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# EU Marketing Authorisation of Orphan Medicinal Products and Its Impact on Related Research

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## Abstract

Over the last 15 years, there has been a steady increase in the development of orphan medicinal products (OMPs). This raises an important question: What impact does the EU marketing authorisation of an OMP have on related research? This article establishes that the key orphan incentive, namely the 10-year market exclusivity provision laid down in Article 8 of the EU Regulation on OMPs (Regulation 141/2000), has a huge potential impact on related research. It is argued that this provision can make it too difficult for researchers/sponsors to attain marketing approval for closely related products. This article advances two proposals to address this problem. First, it argues for new principles for assessing similarity, so as to clarify and narrow the ambit of market exclusivity. Secondly, it argues for improved conditions for a demonstration of ‘clinical superiority’ for similar OMPs.

## Keywords

EU marketing authorisation – orphan medicinal product (OMP) – market exclusivity – similar medicinal product – similar active substance – same therapeutic indication – biological medicinal product – advanced therapy medicinal product (ATMP)

## 1 Introduction

EU Regulation 141/2000 on orphan medicinal products (OMPs) was

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introduced to promote investment in the research and development of medicines to treat patients suffering from rare diseases, i.e., conditions that affect not more than five in 10,000 people in the EU.<sup>1</sup> An EU Regulation, in contrast to an EU Directive, is directly applicable in all EU Member States and does not need to be transposed into national law.<sup>2</sup> Since the Regulation's introduction, there has been a steady increase in the number of marketing authorisations for OMPs in the EU.<sup>3</sup> From 2000 to 2015, the European Commission authorised a total of 114 OMPs to be marketed in the EU for the benefit of rare disease patients.<sup>4</sup> However, this represents only a small proportion of the 1,596 orphan designations granted by the European Commission during the same period.<sup>5</sup> This significant discrepancy between the number of medicinal products designated as OMPs (1,596) and the number of OMPs authorised (114) illustrates that it is difficult in practice to obtain an EU marketing authorisation. This is not the result of a single factor, but regulatory complexity is, in particular, burdensome for not-for-profit organisations and small and medium-sized enterprises (SMEs), which have scarce human and financial resources and only limited regulatory expertise.<sup>6</sup> Overly challenging requirements are likely to hinder the availability of new medicines; including those that fulfil 'unmet medical needs', which a Commission Regulation defines as those medicines that address 'a condition for which there exists no satisfactory method of diagnosis, prevention or treatment' approved in the EU or those that would otherwise 'be of major therapeutic advantage to those affected'.<sup>7</sup> The currently authorised OMPs in the EU, for example, only cover one percent of the 5,000 to 8,000 different types of rare diseases.<sup>8</sup> If the

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<sup>1</sup> European Commission, 'Orphan Medicinal Products', online at [ec.europa.eu/health/human-use/orphan-medicines/index\\_en.htm](http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm), retrieved 11 January 2017. See also Regulation 141/2000, Art. 3(1)(a).

<sup>2</sup> See TFEU, Art. 288.

<sup>3</sup> European Commission, 'Inventory of Union and Member State Incentives to Support Research into, and the Development and Availability of, Orphan Medicinal Products – State of Play 2015', SWD (2015) 13 Final, 22 February 2016, pp. 4, 20.

<sup>4</sup> See European Medicines Agency, 2016, 'Orphan Medicines Figures', p. 9, online at [www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2015/04/WC500185766.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf), retrieved 11 January 2017.

<sup>5</sup> *Ibid.*, pp. 1, 6.

<sup>6</sup> This is the case even though there are additional incentives for SMEs, including administrative and procedural assistance and fee reductions. See European Medicines Agency, 'Orphan Incentives', online at [www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000393.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp), retrieved 11 January 2017.

<sup>7</sup> Commission Regulation 507/2006, Art. 4(2).

<sup>8</sup> *Supra* note 3, p. 4.

regulatory structure is to successfully incentivise both innovation in human medicines and high standards of quality, safety and efficacy, then the relevant provisions need to be regularly updated in the light of scientific and technical developments.

