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**by**

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The views expressed are those of the author and do not necessarily reflect the views  
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## **Affordable Medication with a Dose of Competition**

Malaysia's contribution to the 15<sup>th</sup> Session of the Intergovernmental Group of Experts (IGE) on Competition Law and Policy Round Table on Examining the Interface between the Objectives of Competition Policy and Intellectual Property held from 19 to 21 October 2016 in Geneva, Switzerland.

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## Contents

<b>Introduction</b> .....	<b>3</b>
<b>Malaysia’s Healthcare Sector</b> .....	<b>4</b>
<b>The Malaysian Pharmaceutical Market</b> .....	<b>6</b>
<b>Medicine Prices in Malaysia</b> .....	<b>6</b>
<b>Price Control of Medicines</b> .....	<b>8</b>
<b>Generic Medicines Policy</b> .....	<b>10</b>
<b>Public Procurement of Medicines</b> .....	<b>11</b>
<b>Prescription and Dispensation of Medicines</b> .....	<b>14</b>
<b>Anti-competitive Practices</b> .....	<b>15</b>
<b>Intellectual Property and Competition Law</b> .....	<b>17</b>
<b>Off-label Use of Medication</b> .....	<b>17</b>
<b>Conclusion</b> .....	<b>19</b>
<b>Appendix</b> .....	<b>20</b>
Development of Avastin and Lucentis .....	<b>20</b>
Safety of Avastin for AMD.....	<b>21</b>
Anti-competitive Collusive Conduct.....	<b>22</b>
Off-label Use of Avastin for Wet AMD.....	<b>23</b>

## Affordable Medication with a Dose of Competition

### Introduction

The Competition Act 2010 (CA 2010) of Malaysia is the competition law applicable to the healthcare sector. It is administered by the Malaysian Competition Commission (MyCC) established under the Competition Commission Act 2010 (CCA 2010). The CA 2010, unlike the competition law of many other countries, does not regulate mergers and acquisitions. The focus of the CA 2010 is not the structure of the market but rather the conduct of market actors. The principal areas of focus of the law are horizontal and vertical anti-competitive agreements and abuse of dominant position. The MyCC is empowered to impose a penalty of up to ten percent of the worldwide turnover of an enterprise over the period during which an infringement occurred.<sup>1</sup>

The CA 2010 applies to all “commercial activity” within Malaysia, and those outside Malaysia which have an effect on competition in any market in Malaysia. For the purposes of the CA 2010, “commercial activity” does not include “any activity, directly or indirectly in the exercise of governmental authority”.<sup>2</sup>

However, the CCA 2010 mandates the MyCC to, *inter alia*, undertake the following functions and powers:

- (a) act as an advocate for competition matters;
- (b) advise the Minister or any other public or regulatory authority on all matters concerning competition;
- (c) alert the Minister to the actual or likely anti-competitive effects of current or proposed legislation and to make recommendations to the Minister, if appropriate, for the avoidance of these effects;
- (d) carry out, as it considers appropriate, general studies in relation to issues connected with competition in the Malaysian economy or particular sectors of the Malaysian economy;
- (e) Collect information for the performance of the Commission’s functions.<sup>3</sup>

Based on the powers thus conferred, the MyCC has identified the health and pharmaceutical sector as a priority area and commissioned a sector study of the pharmaceutical industry in Malaysia.

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<sup>1</sup> Competition Act 2010 [Act 712] (Malaysia), s40(4)

<sup>2</sup> Competition Act 2010 [Act 712] (Malaysia), s3(4)

<sup>3</sup> Extracted from:  
Competition Commission Act 2010 [Act 713] (Malaysia), s16.

The MyCC has also begun investigation of a number of cases of alleged anti-competitive agreements and abuse of a dominant position by enterprises in the pharmaceutical sector and has engaged with the Ministry of Health (MoH) which is the regulator of the health care system. The MoH is also the principal funder and provider of healthcare in the country.<sup>4</sup>

This report deals with the possible areas of collaboration between the MyCC and the MoH that can help make medicines in Malaysia more affordable.

## Malaysia's Healthcare Sector

The Malaysian healthcare system is highly rated. Malaysia was ranked 49<sup>th</sup> out of the 191 countries assessed in the only World Health Organization (WHO) evaluation of healthcare systems in 2000. That ranking was based on five indicators - overall level of population health, health inequalities, health system responsiveness, responsiveness to people of varying economic status, and the distribution of the health system's financial burden. It ranked 31 out of 191 for responsiveness of the health system.<sup>5</sup> Other assessments are far more generous. The Baltimore-based US publication *InternationalLiving.com's* 2014 Annual Global Retirement Index reports that Malaysia's healthcare system ranked third after France and Uruguay for the best and most affordable healthcare in the world.<sup>6</sup>

The Malaysian healthcare system was maintained principally by the public sector from independence in 1957 till the 1980s. It has since become a mixed public-private sector system. Of the RM 44,748 million (4.53% of the GDP) that the nation spent on health in 2013, only just over half (51.96%) came from the public sector.<sup>7</sup> User fees, supported by private health insurance and employer payments accounted for the rest.

The WHO Health Financing Strategy for the Asia Pacific Region (2010-2015) set a baseline framework for health systems in the region. The four target health indicators were:

- a. Total health expenditure should be at least 4 to 5 per cent of GDP.

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<sup>4</sup> The MoH maintains a total of 141 hospitals (with 39,728 beds), 1039 health clinics, 1821 community clinics, 212 mobile health clinics and 8 flying doctor services. There are 8 other government hospitals and clinics which come variously under the Ministries of Education and Defence (which together have 3,709 beds). There are 214 private hospitals but they together only have 14,033 beds.

Ministry of Health Malaysia, Planning Division, Health Informatics Centre *Health Facts 2014*, MOH/S/RAN/73.14(TR), June 2014,

<http://www.moh.gov.my/images/gallery/publications/HEALTH%20FACTS%202014.pdf>, (accessed on 3 September 2015).

<sup>5</sup> World Health Organization, *World Health Report 2000, Health Systems: Improving Performance*, 2000, p.200. [http://www.who.int/whr/2000/en/whr00\\_en.pdf](http://www.who.int/whr/2000/en/whr00_en.pdf), (accessed on 3 September 2015)

<sup>6</sup> The Index considers the cost of care and the quality. Also considered are the number of people per doctor, the number of hospital beds per 1,000 people, the percentage of the population with access to safe water, the infant mortality rate, life expectancy, and public-health expenditure as a percentage of a country's GDP.

<sup>7</sup> Ministry of Health Malaysia, Planning Division, Health Informatics Centre, *Health Facts 2015*, MOH/S/RAN/93.15(API), August 2015,

[http://vlib.moh.gov.my/cms/documentstorage/com.tms.cms.document.Document\\_2e8efe25-a0188549-d5315d00-e9ca9560/KKM\\_HEALTH\\_FACTS\\_2015.pdf](http://vlib.moh.gov.my/cms/documentstorage/com.tms.cms.document.Document_2e8efe25-a0188549-d5315d00-e9ca9560/KKM_HEALTH_FACTS_2015.pdf), (accessed on 3 September 2016).

- b. Out-of-pocket expenses should not exceed 30 to 40 per cent of total health expenditure.
- c. Over 90 per cent of the population is covered by prepayment and risk pooling schemes.
- d. Close to 100 per cent coverage of vulnerable populations with social assistance and safety-net programmes.<sup>8</sup>

A 2011 study by Chua and Cheah using 2008 data concluded that Malaysia “fared credibly for all four target indicators with total health expenditure close to 5% of its GDP (4.75%), out-of-pocket payment below 40% of total health expenditure (30.7%), comprehensive social safety nets for vulnerable populations, and a tax-based financing system that fundamentally poses as a national risk pooled scheme for the population”.<sup>9</sup>

The credit for the success of Malaysia’s healthcare system is primarily due to the efforts of the Ministry of Health (MoH).

Higher levels of expectation, a growing population of which an increasing proportion is aged and increased healthcare costs pose serious problems for the nation in continuing to provide affordable healthcare for its 30 million people. A significant contributor to this state of affairs is the high price of pharmaceutical drugs.

As noted by the Director General of the Ministry of Health Malaysia:

Pharmaceuticals are responsible for a large proportion of total healthcare expenditures... In Malaysia ... medicines expenditure [of the MoH] has been increasing from MYR 1.61 billion 2010, 1.76 billion in 2011, 1.98 billion in 2012 and 2.2 billion 2013. Medicine expenditure accounted for approximately 11.4% of the operating budget of the Ministry of Health Malaysia in 2012...

