriminatory licences in return for reasonable royalties.<sup>39</sup>

The application of the proposed *Hazel Tau* test in the case of Roche’s Kadcylla in the UK would yield a similar conclusion, as Roche has refused to licence T-DM1, the price of Roche’s Kadcylla has flatly been declared “unaffordable” by NICE, competition is feasible through the introduction of biosimilars to the market, and there is a substantial market for the medicines in the UK.

The UK CMA has pursued excessive pricing violations as recently as mid-2015, alleging anti-competitive acts by Pfizer and Flynn Pharma, regarding the prices that Pfizer charged Flynn on phenytoin sodium capsules, an anti-epilepsy drug, and then the prices that Flynn then charged wholesalers and distributors for the same drug.<sup>40</sup>

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<sup>37</sup> Case 226/84, 1986 ECR 3263.

<sup>38</sup> James Love, “Evaluation of Excessive Pricing” - Report to The Competition Commission, Republic of South Africa, 31 Aug 2003, In the Matters of: *Hazel Tau et al. v. GlaxoSmithKline, Boehringer Ingelheim, et al.* & *Aids Healthcare Foundation et al v. GlaxoSmithKline, Boehringer Ingelheim, et al.*, Case Numbers 2002sep226 & 2002jan357.

<sup>39</sup> *Id.*, p.12.

<sup>40</sup> See CMA press release, “CMA issues statement of objections to Pfizer and Flynn Pharma in anti-epilepsy drug investigation,” 6 August 2015. Available at <https://www.gov.uk/government/news/cma-issues-statement-of-objections-to-pfizer-and-flynn-pharma-in-anti-epilepsy-drug-investigation>. Complete CMA case information available at <https://www.gov.uk/cma-cases/investigation-into-the-supply-of-pharmaceutical-products>.

### The Failure to Licence Can Constitute Abuse of the Dominant Position

Roche's failure to licence T-DM1 may also constitute an outright abuse of Roche's dominant position, and may provide authority for a compulsory licence on those grounds. European courts have affirmed this principle in intellectual property cases such as *NDC Health/IMS Health* (the "IMS Decision")<sup>41</sup>, the *Magill TV Guide* case<sup>42</sup>, and the 2004 Microsoft decision<sup>43</sup>.

In *Magill*, the European Court of Justice affirmed an order of the compulsory licence of data comprising daily television listings where broadcasters denied newspapers "access to the basic information which is the raw material indispensable for the compilation of such a [television] guide."<sup>44</sup> In the *IMS Decision*, IMS, a pharmaceutical information services provider, refused to licence its copyright in an aggregation of regional sales report data to NDC, a competitor in the German market. The Commission ordered a compulsory licence of this aggregation to NDC, on reasonable and nondiscriminatory terms, where IMS's refusal would have eliminated competition on the German market for regional sales reports.<sup>45</sup> And in 2004, Microsoft was ordered to licence interoperability data on reasonable and nondiscriminatory terms, where the Commission found that the company refused to licence code and interface information to rivals while designing better interoperability between the Windows product and Microsoft's own software.

In *IMS*, the ECJ laid out a four-part test for where the refusal to licence constitutes abuse: (1) the product or service is indispensable; (2) refusal to licence prevents the emergence of a new product for which there is substantial demand; (3) refusal is not objectively justifiable; and (4) the refusal has the effect of excluding competition. "Indispensability" is a measure of the lack of alternatives and the creation of obstacles making it "impossible or at least unreasonably difficult" to create an economically viable alternative.<sup>46</sup>

These factors are met in the case of Roche's refusal to licence T-DM1 in exchange for reasonable royalties. Roche's refusal cuts off all possible competition in the form of new biosimilar products at affordable prices and continues to hold the UK at ransom.

### UK and EU Law Provides for Monetary Fines for Abuse of Dominant Position

A finding of abuse of dominant position creates the possibility for the imposition of substantial penalties against Roche, including potentially on Roche's worldwide revenue, in

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<sup>41</sup> *NDC Health/IMS Health*, Decision (interim measures) of 3 July 2001, OJ 2002 L 59, 18.

<sup>42</sup> *Magill TV Guide* [1989] O.J.L78/43, aff'd by the CFI in Case T-69/89 *RTE v. European Commission* [1991] E.C.R. II-485, [1991] 4 C.M.L.R. 586; Case T-76/89 *ITP v. European Commission* [1991] E.C.R. II-575, [1991] 4 C.M.L.R. 475; Case T-70/89 *BBC v. European Commission*. [1991] E.C.R. II-535, [1991] 4-C.M.L.R. 669; aff'd by the ECJ in Joined Cases C 241 & 242/91 P *RTE and ITP v. European Commission* [1995] E.C.R. I-743, [1995] 4 C.M.L.R. 718.

<sup>43</sup> *Microsoft/Windows 2000* Case No.COMP.37,792, March 24, 2004.

<sup>44</sup> Joined Cases C 241 & 242/91 P *RTE and ITP*, para. 56.

<sup>45</sup> The subsequent case history of the *IMS Decision* is lengthy and complex, but the European Court of Justice ultimately asserted, in Case C-418/01 *IMS Health GmbH & Co OHG v. NDC Health GmbH & Co KG* [2004] 4 C.M.L.R. 28, that a compulsory licence could be granted on such data.