In response to these problems, the European Commission has initiated a number of reforms that are relevant for OMPs. In July 2016, it launched a review of Commission Regulation 847/2000 on the concept of ‘similar medicinal product’.<sup>9</sup> In November 2016, it published a Commission notice on the application of Articles 3, 5 and 7 of Regulation 141/2000 on OMPs,<sup>10</sup> which replaces a Commission Communication from 2003.<sup>11</sup>

The European Medicines Agency (EMA) has also initiated four developments. First, following the publication of the new Commission notice, the EMA updated its post-authorisation guidance on, in particular, extensions of marketing authorisations for OMPs.<sup>12</sup> Secondly, it introduced a scheme in March 2016 aimed at strengthening support for the development of medicinal products that have the potential to fulfil unmet medical needs.<sup>13</sup> Thirdly, the EMA is developing a framework to enhance collaboration with academia by helping academic researchers to understand the regulatory environment and to translate their research results into new medicinal products.<sup>14</sup> Fourthly, together with the United States Food and Drug Administration (FDA), the EMA has set up a new ‘cluster’ on rare diseases that focuses on the sharing of information on the scientific evaluation and development of medicines for rare diseases,

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<sup>9</sup> See European Commission, ‘Concept of “Similar Medicinal Product” in the Context of the Orphan Legislation: Adaption to Technical Progress’, 29 July 2016, online at [ec.europa.eu/health/files/orphanmp/2016\\_07\\_pc\\_orphan/2016\\_07\\_consultation\\_paper.pdf](http://ec.europa.eu/health/files/orphanmp/2016_07_pc_orphan/2016_07_consultation_paper.pdf), retrieved 11 January 2017.

<sup>10</sup> See Commission Notice (2016/C 424/03).

<sup>11</sup> See Commission Communication on Regulation 141/2000 (2003/C 178/02).

<sup>12</sup> EMA, ‘European Medicines Agency Post-Authorisation Procedural Advice for Users of the Centralised Procedure’, EMEA-H-19984/03 Rev. 67, 19 December 2016, ss. 3 and 4. See also EMA, ‘Regulatory Information – New Guidance on Type II Variations and Marketing Authorisation Extensions for Orphan-Designated Medicines’, 18 November 2016, online at [www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2016/11/news\\_detail\\_002645.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/11/news_detail_002645.jsp&mid=WC0b01ac058004d5c1), retrieved 11 January 2017.

<sup>13</sup> PRIME (Priority Medicines): EMA, ‘Launch of PRIME – Paving the Way for Promising Medicines for Patients’, 7 March 2016, online at [www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2016/03/news\\_detail\\_002484.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002484.jsp&mid=WC0b01ac058004d5c1); see also EMA, ‘PRIME: Priority Medicines’, online at [www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general\\_content\\_000660.jsp%26mid%3DWC0b01ac058096f643](http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general_content_000660.jsp%26mid%3DWC0b01ac058096f643), retrieved 11 January 2017.

<sup>14</sup> EMA, ‘Developing a Framework of Collaboration Between the European Medicines Agency (EMA) and Academia’, EMA/424858/2016, 1 August 2016.

including clinical trials in small populations.<sup>15</sup>

In addition, reforms are likely in the field of Advanced Therapy Medicinal Products (ATMPs). An ATMP is defined<sup>16</sup> as a biological medicinal product that can be classified as either: (i) a gene therapy medicinal product (GTMP),<sup>17</sup> (ii) a somatic cell therapy medicinal product (sCTMP),<sup>18</sup> (iii) a tissue engineered product (TEP),<sup>19</sup> or (iv) a combined ATMP.<sup>20</sup> In June 2016, the EMA published a report from a multi-stakeholder meeting held in May 2016 that contains specific proposals to foster ATMP development and authorisation in Europe.<sup>21</sup> The report proposes, for example, more ATMP-specific guidance from regulators and greater harmonisation between the EU Member States on several aspects of the ATMP regulatory framework, such as the implementation of the hospital exemption laid down in Article 28(2) of Regulation 1394/2007.<sup>22</sup> Together with the European Commission and the competent national authorities, the EMA is currently discussing the feasibility of the report's proposals to determine appropriate actions.<sup>23</sup>

This article will focus on the marketing authorisation of OMPs and

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<sup>15</sup> EMA, 'EU-US Collaboration to Boost Medicine Development for Rare Diseases', 26 September 2016, online at [www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2016/09/news\\_detail\\_002609.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/09/news_detail_002609.jsp&mid=WC0b01ac058004d5c1), retrieved 11 January 2017.