The cost of pharmaceuticals seems to be a barrier of access to affordable medicines. Medicine prices in Malaysia have been reported to escalate with significant variations between private and public sectors; prices in private sector were on average four times more than the public sector. World Health Organization/Health Action International (WHO/HAI) study in 2007 reported that medicine prices in our private sectors were among the highest in the region. The drive of free market economy and absence of

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<sup>8</sup> World Health Organization, *Health Financing Strategy for the Asia Pacific Region (2010-2015)*, 2009, p. VI, [http://www.wpro.who.int/publications/docs/Healthfinancingstrategy\\_6188.pdf?ua=1](http://www.wpro.who.int/publications/docs/Healthfinancingstrategy_6188.pdf?ua=1), (accessed on 3 September 2016)

<sup>9</sup> H.T. Chua and J.C.H. Cheah. Financing Universal Coverage in Malaysia: A Case Study, *BMC Public Health* 2012, 12(Suppl 1):S7, doi: 10.1186/1471-2458-12-S1-S7, 2012, <http://bmcpublihealth.biomedcentral.com/articles/10.1186/1471-2458-12-S1-S7>, (accessed on 16 September 2016).

pricing policy in which manufacturers, distributors, and retailers set medicine prices without government control has led to this scenario.<sup>10</sup>

## **The Malaysian Pharmaceutical Market**

Imported generic and patented drugs account for about 75% of the Malaysian pharmaceutical market. These are principally imported from India, China, US, Australia, France, Germany, and the UK. Lifestyle drugs such as cardiovascular drugs, cholesterol lowering and hypertension drugs, antibiotics, and oncology drugs are the major types of drugs imported. The locally produced pharma products can be broadly categorised as prescription or over the-counter drugs (OTC), traditional medicines, and health and food supplements.

Sale and transaction of prescription medicines are confined to doctors and pharmacists. Non-professional outlets may sell OTC, traditional medicines, and health and food supplements.

The structure of pharmaceutical supply chain consists of wholesale and retail pharmacies (2908 premises), medical clinics (7146 clinics), government healthcare facilities (3355 facilities), and private hospitals (183 hospitals).<sup>11</sup> The significance of each of these distribution channels of pharmaceuticals, presumably in terms of value, was estimated to pharmacies (30 per cent), doctors (26 per cent), government hospitals (19 per cent), private hospitals (14 per cent) and others (11 per cent).<sup>12</sup>

The MoH has identified several negative features of the Malaysian pharmaceutical market. The preamble to the Guideline to the Good Pharmaceutical Trade Practice issued on 18 February 2015 succinctly describes the anti-competitive features of the current pharmaceutical market:

[The] high price of medicines is not the only issue in the private sector. The pharmaceutical market failures mainly in the form of information imbalance and failure of competition has led to price disparities within and between distribution channels. Price cutting between giant chains and independent pharmacies, market monopoly, creation of artificial demand, unfair bonusing, discounts and rebates and bundling of unwanted medicines has created an unhealthy and dysfunctional market and business environment.<sup>13</sup>

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<sup>10</sup> Director General of Health, 'Balancing Access, Quality, Affordability & Sustainability', keynote address at the 7th Asia Pacific Future Trends Forum 2014 on 12 September 2014, Posted on 20 September 2014, <https://kpkeshatan.com/2014/09/20/medicine-expenditure-accounted-for-11-4-of-the-operating-budget-of-the-ministry-in-2012/>, (accessed on 3 September 2016).

<sup>11</sup> Ministry of Health Malaysia, Planning Division, Health Informatics Centre *Health Facts 2016*, MOH/S/RAN/17.16(AR), August 2016, <http://www.moh.gov.my/images/gallery/publications/KKM%20HEALTH%20FACTS%202016.pdf>, (accessed on 3 October 2016).

<sup>12</sup> Pharmaceutical Association of Malaysia, *Industry Overview*, 2016, (accessed 3 September 2016).

<sup>13</sup> Pharmaceutical Services Division, Ministry of Health, *Guidelines for Good Pharmaceutical Trade Practice*, February 2015, p. 1, [http://www.pharmacy.gov.my/v2/sites/default/files/document-upload/good-pharmaceutical-trade-practice\\_0.pdf](http://www.pharmacy.gov.my/v2/sites/default/files/document-upload/good-pharmaceutical-trade-practice_0.pdf), (accessed on 3 September 2016).

## Medicine Prices in Malaysia

Medicines in the public sector are given to Malaysian citizens at a nominal charge. At the MoH facilities, Malaysians pay only RM1 for both outpatient consultation and medication per visit. However, not all required medicines are available at the MoH facilities and patients are required to obtain these from the private pharmacies and pay for these themselves except where they may make a claim for these from the government. Government servants and their dependents are entitled to reimbursements. No special arrangement exists with the manufacturers or the pharmacies for lower prices for the medications for which reimbursements are made and thereby reduce the consequential tax payer burden.

Prices in the private sector are not regulated and are wholly dependent on prevailing market forces. In the absence of government control, manufacturers, distributors and retailers set medicine prices. Numerous studies have over the years established that Malaysians pay very high prices for pharmaceutical drugs in the private sector and Malaysia has become a “high price island” for pharmaceutical prices. Babar et al. surveyed twenty public hospitals, thirty-two private sector pharmacies, and twenty dispensing doctors’ clinics from four geographical regions between 2004 and 2005 and reported that in private pharmacies, innovator (branded) drugs were on average priced 16 times higher than the international reference price (IRP), while generics were priced 6.6 times higher. Prices at the clinics of dispensing doctors were 15 times higher for innovator brands and 7.5 times higher for generics. The markup was 25 to 38 percent for innovator brands and 100 to 140 percent for generics.<sup>14 15</sup> A study published in 2012 found that retail drug prices in private pharmacies were 30 – 148% higher than those in Australia.<sup>16</sup>

The MoH Medicine Price Monitoring Survey of 2008 for 100 types of medicines consisting of 711 brands at 93 premises (45 MoH, 40 private retail pharmacies, 5 private hospitals and 3 university hospitals) in both Peninsula and East Malaysia found the median price ratio for the public sector to be 1.3 times higher than the IRP and that in the private sector to be 2.9 times the IRP.<sup>17</sup>

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<sup>14</sup> Z.U.D. Babar et al., ‘Evaluating Drug Prices, Availability, Affordability, and Price Components: Implications for Access to Drugs in Malaysia’, PLoS Med 4(3):e82, doi: 10.1371/journal.pmed.0040082, (accessed on 3 September 2016).

<sup>15</sup> This was also discussed in: P.O. Lee, ‘What Lies Ahead for Malaysian Healthcare’, Economics Working Paper No. 2015-4, ISEAS-Yusof Ishak Institute, December 2015, [https://www.iseas.edu.sg/images/pdf/ISEAS\\_Economics\\_Working\\_Paper\\_2015-04-01.pdf](https://www.iseas.edu.sg/images/pdf/ISEAS_Economics_Working_Paper_2015-04-01.pdf), (accessed on 4 September 2016).

<sup>16</sup> MA Hassali et al., ‘A Study Comparing the Retail Drug Prices between Northern Malaysia And Australia’, Journal of Pharmaceutical Health Services Research, 3: 103 – 107, doi: 10.1111/j.1759-8893.2011.00080.x, June 2012, pp. 103-107, [https://www.researchgate.net/profile/Tahir\\_Khan2/publication/236154980\\_A\\_study\\_comparing\\_the\\_retail\\_drug\\_prices\\_between\\_Northern\\_Malaysia\\_and\\_Australia/links/5685efcf08ae19758395297c.pdf?origin=publication\\_detail](https://www.researchgate.net/profile/Tahir_Khan2/publication/236154980_A_study_comparing_the_retail_drug_prices_between_Northern_Malaysia_and_Australia/links/5685efcf08ae19758395297c.pdf?origin=publication_detail), (accessed on 3 September 2016).

<sup>17</sup> Ministry of Health Malaysia. *Malaysia’s Health 2008*, 2008. pp.163–164, <http://www.moh.gov.my/images/gallery/publications/mh/Malaysia%20Health%202008-2.pdf>, (accessed on 15 September 2016).



Henry and Searles<sup>18</sup> provide a succinct country study statement of the supply chain markups in Malaysia based on data from two earlier studies: a price survey which compared median price ratios of medicines distributed in the private and public sectors with international prices by Baber et al.<sup>19</sup> and an international comparison of prices by Gelders et al.<sup>20</sup>

The country study states:

Despite the expectation that the prices of medicines in the public sector would be relatively low, in some cases, public-sector prices were higher than the international reference price. The study also found that the postmanufacture margins charged in the supply chain were significantly driving prices upward in both the public and private sectors. The authors concluded that the lack of a coherent government policy to regulate medicine prices allowed excessive profits and reduced medicine affordability.