<sup>46</sup> *Id.*, para. 28.

an amount sufficient to reflect the seriousness of the infringement and the need for deterring such behaviour.<sup>47</sup>

Under Section 36(2) of the Act, a finding of infringement of the Chapter II prohibition provides the authority for the Director to “require the undertaking concerned to pay him a penalty in respect of the infringement.” Under Section 36(3), this authority is conditioned upon a finding that the infringement was committed “intentionally or negligently by the undertaking.” Under Section 36(8), the penalty may not exceed 10% of the “turnover of the undertaking (determined in accordance with such provisions as may be specified in an order made by the Secretary of State).” The relevant turnover has been interpreted to include the relevant product market and relevant geographic market affected by the infringement in the last business year, calculated after the deduction of sales rebates, value added tax and other taxes directly related to the turnover.<sup>48</sup> The CMA will apply a rate of up to 30% of the undertaking’s relevant turnover, for the number of years of infringement, and, importantly, for purposes of adjusting the penalty for specific deterrence and proportionality, may take into account infringement that occurs outside of the UK.<sup>49</sup>

Similarly, a finding of abuse of dominant position under Article 102 of the TFEU allows for the imposition of fines of up to 10% of the overall annual turnover, calculated as a percentage of the value of relevant sales (up to 30%) multiplied by the number of years of the infringement, and allowing for increase based upon aggravating circumstances.<sup>50</sup> As with the UK law, the EU guidance on the calculation of the fines provides for the possibility of assessing fines on worldwide revenue, where “the geographic scope of an infringement extends beyond the EEA...the relevant sales of the undertakings within the EEA may not properly reflect the weight of each undertaking in the infringement.”<sup>51</sup> The regulation explains:

In such circumstances, in order to reflect both the aggregate size of the relevant sales within the EEA and the relative weight of each undertaking in the infringement, the Commission may assess the total value of the sales of goods or services to which the infringement relates in the relevant geographic area (wider than the EEA), may determine the share of the sales of each undertaking party to the infringement on that market and may apply this share to the aggregate sales within the EEA of the undertakings concerned. The result will be taken as the value of sales for the purpose of setting the basic amount of the fine.<sup>52</sup>

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<sup>47</sup> OFT’s Guidance as to the Appropriate Amount of a Penalty, OFT 423, September 2012, p.2. Available at [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/284393/oft423.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/284393/oft423.pdf). EU law similarly declares its goals to be punishment and deterrence. See 2006/C 210/02.

<sup>48</sup> *Id.*, p.9.

<sup>49</sup> *Id.*, pp. 8-13.

<sup>50</sup> Guidelines on the method of setting fines imposed pursuant to Article 23(2)(a) of Regulation No 1/2003 EC, 2006/C 210/02. Available at [http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52006XC0901\(01\)&from=EN](http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52006XC0901(01)&from=EN)

<sup>51</sup> *Id.*

<sup>52</sup> *Id.*

Fines for anti-competitive behaviour have been levied in the hundreds of millions of Euros, or more. In the 2004 Microsoft decision, for example, the Commission imposed a fine of €497,196,304, noting the importance of ensuring a deterring effect, and considering, among other factors, the gravity, duration, and nature of the anti-competitive behaviour, as well as the worldwide market for the relevant products.<sup>53</sup> In the 2007 price-fixing case against Compagnie de Saint-Gobain SA, Pilkington PLC, Asahi Glass and Guardian Industries, the European Commission levied fines totaling €486.9 million.<sup>54</sup> And in 2008, the Commission fined automobile glassmakers (again including Asahi, Pilkington, and Saint-Gobain) more than €1.3 billion for illegal market sharing.<sup>55</sup>

## Conclusion

We hope that this document demonstrates that there are many things that the United Kingdom could and should do to increase access to affordable T-DM1 for the many HER2+ breast cancer patients that need it. In light of the ongoing review of T-DM1 by NICE, we request a meeting with the relevant teams within your department to discuss these proposed actions. We look forward to hearing from you.

Yours sincerely,

Diarmaid McDonald  
Lead Organiser, Just Treatment

On behalf of The Coalition for Affordable T-DM1:

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Carolyn Davies, HER 2+ Breast Cancer Patient  
Melanie Kennedy, HER 2+ Breast Cancer Patient  
Julie Blacklaws, HER 2+ Breast Cancer Patient  
James Love, Director, Knowledge Ecology International  
John Pears, Founder, Dying for a Cure  
Lukas Fendel, Executive Director, Universities Allied for Essential Medicines Europe  
Martin Drewry, Director, Health Poverty Action

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<sup>53</sup> *Microsoft/Windows 2000* Case No.COMP.37,792, March 24, 2004, at Section 6.2.

<sup>54</sup> Commission Decision of 28 November 2007 relating to a proceeding pursuant to Article 81 of the EC Treaty and Article 53 of the EEA Agreement (COMP/39165 - Flat Glass). Available at [http://ec.europa.eu/competition/antitrust/cases/dec\\_docs/39165/39165\\_1314\\_1.pdf](http://ec.europa.eu/competition/antitrust/cases/dec_docs/39165/39165_1314_1.pdf). Fines against one of the defendants, Guardian Industries, were later reduced on appeal in *Guardian Industries Corporation and Guardian Europe Sàrl v. Commission*, Case C-580/12 P, 12 November 2014.

<sup>55</sup> Commission Decision of 12 November 2008 relating to a proceeding pursuant to Article 81 of the EC Treaty and Article 53 of the EEA Agreement (COMP/39.125 - Carglass). Available at [http://ec.europa.eu/competition/antitrust/cases/dec\\_docs/39125/39125\\_1865\\_4.pdf](http://ec.europa.eu/competition/antitrust/cases/dec_docs/39125/39125_1865_4.pdf)

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