<sup>16</sup> Regulation 1394/2007, Art. 2(1).

<sup>17</sup> Defined in Annex I, Part IV of Directive 2001/83/EC. E.g., a 'solution of recombinant AAV2 vectors supplied in a vial' (used to treat 'inherited retinal degeneration due to autosomal recessive RPE65 gene mutations'); see EMA, 'Scientific Recommendation on Classification of Advanced Therapy Medicinal Products', EMA/291899/2016, 25 April 2016.

<sup>18</sup> Defined in Annex I, Part IV of Directive 2001/83/EC. E.g., 'autologous T cells in injectable saline suspended in a cryopreservation medium' (used to treat Epstein-Barr Virus positive malignancies); see EMA, 'Scientific Recommendation on Classification of Advanced Therapy Medicinal Products', EMA/291907/2016, 25 April 2016.

<sup>19</sup> Defined in Art. 2(1)(b) of Regulation 1394/2007 as a product that (i) contains or consists of engineered tissues or cells; and (ii) is presented as having properties to be administered to human beings with a view to repairing, regenerating or replacing human tissue. It may contain tissues or cells of animal or human origin (whether viable or non-viable) and additional substances (scaffolds or matrices). E.g., 'a suspension of autologous blood cells, contained in a syringe' (used to treat critical limb ischemia); see EMA, 'Scientific Recommendation on Classification of Advanced Therapy Medicinal Products', EMA/291914/2016, 25 April 2016.

<sup>20</sup> Defined in Art. 2(1)(d) of Regulation 1394/2007. Combined ATMPs incorporate one or more medical devices as an integral part of the product. E.g., cells embedded in a scaffold or biodegradable matrix.

<sup>21</sup> EMA, 'Advanced Therapy Medicines: Exploring Solutions to Foster Development and Expand Patient Access in Europe', EMA/345874/2016, 3 June 2016.

<sup>22</sup> *Ibid.*, pp. 5, 7, 8, 10.

<sup>23</sup> *Ibid.*, p. 10.

address the following question: What impact does the EU marketing authorisation of an OMP have on the development and marketing of closely related products? The analysis will begin by explaining the EU regulatory context, namely the criteria for orphan designation and the centralised authorisation procedure. It will then give an overview of the range of orphan incentives (i.e., incentives that are offered in the EU for OMPs) and examine the most important of these: the 10-year market exclusivity provision laid down in Article 8 of Regulation 141/2000. To answer the question we have just posed, the analysis will make use of a real-life example: Holoclar is an ATMP and OMP, and the first stem cell-based medicinal product approved for use in the EU. In this way, we will also draw attention to often overlooked aspects of the regulatory scheme applying to stem cell research.<sup>24</sup>

This article will establish that the principle of market exclusivity has a huge potential impact on related research, making it too difficult for researchers/sponsors<sup>25</sup> to obtain an EU marketing authorisation for closely related products. We will make two proposals to address the identified problem without losing the benefits of the market exclusivity provision. First, we will propose new principles for assessing similarity. Our analysis will go beyond the European Commission's proposals of 29 July 2016 and give particular emphasis to the criterion of 'same therapeutic indication'. In particular, we will argue that in cases where there is an overlap of the target populations, a medicinal product should be considered (compared to a currently authorised OMP) as follows: (i) with regard to the overlap, it is intended for the same therapeutic indication; and (ii) where there is no overlap of the target populations, the medicinal product has a different therapeutic indication. Secondly, we will propose improved conditions for a demonstration of 'clinical superiority' in relation to Article 3(3)(d) of Commission Regulation 847/2000. Our proposal will give effect to the aim of orphan incentives, i.e., to support research, development and marketing with regard to OMPs.