The survey also found substantial price differences within the private sector between dispensing doctors and pharmacies. Compared with pharmacies, brand-name medicines tended to be cheaper when purchase from a dispensing doctor, but generic medicines were more expensive. Overall, the study found the dispensing doctors had excessive profit margins, particularly on some lower-priced generic medicines.<sup>21</sup>

### **Price Control of Medicines**

In principle, competition agencies are against the regulatory control of prices, preferring that prices be determined by market forces. However, as noted by the renowned economist and Nobel Laureate Kenneth Arrow in his celebrated work entitled *Uncertainty and the Welfare Economics of Medical Care*:

[T]he failure of the market to insure against uncertainties has created many social institutions in which the usual assumptions of the market are to some extent contradicted. The medical profession is only one example, though in many respects an extreme one... The logic and limitations of ideal competitive behaviour under

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<sup>18</sup> D. Henry and A. Searles, *MDS-3 Managing Access to Medicines and Health Technologies*, p. 9.13 <http://apps.who.int/medicinedocs/documents/s19585en/s19585en.pdf> (accessed on 15 September 2016).

<sup>19</sup> Z.U.D. Babar et al., 'A Survey of Malaysian Prices Availability, Affordability and Price Components in Malaysia Using the HAI/WHO Methodology', Research Report, University College Sedaya International and Universiti Sains Malaysia in collaboration with the World Health Organization and Health Action International, October 2005, [http://www.haiweb.org/medicineprices/surveys/200410MY/survey\\_report.pdf](http://www.haiweb.org/medicineprices/surveys/200410MY/survey_report.pdf), (accessed on 15 September 2016).

<sup>20</sup> S. Gelders et al., 'Price Availability and Affordability: An International Comparison of Chronic Disease Medicines, Background Report Prepared for the WHO Planning Meeting on the Global Initiative for Treatment of Chronic Diseases held in Cairo in December 2005, WHO-EM/EDB/068/E, Cairo: World Health Organization Regional Office for the Eastern Mediterranean and Health Action International, 2006, <http://www.haiweb.org/medicineprices/08092008/EDB068final.pdf>, (accessed on 15 September 2016).

<sup>21</sup> D. Henry and A. Searles, 'Chapter 9 Pharmaceutical Pricing Policy' in *Management Sciences for Health 2012, MDS-3 Managing Access to Medicines and Health Technologies*, p. 9.13

uncertainty force us to recognize the incomplete description of reality supplied by the impersonal price system.<sup>22</sup>

Section 106 of the Private Healthcare Facilities and Services Act 1998 [Act 586] empowers the Minister of Health to make regulations prescribing a fee schedule for any or all private healthcare facilities or services or healthcare related facilities or services. However, the Minister has not used this power to control the price of medicines supplied, though a schedule of fees has been prescribed for the other services provided by doctors (but not of the private hospitals).<sup>23</sup> <sup>24</sup> There is also no requirement for private healthcare facilities to even display the price of the medications they supply.

The Pharmaceutical Services Division of the MoH has, with the support of the MyCC, issued a Guideline for Good Pharmaceutical Trade Practice on 18 February 2015<sup>25</sup> specifying that:

- A standard price and bonus scheme apply to all channels and healthcare providers;
- An official wholesale list and formal announcement on price revision or any change of trading terms be provided by suppliers to consumers;
- There be no market exclusivity for a product to any channel unless administratively advised or directed by the MoH;
- Promotion of products and services be done responsibly and within existing codes of conduct/practice; and
- Requiring the establishment of an appropriate system of control and accountability of samples provided to healthcare professionals.

What was issued is only a guideline; it has no mandatory effect. The complaints received by the MyCC suggest that the Guideline has not had the intended effect. The MoH has sought the power to regulate the price of medicines and the power to do so, it has been reported, is being provided for in the Pharmacy Bill which is in the final stages of drafting.<sup>26</sup>

Price regulation is a complex task and the manner in which it is introduced needs to be carefully considered with appropriate regulatory impact assessments so as to ensure that the desired outcomes are achieved. The WHO has issued in 2015 a useful report entitled *WHO Guideline on Country Pharmaceutical Pricing Policies*<sup>27</sup> and recommends a number of

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<sup>22</sup> K.J. Arrow, 'Uncertainty and the Welfare Economics of Medical Care', *The American Economic Review*, Vol LIII, No 5, December 1963, pp. 941 – 973 at p. 967

<https://assets.aeaweb.org/assets/production/journals/aer/top20/53.5.941-973.pdf>, (accessed on 3 October 2016).

<sup>23</sup> Private Healthcare Facilities and Services Act 1998 [Act 586] (Malaysia).

<sup>24</sup> Private Healthcare Facilities and Services (Private Hospitals and Other Private Healthcare Facilities) (Amendment) Order 2013 (Malaysia).

<sup>25</sup> Pharmaceutical Services Division, Ministry of Health, *Guidelines for Good Pharmaceutical Trade Practice*, February 2015, p. 1.

<sup>26</sup> 'Pharmacy Bill Being Redrafted', *The New Sunday Times*, 18 September 2016, p. 4.

<sup>27</sup> World Health Organization, *WHO Guideline on Country Pharmaceutical Pricing Policies*, 2015, [http://apps.who.int/iris/bitstream/10665/153920/1/9789241549035\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/153920/1/9789241549035_eng.pdf), (accessed on 3 September 2016.)

policy initiatives for price regulation. The MoH will no doubt take cognizance of the recommendations in the report.

The report recommends the regulation of markups in the pharmaceutical supply and distribution chain as part of an overall pharmaceutical pricing strategy:

[C]ountries should consider regulating distribution chain mark-ups (distributors/wholesalers)... [and] retail chain mark-ups and fees (pharmacies, dispensing doctors, dispensaries). And, if mark-ups are regulated, countries should consider using regressive mark-ups (lower mark-up for higher-priced products) rather than fixed percentage markups, given the incentive that the latter provides for higher-priced products to receive a higher net margin.<sup>28</sup>

### **Generic Medicines Policy**

The world over, healthcare systems have relied on generics as a significant means of reducing the costs of medicines. Even in the US, the home of many of the world's largest pharma companies, and where total spending on medication was US\$ 325.8 billion in 2012, 84% of prescriptions dispensed were for generic drugs.<sup>29</sup>

The MoH has a Generic Medicines Policy to foster healthy competition in medicines pricing that applies to all public sector facilities. It is meant to guide the use and procurement of medicines as follows:

- Prescribing in generic International Non-proprietary Name (INN) shall be practised at all channels
- Procurement of all medicines by generic INN shall be promoted
- In selection for procurement, priority shall be given to domestically manufactured medicines
- All dispensed medicines shall be labelled prominently with the generic INN of the medicine with or without the brand name
- A list of interchangeable and non-interchangeable medicines shall be made available
- Generic substitution shall be permitted and legislated for all interchangeable medicines

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<sup>28</sup> World Health Organization, *WHO Guideline on Country Pharmaceutical Pricing Policies*, 2015, p. vii.

<sup>29</sup> IMS Institute for Healthcare Informatics, 'Declining medicine use and costs: for better or worse? A review of the use of medicines in the US in 2012' Report by the IMS Institute of Healthcare Informatics, 2013, p. 8 <http://static.correofarmaceutico.com/docs/2013/05/20/usareport.pdf>, (accessed on 11 September 2016).

- Appropriate incentives to promote the use of generic medicines and their production in the country shall be introduced.<sup>30</sup>

The Generic Medicine Policy is a general guideline for the Malaysian healthcare industry but currently is being given effect only at MoH facilities. The labeling of all dispensed medicines in the MoH healthcare facilities is now with the INN but in the private sector, this is not yet required or practiced except for scheduled poisons as mandated by the Poisons Act 1952 (Revised 1989) (Act 366). The policy specification that generic substitution shall be permitted and legislated for all interchangeable medicines, has not yet been achieved.

Malaysia has regulations to ensure that generic drugs have to be identical to the branded drug in terms of efficacy, safety, usage, route of drug administration, pharmacokinetics and pharmacodynamics.<sup>31</sup> Also, the generic name is what doctors are trained to use. Nevertheless, as in many countries<sup>32</sup>, many doctors regard innovator drugs as the ‘gold standard’ and are resistant to the use of generic drugs.

Policy coherence, a clear statement of objectives and concerted effort will be necessary to get all doctors to increase the prescription of generics.<sup>33</sup>

### **Public Procurement of Medicines**

The objective of procurement is principally economic; it is to ensure value for money and avoid abuse of the procurement process. However, public procurement can and often does have a number of collateral social and industrial objectives. Malaysia places importance on local produce and *bumiputra* (indigenous community) participation.

The procurement of pharmaceutical supplies by all public sector institutions is governed by rules specified by the Ministry of Finance. These relate to the level at which the procurement may be made (MoH, state department of health, district department of health or hospital), how the medicines may be procured (from the Concession Company, by tender, quotation or direct purchase), by whom the procurement may be approved (a committee chaired by the Secretary General of the MoH, the Deputy Secretary General of the MoH, or the relevant head of department) and who may supply the medicines (concession company for products in

<sup>30</sup> Ministry of Health Malaysia, *Malaysian National Medicines Policy*, 2<sup>nd</sup> edn. 2013, p. 15, <http://www.pharmacy.gov.my/v2/sites/default/files/document-upload/buku-dunas.pdf> (accessed on 11 September 2016).