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<sup>24</sup> Cf., e.g., S. Devaney, *Stem Cell Research and the Collaborative Regulation of Innovation* (Abingdon, Oxon: Routledge, 2014), which makes no mention of Regulation 141/2000.

<sup>25</sup> A sponsor is defined in Art. 2(c) of Regulation 141/2000 as 'any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product'.

## 2 The EU Regulatory Context: Orphan Designation and the Centralised Authorisation Procedure

For a medicinal product to be marketed within the EU as an OMP, it must first receive ‘orphan designation’ and then ‘marketing authorisation’.<sup>26</sup>

Three criteria must be met for *orphan designation*. First, the medicinal product must be intended for the prevention, diagnosis or treatment of a condition that is ‘life-threatening’ or ‘chronically debilitating’.<sup>27</sup> Secondly, the condition must affect not more than five in 10,000 people in the EU (prevalence criterion) or it must be improbable that the marketing of the medicinal product in the EU ‘would generate sufficient return to justify the necessary investment’ (profitability criterion).<sup>28</sup> Thirdly, there must be ‘no satisfactory method of diagnosis, prevention or treatment of the condition in question’ already approved in the EU or, if there is such a method, the medicinal product must ‘be of significant benefit to those affected by that condition’.<sup>29</sup> The term ‘significant benefit’ is defined as ‘a clinically relevant advantage or a major contribution to patient care’.<sup>30</sup> Thus, orphan designation is available for medicinal products aimed at addressing an evidenced clinical need with regard to severe, rare conditions.

Procedurally, an application for orphan designation must be submitted to the EMA before the marketing authorisation application is made.<sup>31</sup> The Committee for Orphan Medicinal Products (COMP) is tasked with examining and making recommendations on these applications within 90 days.<sup>32</sup> The European Commission then makes its final decision within 30 days of receipt of the COMP opinion.<sup>33</sup> A medicinal product that is designated as an OMP is entered in the Community Register of Orphan Medicinal Products.<sup>34</sup> From 2000 to 2015, a total of 1,596 medicinal products have been designated as OMPs by the European Commission.<sup>35</sup> The most common designated orphan conditions include cystic fibrosis, multiple myeloma, acute myeloid leukaemia, chronic lymphoblastic

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<sup>26</sup> A medicinal product is defined in Art. 2(a) of Regulation 141/2000 as ‘a medicinal product for human use, as defined in Article 2 of Directive 65/65/EEC’.

<sup>27</sup> Regulation 141/2000, Art. 3(1)(a).

<sup>28</sup> *Ibid.*

<sup>29</sup> *Ibid.*, Art. 3(1)(b).

<sup>30</sup> Commission Regulation 847/2000, Art. 3(2).

<sup>31</sup> Regulation 141/2000, Art. 5(1).

<sup>32</sup> *Ibid.*, Arts. 4 and 5(5).

<sup>33</sup> *Ibid.*, Art. 5(8).

<sup>34</sup> *Ibid.*, Art. 5(9). For the removal from the register see Art. 5(12).

<sup>35</sup> *Supra* note 4, pp. 1, 6.

leukaemia, pancreatic carcinoma ovarian cancer and glioma.<sup>36</sup> However, an orphan designation is not a marketing authorisation, which means that the quality, safety and efficacy of the medicinal product still needs to be demonstrated.

The marketing of medicinal products within an EU Member State requires authorisation by the competent authorities of that Member State or, in some case, by the European Commission.<sup>37</sup> Since 20 November 2005, marketing authorisation for OMPs has been granted by the European Commission, i.e., they have been subject to the centralised authorisation procedure that is carried out by the EMA.<sup>38</sup> Before this date, 22 OMPs had been authorised through the centralised procedure and two OMPs through national procedures.<sup>39</sup> A total of 128 OMPs have been approved to date by the European Commission for the benefit of rare disease patients.<sup>40</sup> A centralised marketing authorisation is valid for five years on a renewable basis throughout the EU.<sup>41</sup>

Under the centralised authorisation procedure, there is the possibility of submitting a request for an ‘accelerated assessment’ and a ‘conditional marketing authorisation’.<sup>42</sup> These regulatory tools in European legislation allow patients to gain early access to new medicinal products that address unmet medical needs.<sup>43</sup> An accelerated assessment procedure allows for a faster evaluation of an application for a marketing authorisation of a medicinal product that is ‘of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation’, i.e., the time-limit is reduced from a maximum of 210 days to 150 days.<sup>44</sup> A conditional marketing authorisation may be granted on

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<sup>36</sup> *Supra* note 3, p. 3.

<sup>37</sup> Directive 2001/83/EC, Art. 6(1). A medicinal product is defined in Art. 1(2).

<sup>38</sup> Regulation 726/2004, Arts. 3(1), 90 and Annex 4.

<sup>39</sup> *Supra* note 3, pp. 4, 21–23.

<sup>40</sup> Status as of 11 January 2017. *Supra* note 1.

<sup>41</sup> See Regulation 726/2004, Arts. 13(1) and 14(1)–(3). See also EMA, 2015, ‘Applying for EU Marketing Authorisation’, online at [www.ema.europa.eu/docs/en\\_GB/document\\_library/Leaflet/2011/03/WC500104233.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2011/03/WC500104233.pdf), retrieved 11 January 2017.

<sup>42</sup> Regulation 726/2004, Art. 14(7) and (9). Other possibilities are a request for a marketing authorisation under exceptional circumstances under Art. 14(8) of Regulation 726/2004 or a request for a CHMP compassionate use opinion under Art. 83 of that Regulation.

<sup>43</sup> EMA, ‘Fast Track Routes for Medicines That Address Unmet Medical Needs’, 27 July 2015, online at [www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2015/07/news\\_detail\\_002381.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002381.jsp&mid=WC0b01ac058004d5c1), retrieved 11 January 2017.

<sup>44</sup> Regulation 726/2004, Arts. 14(9) and 6(3), subpara. 1.

the basis of less complete clinical data than is usually required for a medicinal product that belongs to a particular category, including OMPs, and fulfils certain requirements such as a positive risk-benefit balance and unmet medical needs.<sup>45</sup> Such authorisation is valid for one year, on a renewable basis.<sup>46</sup> It will convert into a ‘standard’ marketing authorisation as soon as the applicant provides comprehensive data.<sup>47</sup>

To optimise the process of such key regulatory tools, the EMA has recently revised its guidelines on the implementation of ‘accelerated assessment’ and ‘conditional marketing authorisation’.<sup>48</sup> The revised guidelines came into effect on 1 June 2016 and provide more detailed guidance on how to justify fulfilment of the legal requirements and emphasise the importance of early dialogue with EMA.<sup>49</sup>

### 3 Market Exclusivity: Impact on Related Research

#### 3.1 *Orphan Incentive: The Principle of Market Exclusivity*

As mentioned earlier, a total of 128 OMPs have been authorised by the European Commission for the benefit of patients with rare diseases, but this covers only one per cent of those diseases. Orphan incentives are crucial to promoting investment in this field. The current orphan incentives include reduction of fees or fee waivers; scientific advice and protocol assistance; grants (such as Horizon 2020 and its call ‘New Therapies for Rare Diseases’); access to the centralised authorisation procedure and 10 years of market exclusivity in the EU.<sup>50</sup>

The key orphan incentive is the market exclusivity provision laid down in Article 8 of Regulation 141/2000. This provides that marketing authorisation shall not be granted for a 10-year period for a second

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<sup>45</sup> *Ibid.*, Art. 14(7); Commission Regulation 507/2006, Arts. 2 and 4.

<sup>46</sup> Regulation 726/2004, Art. 14(7).

<sup>47</sup> See EMA, ‘Conditional Marketing Authorisation’, online at [www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000925.jsp&mid=WC0b01ac05809f843b](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b), retrieved 11 January 2017.