<sup>31</sup> National Pharmaceutical Control Bureau, Ministry of Health Malaysia, *Drug Registration Guidance Document*, G/TBT/N/MYS/5, 2004, <http://www.sirim.my/srmc/files/WTO-TBT-Enquiry/mys-notifications/mys5-text.pdf> (accessed on 11 September 2016).

<sup>32</sup> For a sample of the views of American Ophthalmologists see V. Pickles, *Branded vs. Generic Ophthalmic Drugs: Balancing Cost and Care*, [website], 2013. <http://www.ophtalmologymanagement.com/articleviewer.aspx?articleID=108616> (accessed 3 September 2016).

<sup>33</sup> Organisation for Economic Co-operation and Development, Directorate for Financial and Enterprise Affairs Competition Committee, *Annex to the Summary record of the 121st Meeting of the Competition Committee held on 18-19 June 2014 -- Summary Record of the Discussion on Competition and Generic Pharmaceuticals--*, DAF/COMP/M(2014)2/ANN6/FINAL, 2014, [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DAF/COMP/M\(2014\)2/ANN6/FINAL&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DAF/COMP/M(2014)2/ANN6/FINAL&doclanguage=en), (accessed on 3 October 2016).

an Approved Pharmaceutical Product List, local contractors only with a margin of preference for *bumiputra* contractors, or where none exists, other local contractors).

Pharmaniaga, the Concession Company, took over the government's medical stores and laboratory in 1994, initially for a fifteen-year concession and then renewable for periods of ten years. It supplies multisource products, the price of which are referenced to the International Reference Price (IRP) and fixed for a period of three years. In 2015, Pharmaniaga supplied 38.5% by value of the medicines procured by the MoH. National tenders are conducted by the MoH with preference for local produce. The price of single source products is negotiated. Purchase at the institutional level is by way of Direct Purchase for procurement below RM 20,000 and by Quotation for between RM 20,000 and RM 500,000.<sup>34</sup>

Procurement itself has to be preceded by registration of the drug by the National Pharmaceutical Regulatory Agency (NPRA), its inclusion in the MoH or relevant hospital formulary and selection from these of the medicine and quantity to be purchased. The drugs listed in the MoH Drug Formulary have to be approved by the MoH Drug List Review Panel. It serves as the guide for MoH hospitals to select medicines for their own local formulary.

Procurement by the non-MoH public sector facilities are also governed by the guidelines issued by the Ministry of Finance, but their procurement comes under the purview of their respective Ministries or statutory bodies.

Malaysia was one of the first four countries that participated in the WHO organised project on good governance for medicine. The first phase of the project which was carried out in December 2004 was an assessment of the level of transparency and potential vulnerability to corruption of three pharmaceutical sector functions: registration of medicines, selection of essential medicines, and procurement of medicines.

The project employed a quantification method with the results converted to a zero to ten (0.0 to 10.0) scale. It gave Malaysia an average score of 6.5 - more favourable than Laos (6.2) but less favourable than the Philippines (7.1) and Thailand (7.3). Malaysia scored relatively high for registration (6.8) and procurement (7.1). The overall score was affected by the low score in the selection of drugs for which it obtained a 5.7.

As stated in the report:

It is important to note that this scoring indicates vulnerability to corruption, given the policy/regulatory and administrative procedures in place at the time of the survey. It does not imply in any way that one country's system is more corrupt than another. At the time of writing, many countries have already taken steps to develop national ethical frameworks and to revise some administrative procedures, so that a new assessment would result in higher scores. The scoring system is meant to help

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<sup>34</sup> Communication from the Pharmaceutical Services Division, Ministry of Health Malaysia to the principal author, [e-mail], 10 October 2016.

countries monitor progress in their efforts to improve transparency and good governance practices in the public pharmaceutical sector over time.<sup>35</sup>

Based on the findings of the project, the Pharmaceutical Services Division (PSD) of the MoH reviewed all major work processes within the PSD including in its regulatory, enforcement and the pharmaceutical practice divisions to identify the weaknesses and areas of vulnerability. It then put in place the following remedial measures:

- The applicable Standard Operating Procedures were amended and appropriate counter-measures developed.
- A conflict of interest form was designed and put into effect for all committees making decisions;
- The terms of reference and the membership of the committee that determines the selection of drugs for the MoH formulary were included in the PSD's official portal; and
- A Framework for Good Governance in Medicine (GGM) in the Public Pharmaceutical Sector was developed.

Malaysia was the first country to develop such a framework and the framework has become a guide for other countries. The PSD has on several occasions been called upon by the WHO to share its experience in developing the framework with other countries.

In 2012, two other guidelines were published: the Guidelines for Pharmacy Members in Dealing with Pharmaceutical Company Representatives and Suppliers and the Guidelines on Giving and Receiving Gifts for Civil Servants.

Malaysia is currently in Phase III - Implementation of the National GGM Programme. Beginning in 2013, the MoH has conducted GGM Training of Trainers Workshops for pharmacy staff in the public sector and more recently extended the training to the private pharmaceutical sector.<sup>36</sup>

Any system needs to be continually improved and that is true of the Malaysian healthcare system as well. An aspect that was criticized in a WHO-HAI publication, also of 2006, on the selection and procurement relates to the preference for originator drugs as compared to generic drugs:

It might be expected that, for off-patent medicines, only generic versions would be available in the public sector, as they are known to be cheaper, but this is not always the case. In Malaysia, many medicines on the National Essential Drugs List that were

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<sup>35</sup> World Health Organization, *Measuring Transparency in Medicines Registration, Selection and Procurement Four Country Assessment Studies*, WHO/PSM/PAR/2006.7, 2006, pp.6 -7, <http://www.who.int/medicines/areas/policy/goodgovernance/Transparency4CountryStudy.pdf>, (access on 11 September 2016).

<sup>36</sup> Communication from the Pharmaceutical Services Division, Ministry of Health Malaysia to the principal author, [e-mail], 10 October 2016.

off-patent long ago, were available only as originator brands, for instance beclometasone inhaler, phenytoin and prazosin.<sup>37</sup>

The current published National Essential Medicine List (NEML) does not mention brand names.<sup>38</sup> It merely includes the medicines' chemical entity (generic names). However, the practice of procuring branded drugs appears to have continued. In 2015, medicine use at the MoH facilities comprised only "almost half generic medicine". The Deputy Minister of Health has committed to remedy this with a greater use of generics with effect from 2017.<sup>39</sup>

Selection and procurement should only be confined to generics whenever possible; exception being made only on the grounds of safety, efficacy and economy.

### **Prescription and Dispensation of Medicines**

In Malaysia, doctors are permitted to both prescribe and supply medicines. The concern is that prescriptions would be on the basis of the profits to be made from the drug prescribed rather than the interest of the patient concerned. As stated in a UNCTAD note, the practices of bribe and rebate – not price and quality – may determine which drugs are chosen.<sup>40</sup>

Doctors in private practice do not issue a prescription to patients and refuse to give itemised bills after consultation and dispensation of the drugs. Such practice removes price competition in the pharmaceutical retail sector as the patient has no basis to compare the price paid with the price of the same medicine at any other source.

Many countries the world over have moved towards separation of the functions of prescription and dispensation of medicines, a move consistently sought by pharmacists. However, this is not a universal practice and from a competition point of view will not, by in itself, address the concern that the choice of drug to be dispensed would be that which is more profitable for the dispenser, be it the doctor or the pharmacist.

The South Korean experience is instructive. In South Korea, the practice was for doctors to both prescribe and dispense. The separation of functions was effected through the Korean Health Care System Reform Act of 2000. As reported by Kim and Ruger:

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<sup>37</sup> S. Gelders et al., Price, availability and affordability An international comparison of chronic disease medicines, p. 53.

<sup>38</sup> The latest list contains 321 chemical entities within 30 therapeutic groups. The therapeutic groups are further divided into sub-therapeutic groups followed by the medicines' chemical entities (generic names). For each chemical entity, the corresponding dosage form and the level of care are stated on the same row. Pharmaceutical Services Divisions, Ministry of Health, *National Essential Medicine List Fourth Edition*. 2016. <http://www.pharmacy.gov.my/v2/sites/default/files/document-upload/national-essential-medicines-list-fourth-edition-upload-update-preparations-321-2.pdf> (accessed on 3 October 2016).