<sup>48</sup> EMA, ‘Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement the Procedure for Accelerated Assessment Pursuant to Article 14(9) of Regulation 726/2004’, EMA/CHMP/671361/2015 Rev. 1, 25 February 2016; EMA, ‘Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement Commission Regulation 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use Falling Within the Scope of Regulation 726/2004’, EMA/CHMP/509951/2006, Rev.1, 25 February 2016.

<sup>49</sup> *Ibid.*; *supra* note 43.

<sup>50</sup> See Regulation 141/2000, Arts. 6–9. See also *supra* note 6.

medicinal product ‘for the same therapeutic indication, in respect of a *similar medicinal product*’.<sup>51</sup> Where a paediatric investigation plan is completed, the period of market exclusivity may be extended to 12 years.<sup>52</sup>

The market exclusivity provision does not apply where a second medicinal product is *not* similar to an authorised OMP. The definition of ‘similar medicinal product’ is therefore a decisive factor in the granting or refusal of marketing authorisation for a second medicinal product and this is provided by the key implementing legislation: Commission Regulation 847/2000. A medicinal product is defined as similar if (a) it contains ‘a similar active substance’ *and* (b) ‘is intended for the same therapeutic indication’ as the currently authorised OMP.<sup>53</sup>

A ‘*similar active substance*’ is an active substance (i.e., ‘a substance with physiological or pharmacological activity’)<sup>54</sup> that is either identical or has ‘the *same principal molecular structural features* (but not necessarily all of the same molecular structural features) and which *acts via the same mechanism*’.<sup>55</sup> Specific examples are provided, such as the same radiopharmaceutical active substance.

The ‘*same therapeutic indication*’ is not defined in either Regulation 141/2000 or Commission Regulation 847/2000. The Commission has, however, provided guidance. A Commission Guideline clarifies that the therapeutic indication of an OMP is set by the marketing authorisation and must be subsumed under the (usually broader) designated orphan condition.<sup>56</sup> In cases where the therapeutic indication authorised through the marketing approval procedure is a subset of the designated condition, the marketing authorisation holder (MAH) for the original OMP will benefit from a 10-year period of market exclusivity for this medicinal product, for this approved indication.<sup>57</sup>

There are, however, three derogations from market exclusivity, where a marketing authorisation may be granted to a similar medicinal product

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<sup>51</sup>Regulation 141/2000, Art. 8(1), emphasis added. Under Art. 8(2) of Regulation 141/2000, the period of market exclusivity can be reduced to six years if it is established at the end of the fifth year that the criteria for designation under Art. 3 are no longer fulfilled.

<sup>52</sup> Regulation 1901/2006, Art. 37.

<sup>53</sup> Commission Regulation 847/2000, Art. 3(3)(b).

<sup>54</sup> *Ibid.*, Art. 3(3)(a).

<sup>55</sup> *Ibid.*, Art. 3(3)(c), emphasis added.

<sup>56</sup> Commission Guideline 2008/C 242/08, *Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity*, s. 2.3, para. 1.

<sup>57</sup> *Supra* note 10, s. D.1.

for the same therapeutic indication. These are specified by Article 8(3) of Regulation 141/2000 and will be examined below in relation to a real-life example.

In sum, subject to three derogations, the MAH for an OMP will have a 10-year period of market exclusivity over the OMP, during which any ‘similar medicinal product’ cannot be put on the EU market. Three criteria must be taken into consideration, when assessing the similarity between a second medicinal product and an authorised OMP: (1) principal molecular structural features, (2) mechanism of action and (3) therapeutic indication. If there are significant differences within one or more of these criteria, then the second medicinal product will be considered as not similar to the authorised OMP,<sup>58</sup> and the second applicant could then obtain marketing authorisation for their own medicinal product.

We will now seek to show that the derogations and the criteria for a similar medicinal product sometimes hinder the rationale for granting market exclusivity, namely, incentivising research and development of medicines to treat patients suffering from rare diseases.

### **3.2 *Impact on Related Research***

The impact of EU marketing authorisation of an OMP on related research can best be illustrated by looking at a real-life example. Holoclar is the first stem cell-based medicinal product approved for use in the EU.<sup>59</sup> The product was given conditional marketing authorisation by the European Commission on 17 February 2015.<sup>60</sup> Holoclar’s active substance is: ‘Ex vivo expanded autologous human corneal epithelium cells containing stem cells’<sup>61</sup> and its approved indication is:

Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral

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<sup>58</sup> *Supra* note 56, s. 2.