<sup>39</sup> Quantity is presumably by value. Statement of the Deputy Minister of Health Datuk Dr Hilmi Yahaya, as reported by:

N. Cheng, 'Health Ministry hopes for 'caring' Budget 2017', *The Star*, 11 October 2016, p. 4.

<sup>40</sup> United Nations Conference on Trade and Development, *The Role of Competition in the Pharmaceutical Sector and Its Benefits for Consumers*, Note By UNCTAD Secretariat, TD/RBP/CONF.8.3., 27 April 2015, p. 5. [http://unctad.org/meetings/en/SessionalDocuments/tdrbpconf8d3\\_en.pdf](http://unctad.org/meetings/en/SessionalDocuments/tdrbpconf8d3_en.pdf), (accessed on 11 September 2016).

But doctors and hospitals intensified their opposition to the new system, fearing that it would severely cut their earnings because their businesses had become heavily dependent on drug sales. Members of the KMA (Korea Medical Association) threatened collectively to close their clinics unless the government abandoned the plan or increased consultation fees to offset lost income. Responding to doctors' demands for concessions in exchange for reform, and to avert the threat of hospital and clinic closures, the MOHW [Ministry of Health and Welfare] authorized a 72 percent increase in consultation fees for seeing outpatients and a fivefold increase in prescribing fees for the year 2000. The legislation's final form incorporated these concessions.<sup>41</sup>

The MOHW itself concluded that the "reform might have been more successful if the government had provided economic incentives to doctors to select medical products appropriately and cost-effectively".<sup>42</sup>

As in Malaysia, Singapore also permits doctors to prescribe and dispense medication. In Singapore, private hospitals and clinics are required by law to provide information to the patient before<sup>43</sup> and after treatment<sup>45</sup> and this includes an itemised bill stating the drug supplied and the price of each.

It is likely that the MoH will make such a measure also mandatory in Malaysia especially since such a move has been endorsed by the Federation of Malaysian Consumers Association (FOMCA), the Malaysian Medical Association (MMA), the Malaysian Dental Association (MDA) and the Malaysian Pharmaceutical Society (MPS) in the Malaysian Patients Charter

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<sup>41</sup> H.J. Kim and J.P. Ruger, Pharmaceutical Reform in South Korea and the Lessons It Provides, *Health Affairs* 27, no.4 (2008): w260-w269 at w262, <http://content.healthaffairs.org/content/27/4/w260.long>, (accessed on 3 October 2016).

<sup>42</sup> H.J. Kim and J.P. Ruger, w.267

<sup>43</sup> "Every manager of a private hospital shall ensure that every *patient be informed, on or before his admission to the private hospital, of the estimated total charges which are likely to be incurred in respect of his hospitalisation and treatment.*" Extracted from:

Private Hospitals and Medical Clinics Regulations (Singapore), Regulation 11, 2002.

<sup>44</sup> "All patients shall receive an itemised bill for every item charged for the treatment and/or hospitalisation e.g. consultation, procedures ward charges, operating theatre fees, investigations, medications, and other services or items." from:

Ministry of Health Singapore, *Licensing Terms and Conditions on Provision of Information on Charges and Financial Counselling Imposed under Section 6(2)(a) and (6)(5) of the Private Hospitals and Medical Clinics Act (Cap 248)*, 2011, Para 16, <https://elis.moh.gov.sg/elis/publishInfo.do?task=download&pkId=108>, (accessed on 13 September 2016).

<sup>45</sup> The Singapore Ministry of Health separately issued the requirement via a circular to medical and dental clinics licensees on 1 October 2007 (TC 2007 Provision of Information on Charges 1-10-2007) which *inter alia* provides "Patients should be informed of every item charged for the clinic visit, e.g. consultation fee, medication (itemized) charges, investigation charge, etc. through itemized billing." from: Ministry of Health Singapore, *Guidelines under the Private Hospitals and Medical Clinics Act (1980) and Regulations (1981)*, p. 53, <https://elis.moh.gov.sg/elis/publishInfo.do?task=download&pkId=129>, (accessed on 13 September 2016).

<sup>46</sup> This is further explained via a set of Frequently Asked Questions for doctors/dentists on how the itemized billing requirement should be operationalised (TC 2007 FAQs 3 Apr 2008, questions 8 to 11) Ministry of Health Singapore, *Frequently Asked Questions*, 2008, Questions 8 to 11 <https://elis.moh.gov.sg/elis/publishInfo.do?task=download&pkId=128>, (accessed on 13 September 2016).



agreed to by the parties on 21 August 1995.<sup>47</sup> Also, an advisory has already been issued by the Director General of Health Malaysia to all medical practitioners in November 2015, specifying that a prescription stating the generic name (INN) of the drug and the indication for its use should be given to all patients so as to permit them the choice to purchase the drug from the medical practitioner or from a retail pharmacy.<sup>48</sup>

The advisory has no legal effect and is not generally followed by private medical practitioners. The MoH needs to adopt regulations to make it mandatory for all prescribers to issue a prescription as described in the advisory.

### **Anti-competitive Practices**

As noted in the introduction, Malaysian competition law does not regulate mergers and acquisitions. The focus of the CA 2010 is anti-competitive practices on the part of enterprises – horizontal and vertical anti-competitive agreements, and abuse of a dominant position.

#### ***Anti-competitive Agreements***<sup>49</sup>

A horizontal or vertical agreement between enterprises is prohibited insofar as the agreement has the object or effect of significantly preventing, restricting or distorting competition in any market for goods or services. The Commission need not establish any effect for the following forms of horizontal agreements:

- (a) Fix, directly or indirectly, a purchase or selling price or any other trading conditions;
- (b) Share market or sources of supply;
- (c) Limit or control— (i) production; (ii) market outlets or market access; (iii) technical or technological development; or (iv) investment; or
- (d) Perform an act of bid rigging.

Such agreements, popularly referred to as cartels, boycotts and bid-rigging are a major concern of competition authorities the world over. They are the conventional tools that are used to fix prices and earn monopoly profits.<sup>50</sup>

#### ***Abuse of Dominant Position***<sup>51</sup>

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<sup>47</sup> “A Patient shall have the right to an itemized account after any treatment or consultation and to have this explained.” from

Patient’s Charter (Malaysia), 1995, Item IV. Right to Adequate Information and Consent, Para 4.

<sup>48</sup> Director General of Health Malaysia, Ministry of Health Malaysia, Keperluan Untuk Mengeluarkan Preskripsi Bagi Pembekalan Ubat-Ubatun Untuk Tujuan Rawatan’, Ref: KKM-55-BPF/213/002/03(25)JLD4, [Circular], 18 November 2015.

<sup>49</sup> Competition Act 2010 [Act 712] (Malaysia), s4

<sup>50</sup> United Nations Conference on Trade and Development, *The Role of Competition in the Pharmaceutical Sector and Its Benefits for Consumers*, Note By UNCTAD Secretariat, TD/RBP/CONF.8.3. 2015

<sup>51</sup> Competition Act 2010 [Act 712] (Malaysia), s10

The CA 2010 imposes special duties on dominant firms. It prohibits dominant enterprises from engaging, whether independently or collectively, in conduct which amounts to an abuse of its dominant position. Such abuse may include—

- (a) Directly or indirectly imposing unfair purchase or selling price or other unfair trading condition on any supplier or customer;
- (b) Limiting or controlling production, market outlets or market access, technical or technological development, or investment, to the prejudice of consumers;
- (c) Refusing to supply to a particular enterprise or group or category of enterprises;
- (d) applying different conditions to equivalent transactions with other trading parties to an extent that may discourage new market entry or expansion or investment by an existing competitor, force from the market or otherwise seriously damage an existing competitor which is no less efficient than the enterprise in a dominant position, or harm competition in any market in which the dominant enterprise is participating or in any upstream or downstream market;
- (e) Making the conclusion of contract subject to acceptance by other parties of supplementary conditions which by their nature or according to commercial usage have no connection with the subject matter of the contract;
- (f) Any predatory behaviour towards competitors; or
- (g) Buying up a scarce supply of intermediate goods or resources required by a competitor, in circumstances where the enterprise in a dominant position does not have a reasonable commercial justification for buying up the intermediate goods or resources to meet its own needs.

The above mentioned duties do not however prohibit an enterprise in a dominant position from taking any step which has reasonable commercial justification, or is a reasonable commercial response, to the market entry or market conduct of a competitor.

### **Intellectual Property Law and Competition Law**

Malaysian patent law, in compliance with the Trade Related Intellectual Property Agreement of the World Trade Organization, grants a twenty year monopoly right to originator drug producers, after which generic drug producers may access the market.

Originator drug producers seek to extend their monopoly period by a number of ways<sup>52</sup>, some of which have been regarded by competition authorities as anticompetitive or an abuse of

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<sup>52</sup> See for instance

H. Gupta et al., 'Patent Protection Strategies', *Journal of Pharmacy and Bioallied Sciences*, Jan-Mar 2010, 2(1): 2–7. doi: 10.4103/0975-7406.62694, 2010, pp. 2-7, [https://www.researchgate.net/publication/51545251\\_Patent\\_protection\\_strategies](https://www.researchgate.net/publication/51545251_Patent_protection_strategies), (accessed on 13 September 2016).

dominance. These include refusal by a patent holder of a license to produce locally or to charge unreasonably high royalties (considered as an implicit refusal to license).

Similarly, use of patent protection laws to block or delay development or market access of generic products through evergreening (use of patent clusters and divisional patent), product hopping/switching (by the introduction of new formulations of patented drugs shortly before the expiry of patent protection on the older version) and sham litigation against generic producers.

Of particular concern in recent years to both the US and EU authorities has been what is termed as ‘pay-for-delay’ agreements. This is where a patent holder pays a competitor to delay the introduction of a competing drug, usually a generic. In 2010, the US Federal Trade Commission estimated that pay-for-delay settlements cost US consumers US\$3.5 billion annually.<sup>53</sup>

### **Off-label Use of Medication**

Off-label use means the medication is being prescribed for an indication for which it has not been approved by the country’s drug approval authority, which in the Malaysian context is the Malaysia Drug Regulation Authority. Approval for use of a medication is based on the results of clinical studies that the drug maker has submitted to the approving authority.

Drug regulation authorities approve medication; they do not regulate prescription. The use of off-label medication in most countries is at the discretion of the doctor guided by the Guidelines of the profession and the law of liability. Off-label use is common and even considered necessary in some fields of medicine, notably paediatrics and oncology. It is also a practice that has been much abused. Cavalier physicians who consider such practice as “cutting edge” medicine and those who do so for rewards from manufacturers have to be restrained. Unethical and even illegal promotion of off-label medication has been censured and is the subject of much litigation by the US Federal Drug Administration.<sup>54</sup>

Strange as it may seem, what has also been of concern to competition authorities is the unwillingness of manufacturers to sanction or at least cooperate in the off-label use of medication. The Appendix to this paper details the off-label use of Avastin for Age-related

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<sup>53</sup> Organisation for Economic Co-operation and Development, Directorate for Financial and Enterprise Affairs Competition Committee, *Annex to the Summary record of the 121st Meeting of the Competition Committee held on 18-19 June 2014 -- Summary Record of the Discussion on Competition and Generic Pharmaceuticals—*, 2014.

<sup>54</sup> In 2012, GlaxoSmithKline paid a record \$3 billion to settle a dispute, including alleged illegal off-label marketing involving paroxetine in children (approved only for use in adults), the antidepressant bupropion as a weight loss aid, and failure to report safety information about the antidiabetes medication rosiglitazone. In 2012, Abbott paid \$1.6 billion in penalties for alleged off-label marketing of valproic acid. In 2009, Eli Lilly paid \$1.4 billion in a settlement for alleged off-label marketing of olanzapine for dementia. That same year, Pfizer paid \$2.3 billion for alleged off-label marketing of 4 of its medications. C.M. Wittich, C.M. Burkle and W.L. Lanier, ‘Ten Common Questions (and Their Answers) About Off-label Drug Use’, *Mayo Clin Proceedings*. Oct 2012; 87(10):982-990, doi:10.1016/j.mayocp.2012.04.017, 2012, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/>, (accessed on 1 October 2016).

Macular Degeneration (wet AMD). The patent for Avastin and Lucentis are both held by Genentech in the US; but in the rest of the world they are held by Roche for Avastin and by Novartis for Lucentis. In 2014, the Italian Competition Authority fined Roche Euro 90,593,369 and Novartis Euro 92,028,750 because they colluded “by raising and spreading concerns related to the safety of ophthalmic uses of Avastin in order to boost the sale of Lucentis, from which both groups were expecting their own returns...”.<sup>55</sup>

In Italy and France, the healthcare authorities have specifically approved the off-label use of Avastin in the public sector for the treatment of wet AMD, and done so despite Roche not applying for registration of Avastin for that indication. (The Appendix to this paper deals with the response of regulatory and competition to the unwillingness of Roche to seek registration.)

In Malaysia, the use of off-label medication is permitted subject to procedural guidelines. At the MoH facilities, off-label use has to be with the informed consent of the patient, approved in each instance by the Director General of Health and reported via a standardized form.<sup>56</sup> However, Avastin is not included in the MoH formulary and consequently not prescribed; the higher cost alternatives, Lucentis and Eylea, are included in the formulary and are consequently routinely prescribed. The University of Malaya Medical Centre, also a public sector facility, includes Avastin in its formulary. It would be appropriate for the MoH to also review its procedure for use of Avastin in the MoH facilities as this would result in a significant cost saving for the government; it will also help reduce the price paid by consumers for such treatment in the private sector.

The manner in which competition and regulatory authorities respond to the challenges that the conduct of patent holders pose, impacts on the availability of affordable medication. This is a challenge that the MyCC and the MoH need to jointly address.

## **Conclusion**

The right to health is predicated on the availability of safe, efficacious and affordable medication. Ensuring this is a task that has hitherto been the sole responsibility of the Ministry of Health which is the regulator of the national healthcare system and the repository of expertise on the management of the healthcare system.

The rising cost of medication both for the highly subsidized public sector, and in the private sector, threatens the viability of the highly rated Malaysian healthcare system. This paper has identified some areas in which reform may be appropriate to help make medicines affordable for all Malaysians.

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<sup>55</sup> L. Arnaudo, ‘The Avastin-Lucentis Case: An Illicit Agreement Between Roche and Novartis Condemned by the Italian Competition Authority’, *Italian Antitrust Review*, Vol 1, No 2, 2014, p. 128, <http://iar.agcm.it/article/view/10200/9491>, (accessed on 10 September 2016).

<sup>56</sup> Pharmaceutical Services Divisions, Ministry of Health Malaysia, *Consent Form for Treatment Using Medicine with Unregistered Medicine/Indication (Off Label)*, [website], 2016 <http://www.pharmacy.gov.my/v2/en/documents/consent-form-treatment-using-medicine-unregistered-medicine-indication-label.html>, (accessed on 3 October 2016).

Since the adoption of the CA 2010, the MyCC has been mandated to play a supportive role to achieve the objective of affordable medication. This it does by being an advocate for competition and focusing on the eradication of anti-competitive practices.

The MyCC is constrained by the powers conferred by the CA 2010; it only can deal with instances of anti-competitive agreements and abuse of dominance cases. It applies an ex-post harm based approach relying principally on complaints and historical evidence. It works on the basis of a narrow product and geographic market definition determined in each instance by the particular specific case it is handling. The MoH, as the regulator of the nation's healthcare sector, is able to monitor detailed conduct in all of the healthcare market and impose ex ante behavioral remedies.

The close collaboration that has been established between the MoH and the MyCC will facilitate coherence between the regulatory policies of the MoH and the competition policies of the MyCC.

## APPENDIX

### Use of Avastin for Wet Age-related Macular Degeneration – Competition and Regulatory Authority Response

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*This Appendix deals with the off-label use of the drug Avastin for the treatment of wet Age-related Macular Degeneration in the face of the resistance of the patent holders to facilitate its use.*

#### Development of Avastin and Lucentis

The central portion of the inside back layer of the eye is known as the retina. It is the part of the eye that records the images we see and sends them via the optic nerve from the eye to the brain. The central portion of the retina, known as the macula is what focuses central vision which is essential to see objects in fine detail and hence essential for tasks such as reading, recognizing colours and faces, and driving.

Macular degeneration, also known as Age-Related Macular Degeneration (ARMD) or simply AMD, is of two types – dry AMD and wet AMD. Both forms of AMD were for long regarded as incurable and many older persons endured gradual loss of central vision.

This was the case until the discovery of the physiological process of blood-vessel formation called angiogenesis by the Italian scientist Dr Napoleone Ferrara. He and his colleagues, at the pharmaceutical company Genetech, discovered Vascular Endothelial Growth Factor (VEGF) and developed the first anti-VEGF antibody.<sup>57</sup> This led to the development of the first clinically available anti-VEGF monoclonal antibody *bevacizumab* which inhibits blood vessel growth and suppresses cancer tumour growth. “Clinical trials were made of *bevacizumab* as a treatment for several solid tumours and also outside of cancer, for example, in the treatment of age-related macular degeneration”.<sup>58</sup>

*Bevacizumab* entered the US market in 2004 as a Genetech product with the commercial name Avastin for cancer treatment, but not for treatment of AMD. Nevertheless, an

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<sup>57</sup> H. Chong, ‘Interview with Dr. Napoleone Ferrara: The VEGF Story, From Basic Discovery to Treating Cancer and Preventing Blindness’, *Science of Aging The Buck Institute’s Blog*, 2015, <http://sage.buckinstitute.org/interview-with-dr-napoleone-ferrara-the-vegf-story/> (accessed on 10 September 2016).