<sup>59</sup> For product information see EMA, ‘Holoclar’, online at [www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002450/human\\_med\\_001844.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002450/human_med_001844.jsp&mid=WC0b01ac058001d124), retrieved 11 January 2017.

<sup>60</sup> MA number: EU/1/14/987. See Commission Implementing Decision of 17 February 2015, C(2015)1028(final).

<sup>61</sup> European Commission, ‘Community Register of Medicinal Products for Human Use’, online at [ec.europa.eu/health/documents/community-register/html/h987.htm](http://ec.europa.eu/health/documents/community-register/html/h987.htm), retrieved 11 January 2017.

or bilateral, due to physical or chemical ocular burns. A minimum of 1-2 mm<sup>2</sup> of undamaged limbus is required for biopsy.<sup>62</sup>

Limbal stem cell deficiency (LSCD) is a condition that is characterised by the loss or dysfunction of corneal epithelial stem cells (CESCs), also known as limbal stem cells, i.e., stem cells that can be found in the basal layer of the limbal epithelium.<sup>63</sup> LSCD may result from a variety of causes such as hereditary diseases, inflammatory diseases, chemical or thermal burns and contact lens related eye disease.<sup>64</sup> When the CESCs are destroyed or absent or when the stem cell niche is damaged, clinical symptoms can include pain, irritation, tearing and extreme sensitivity to light.<sup>65</sup> In addition, it can lead to a process resulting in significant visual impairment and even total blindness.<sup>66</sup> Holoclar has been designated an OMP and an ATMP.<sup>67</sup> Its designated orphan condition is: 'Treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns'.<sup>68</sup> The MAH for Holoclar benefits from orphan market exclusivity for a 10-year period from 19 February 2015.<sup>69</sup>

Applying the regulatory conditions outlined above, assessing the similarity between a second medicinal product and Holoclar requires

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<sup>62</sup> *Ibid.*

<sup>63</sup> S. Ahmad, F. Figueiredo and M. Lako, 'Corneal Epithelial Stem Cells: Characterization, Culture and Transplantation', *Regenerative Medicine* 1(1) (2006) 29–44; S. Kolli et al., 'Successful Application of Ex Vivo Expanded Human Autologous Oral Mucosal Epithelium for the Treatment of Total Bilateral Limbal Stem Cell Deficiency', *Stem Cells* 32(8) (2014) 2135–2146; see also <http://youtu.be/qUQRhxjtbpQ>, retrieved 11 January 2017.

<sup>64</sup> S. Kolli et al., 'Corneal Epithelial Stem Cells and Their Therapeutic Application', in: H. Baharvand (ed.), *Trends in Stem Cell Biology and Technology* (New York: Humana Press, 2009) pp. 319, 338.

<sup>65</sup> *Ibid.*, pp. 319, 338, 339.

<sup>66</sup> This process is known as 'conjunctivalisation': *Ibid.*, pp. 319, 339.

<sup>67</sup> See EMA, 'Summaries of Scientific Recommendations on Classification of Advanced Therapy Medicinal Products', online at [www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000301.jsp&mid=WC0b01ac05800862c0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0) and European Commission, 'Community Register of Orphan Medicinal Products', online at [ec.europa.eu/health/documents/community-register/html/o579.htm](http://ec.europa.eu/health/documents/community-register/html/o579.htm), retrieved 11 January 2017.

<sup>68</sup> European Commission, *supra* note 67.