<sup>58</sup> D. Rbatti, ‘Napoleone Ferrara and the Saga of Vascular Endothelial Growth Factor’, *Endothelium*, 2008 Jan-Feb; 15(1):1-8, doi: 10.1080/10623320802092377, 2008, pp. 1-8.

unregistered (“off-label”) use of Avastin was established among ophthalmologists for treating AMD. In 2006, Genetech registered *ranibizumab* with the commercial name Lucentis for treatment of wet AMD. Off-label use of Avastin continued after the introduction of Lucentis especially since an eye-injection of Avastin cost roughly US\$50 whilst the same treatment with Lucentis was priced at US\$2,000 by Genetech.<sup>59</sup> As noted by Luca Arnaudo, perhaps it will never be known whether the decision to develop *ranibizumab* was motivated for product differentiation of *bevacizumab* and to extract a much bigger commercial value per ml.<sup>60</sup>

The continued use of Avastin for AMD has led to a battle between ophthalmologists, competition regulators and its patent holders; and healthcare regulators have been compelled to take sides.

In the US, Genetech holds the patent for both drugs. In the rest of the world, the patent rights for Avastin and Lucentis are not held by Genetech. Rather they are held by Roche and Novartis on the basis of two separate licensing agreements entered in 2003.<sup>61</sup> As in the US, the drugs were patented for different uses. However, ophthalmologists continued to make off-label use of Avastin.

### **Safety of Avastin for AMD**

The safety and efficacy of Avastin for ophthalmic purposes has been repeatedly confirmed since 2011 in independent comparative studies carried out at the expense of public healthcare organizations in the US (CATT)<sup>62</sup>, UK (IVAN)<sup>63</sup>, Austria (MANTA)<sup>64</sup>, France (GEFAL)<sup>65</sup> and Norway (LUCAS)<sup>66</sup>. The five-year outcomes of the CATT results were published on 2

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<sup>59</sup> R. Mukamal, *Avastin, Eylea and Lucentis – What is the Difference*, [website], Jul 20, 2015, <http://www.aoa.org/eye-health/diseases/avastin-eylea-lucentis-difference>, (accessed on 10 September 2016).

<sup>60</sup> L. Arnaudo, ‘The Strange Case of Dr. Lucentis and Mr. Avastin, The Italian Competition Authority Fines Roche and Novartis for Collusion’, *European Competition Law Review*, vol. 35, issue 7, 2014.

<sup>61</sup> L. Arnaudo, *European Competition Law Review*

<sup>62</sup> “In each of the head-to-head comparisons of ranibizumab with bevacizumab, the drugs had equivalent effects on visual acuity at all time points throughout the first year of follow-up.” from The CATT Research Group, ‘Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration’. *The New England Journal of Medicine*; vol 364, no. 20, doi: 10.1056/NEJMoa1102673, May 19, 2011, pp. 1897-1908, <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1102673>, (accessed on 10 September 2016).

<sup>63</sup> “Bevacizumab and ranibizumab have similar efficacy and can be considered equivalent in this respect in the treatment of neovascular age-related macular degeneration.” from U. Chakravarthy et al., ‘Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation: 2-Year Findings of the IVAN Randomised Controlled Trial’, *Lancet* vol. 382 no. 9900), 12 October 2013, pp. 1258-1267 at p.1266, [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)61501-9/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61501-9/fulltext), (accessed on 11 September 2016).

<sup>64</sup> ClinicalTrials.gov, *Manta Study: Avastin Versus Lucentis in Age Related Macular Degeneration*, [website], 2010, <https://clinicaltrials.gov/ct2/show/NCT00710229>, (accessed on 10 September 2016).

<sup>65</sup> ClinicalTrials.gov, *Group d’Evaluation Francais Avastin vs Lucentis (GEFAL)*, 2013, <https://clinicaltrials.gov/ct2/show/study/NCT01170767>, (accessed on 10 September 2016).

<sup>66</sup> ClinicalTrials.gov, *Lucentis Compared to Avastin Study (LUCAS)*, 2015, <https://clinicaltrials.gov/ct2/show/NCT01127360>, (accessed on 10 September 2016).

May 2016 in the journal *Ophthalmology*.<sup>67</sup> All the studies confirm that that both Avastin and Lucentis are equally effective in treating wet AMD.

The cost implications of such a conclusion are immense. The two year results of the UK (IVAN) study published on 19 July 2013 in the *Lancet* estimated that the UK National Health Service could save GBP84.5 million (US\$130 million) annually by switching from Lucentis to Avastin.<sup>68</sup>

Avastin has been included by the WHO in the list of essential medicines prepared as anti-vascular endothelial growth factor (VEGF) in the ophthalmological preparation section<sup>69</sup> based on the recommendation of the International Council of Ophthalmology.<sup>70</sup> In fact, it is the only medication listed in the section. The WHO Model List of Essential Medicines serves as a guide for the development of national and institutional essential medicine lists.

Despite international pressure, Roche has resisted expanding Avastin's indication, maintaining its stance that Avastin should not be used to treat AMD.

### **Anti-Competitive Collusive Conduct**

In Italy, complaints by an association of private healthcare clinics and by the Italian Ophthalmological Society claimed that Roche and Novartis Groups were colluding to impede the use of Avastin in favour of Lucentis. They were supported in this by the Emilia-Romagna region and a consumer association. The Italian Competition Authority (ICA) opened investigations in February 2013 and in 2014 found both groups liable. In the ICA's view, Roche and Novartis colluded "by raising and spreading concerns related to the safety of ophthalmic uses of Avastin in order to boost the sales of Lucentis, from which both groups were expecting their own returns..."<sup>71</sup> Roche was fined Euro 90,593,369 and Novartis was fined Euro 92,028,750. Roche and Novartis appealed the decision to the administrative court but had their appeal rejected.

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<sup>67</sup> M.G. Maguire et al., 'Five-Year Outcomes with Anti-VEGF Treatment of Neovascular Age-Related Macular degeneration (AMD)', *Ophthalmology*, vol. 123, no. 8, doi:10.1016/j.Optha.2016.03.045., May 2016, pp. 1751-1761, [http://www.aaajournal.org/article/S0161-6420\(16\)30092-6/pdf](http://www.aaajournal.org/article/S0161-6420(16)30092-6/pdf), (accessed on 11 September 2016).

<sup>68</sup> Review of *Ophthalmology*, *Two-Year IVAN Results: Avastin, Lucentis Equally Effective*, [website], 5 August 2013, <https://www.reviewofophthalmology.com/article/two-year-ivan-results-avastin-lucentis-equally-effective-42255>, (accessed on 1 September 2016).

<sup>69</sup> World Health Organization, *Annex 1, 19th WHO Model List of Essential Medicines*, April 2015, p. 38. [http://www.who.int/medicines/publications/essentialmedicines/EML2015\\_8-May-15.pdf](http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf), (accessed on 10 September 2016).

<sup>70</sup> International Council of Ophthalmology, *Section 21 Ophthalmological Preparations Bevacizumab - Addition Application submitted by International Council of Ophthalmology to the World Health Organization*, 2013, [http://www.who.int/selection\\_medicines/committees/expert/19/applications/Bevacizumab\\_21\\_A\\_Ad.pdf?ua=1](http://www.who.int/selection_medicines/committees/expert/19/applications/Bevacizumab_21_A_Ad.pdf?ua=1), (accessed on 3 September 2016).

<sup>71</sup> L. Arnaudo, 'The Avastin-Lucentis Case: An Illicit Agreement Between Roche and Novartis Condemned by the Italian Competition Authority', *Italian Antitrust Review*, vol. 1, no. 2, 2014, p. 128 <http://iar.agcm.it/article/view/10200/9491>, (accessed on 10 September 2016).



Following on the decision of the Italian Competition Commission and the Courts, Italy has changed its law to allow general off-label uses of Avastin and this has resulted in the approval of the use of Avastin in the Italian National Health Service.<sup>72</sup>

### **Off-label Use of Avastin for Wet AMD**

Dosages of Avastin are much higher when used to treat cancer than for AMD. Because Roche refuses to itself package Avastin in the smaller doses that are required for AMD treatment, doctors administering the drug must use smaller quantities of the drug, either by obtaining repackaged doses or measuring out fractions of a vial. Health authorities have had to contend with the concern that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections.

In the US, Genetech announced in October 2007 a strategy to limit availability of Avastin for ocular uses. It cited safety issues and halted sales of Avastin to compounding pharmacies that had been dividing Avastin into the smaller quantities needed for treating the eye. The American Academy of Ophthalmology (AAO) protested and in this, was supported by the International Academy of Compounding Pharmacists (IACP). Ophthalmologists contended that only compounding pharmacies could deal with sterility issues involved with repackaging Avastin for injection into the eye. Genetech responded to the widespread protest by announcing that Avastin can still be sold directly to physicians and delivered to destinations of their choice – including compounding pharmacies.<sup>73</sup> Avastin is now the market leading drug in the US for wet AMD.<sup>74</sup>

In July 2014, French lawmakers voted to substitute Avastin for Lucentis. France's medicine regulator, l'Agence Nationale de Sécurité du Médicament (ANSM) requested data from Roche as regards use of Avastin for AMD. Having considered available data and other studies conducted, ANSM issued in March 2015 a temporary recommendation of use (RTU) for Avastin to treat AMD. (An RTU is a procedure that allows ANSM to recommend an authorized product for additional indications outside of its marketing authorization.) It has also required Roche to monitor the use of Avastin for wet AMD in accordance with the French Public Code of Health.<sup>75</sup>

In India, an alert notice was issued on 21 January 2016 by the Drug Controller General of India on the off-label use of Avastin to treat wet AMD. This was as a precautionary measure. It was taken following on cases of reported blindness in Gujarat. Following on a review by an expert committee, the Drug Controller General passed an order on 11 March 2016 removing

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<sup>72</sup> Arnaudo, p. 129.

<sup>73</sup> M. Haddrill . Lucentis Vs. Avastin: A Molecular Degeneration Treatment Controversy, All About Vision.com, March 2014, <http://www.allaboutvision.com/conditions/lucentis-vs-avastin.htm>, (accessed 10 September 2016).

<sup>74</sup> L.H. Curtis et al., Risks of Mortality, Myocardial Infarction, Bleeding, and Stroke Associated with Therapies for Age-Related Macular Degeneration. *Arch Ophthalmol* vol. 128, no. 10, October 11, 2010, pp. 1273-1279. <http://jamanetwork.com/journals/jamaophthalmology/fullarticle/426228> (accessed on 3 September 2016.)

<sup>75</sup> M. Mezher, French Regulator and Roche Trade Blows over Off-label Avastin Use, [website], 25 June 2015, <http://www.raps.org/Regulatory-Focus/News/2015/06/25/22778/French-Regulator-and-Roche-Trade-Blows-Over-Off-Label-Avastin-Use/#>, (accessed on 3 September 2016).

the alert notice. The expert committee cited over 2500 studies that proved Avastin safe in intravitreal use. The All India Ophthalmological Society (AIOS) and the Vitreo Retinal Society of India have undertaken to jointly formulate guidelines for the safe and effective use of Avastin for ophthalmic purpose based on the written-informed consent of patients.<sup>76</sup>

In the UK, Roche did not apply for the use of Avastin in the treatment of wet AMD and its use as such is 'unlicensed'. The General Medical Council (GMC) is categorical in that doctors may only prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, the doctor concludes, "for medical reasons, that it is necessary to do so to meet the specific needs of the patient".<sup>77</sup> Avastin is therefore not prescribed in the National Health Service (NHS); nevertheless its use is widespread outside the NHS. Doctors feel reassured to use Avastin since repackaged Avastin is available with assessments of safety.<sup>78</sup> The two major suppliers are the Moorfields Pharmaceuticals, which is the manufacturing arm of the Moorfields Eye Hospital NHS Foundation Trust, and Liverpool and Broadgreen University Hospitals pharmacy. Both hold special licences and began producing these preparations originally to service clinical trials within the NHS.<sup>79</sup>

Responding to criticism from the Editor of the British Medical Journal, the Chief Executive of the GMC stated:

The critical factor here is that our guidance must be lawful, and the law on this matter is unequivocal. Doctors cannot prescribe an unlicensed medicine on grounds of cost where a licensed product is available. This was confirmed by a ruling in the case of European Commission v Republic of Poland (C-185/10) in 2012.

At the same time we do support the efficient use of NHS resources and we are sympathetic to the argument that a better solution needs to be found for the use of Avastin in the treatment of wet age-related macular degeneration (AMD). We recognise too that doctors are placed in an invidious position as things currently stand.<sup>80</sup>

The Royal College of Ophthalmologists has made its position clear: "There is clear evidence that, despite the lack of a licence, Avastin is a safe and effective drug for the treatment of neovascular AMD. The College would therefore welcome an urgent review of this issue by

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<sup>76</sup> Office of Drug Controller General of India, *F.No.12-52/2004-DC/Part L*, 11 March 2016, <http://www.cdsc0.nic.in/writereaddata/AVASTIN.pdf>, (accessed on 3 September 2016).

<sup>77</sup> General Medical Council (GMC), *Good practice in prescribing medicines - guidance for doctors*, March 2013, Paragraph 68. [http://www.gmc-uk.org/Prescribing\\_guidance.pdf\\_59055247.pdf](http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf), (accessed on 1 October 2016).

<sup>78</sup> H. Khalil et al., 'Storage Stability Of Bevacizumab In Polycarbonate And Polypropylene Syringes', *Eye (Lond)*. vol. 29 Issue 6, doi: 10.1038/eye.2015.28., June 2015, pp. 820-827, <http://www.nature.com/eye/journal/v29/n6/pdf/eye201528a.pdf>, (accessed on 12 September 2016).

<sup>79</sup> E. Poku et al. 'A. Bevacizumab in Eye Conditions: Issues Related to Quality, Use, Efficacy and Safety', *Report by the Decision Support Unit, School of Health and Related Research, University of Sheffield*. August 2012, <http://www.nicedsu.org.uk/Bevacizumab%20report%20-%20NICE%20published%20version%2011.04.13.pdf>, (accessed on 15 September 2016).

<sup>80</sup> General Medical Council, *Response to BMJ article about unlicensed prescribing of Avastin for AMD*, [GMC Statement], 2 April 2015, <http://www.gmc-uk.org/news/26457.asp>, (accessed on 1 October 2016).

the United Kingdom Health Regulatory Bodies to consider how this unusual situation can be remedied”.<sup>81</sup>

Malaysia has granted patent protection for both Avastin and Lucentis. As in other jurisdictions, Avastin has not been registered for use for wet AMD because Roche did not apply for it to be so. However, doctors in the private sector make off-label use of Avastin for treating wet AMD.

The Ministry of Health (MoH) formulary does not list Avastin and consequently neither does the National Essential Medicines List. The MoH has only listed Lucentis and Eylea (*aflibercept*) for use for wet AMD<sup>82</sup> and hence Avastin is not utilized.

All medicines and indications to be used in MoH facilities must be registered with the national Drug Control Authority (DCA). In addition, they have to be listed in the MoH Medicines Formulary (MOHMF). There is provision for the off-label use of medication at MoH facilities when requested by a specialist doctor<sup>83</sup> but each such use requires special approval from the Director General of Health (DG) Malaysia, on a name-patient basis. Blanket approval for off-label use of medication may also be granted by the Director General of Health on the recommendation of the Therapeutic Drug Working Committee of the MoH. Such an application has to be submitted with strong justification as to why other alternative medicines cannot be used, the proposed guidelines for such off-label use, and the monitoring and management process of side-effects. Avastin has not yet been granted blanket off-label use in the MoH facilities.<sup>84</sup>

The University of Malaya Medical Centre, located in the nation’s capital Kuala Lumpur, also a public healthcare facility, lists both Avastin and Lucentis as part of its formulary having obtained the required permission.

Novartis has now introduced Accentrix in Malaysia, a rebranding of *ranibizumab*, formerly marketed as Lucentis. It offers Accentrix at a significantly lower price than it did Lucentis but still at a substantially higher price than Avastin.

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<sup>81</sup> Royal College of Ophthalmologists, *Use of Avastin (bevacizumab) on age related macular degeneration*, [Statement], 15 December 2014, <https://www.rcophth.ac.uk/2014/12/use-of-avastin-bevacizumab-in-age-related-macular-degeneration/> (accessed 1 October 2016).

<sup>82</sup> In the MoH formulary *Ranibizumab* (Lucentis) is used for the following indications: Treatment of neovascular (wet) age-related macular degeneration; Treatment of visual impairment due to diabetic macular edema (DME); Treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO); Treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM). Eylea is only used for Treatment of neovascular (wet) age-related macular degeneration. Ministry of Health Malaysia, *Ministry of Health Medicines Formulary – 1/2015*, 2015, <http://www.pharmacy.gov.my/v2/sites/default/files/document-upload/ministry-health-medicines-formulary-1-2015.pdf>, (accessed on 1 October 2016).

<sup>83</sup> Pharmaceutical Services Divisions, Ministry of Health Malaysia, *Consent Form for Treatment Using Medicine with Unregistered Medicine/Indication (Off Label)*, [website], 2016, <http://www.pharmacy.gov.my/v2/en/documents/consent-form-treatment-using-medicine-unregistered-medicine-indication-label.html>, (accessed on 3 October 2016).

<sup>84</sup> Communication from the Pharmaceutical Services Division, Ministry of Health Malaysia to the principal author, [e-mail], 10 October 2016.

If Avastin is included in the MoH formulary and made available at all MoH facilities, it will not only help reduce cost for the tax payer funded MoH but also in the private sector.