<sup>69</sup> See *supra* note 61. This applies provided that the MAH for Holoclar (i.e., Chiesi Farmaceutici S.P.A.) completes the post-approval measures for the conditional approval under Art. 14(7) of Regulation 726/2004, i.e., to carry out study HLSTM03 (due date: December 2020). See further EMA, 'Assessment Report', EMA/25273/2015, 18 December 2014, pp. 79–81.

consideration of whether the second medicinal product contains a ‘similar active substance’ and is intended for the ‘same therapeutic indication’ as Holoclar. The three criteria – principal molecular structural features, mechanism of action and therapeutic indication – must therefore be taken into account and any significant differences with regard to one or more of these criteria will mean that the second medicinal product is not similar to Holoclar. Only if this is the case (i.e., the second product is not similar), may it be marketed within the EU without reliance on one of the three derogations from Holoclar’s market exclusivity.

Consider a second medicinal product that consists of *ex vivo* expanded human autologous oral mucosal epithelium and is intended to be used to treat patients with total bilateral LSCD.<sup>70</sup> It seems to us that such product would not be similar to Holoclar. Regardless of whether the active substance is similar,<sup>71</sup> the second medicinal product is intended for a different therapeutic indication. The approved indication of Holoclar does not cover the treatment of *total bilateral* LSCD since Holoclar requires a minimum of 1-2 mm<sup>2</sup> of undamaged limbus for biopsy. Consequently, in our view, the 10-year market exclusivity provision laid down in Article 8 of Regulation 141/2000 would not apply in this case and thus would not prevent the granting of marketing authorisation to such a second product.

It is, however, not difficult to imagine a situation for which the assessment of similarity becomes more complex. Let us consider the example of another medicinal product designated as an OMP and an ATMP that includes *ex vivo* expanded autologous human CESC and is intended for the treatment of total unilateral LSCD in both adult and child patients.<sup>72</sup> This medicinal product contains a ‘similar active substance’,<sup>73</sup>

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<sup>70</sup> An example for such a product is: S. Kolli et al., *supra* note 63.

<sup>71</sup> It is difficult in practice to assess whether an active substance is similar under the definition in Art. 3(3)(c) of Commission Regulation 847/2000. However, the European Commission has stressed in its consultation document concerning the revision of the definition of ‘similar active substance’ that two related cell-based medicinal products shall not be considered similar if ‘there are differences in starting materials...which have significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product. The different source of the starting materials (e.g. as in the case of autologous ATMPs) is not sufficient to support a claim that two products are non-similar’: *supra* note 9, lines 104–108. This suggests that the two active substances here are probably similar, because oral mucosal epithelial cells are an alternative *source* of autologous epithelial stem cells for ocular reconstruction; see S. Kolli et al., *supra* note 63.

<sup>72</sup> An example of such a product is: S. Kolli et al., ‘Successful Clinical Implementation of Corneal Epithelial Stem Cell Therapy for Treatment of Unilateral Limbal Stem Cell Deficiency’, *Stem Cells* 28(3) (2009) 597–610.

<sup>73</sup> As per the definition in Commission Regulation 847/2000, Art. 3(3)(c).

because Holoclar consists of ex vivo expanded autologous human corneal epithelial cells containing CESC. It is therefore crucial to assess whether it is intended for the ‘same therapeutic indication’. The approved indication of Holoclar (quoted above) covers the treatment of ‘adult patients with moderate to severe’ LSCD ‘due to physical or chemical ocular burns’. It therefore does not cover (i) patients under 18 years, (ii) milder forms of LSCD, or (iii) LSCD due to causes other than physical or chemical ocular burns.<sup>74</sup>

The alternative medicinal product we are considering is intended to be used to treat patients of all ages with total unilateral LSCD, including such due to physical or chemical ocular burns. There is therefore an overlap of the target populations for the two OMPs with regard to adult patients with total unilateral LSCD due to physical or chemical ocular burns. The Commission Guideline says that, in cases overlap of target populations, the extent of overlap will be a decisive factor for determining whether a second medicinal product has a different therapeutic indication to an authorised OMP.<sup>75</sup> In the case of a designated OMP, as here, the competent assessing body will be the Committee for Medicinal Products for Human Use (CHMP) at the EMA.<sup>76</sup>

If the CHMP concludes in the present case that the overlap of the target populations is not significant and that therefore the second medicinal product and Holoclar are intended for different therapeutic indications and are *not similar*, the European Commission will grant a marketing authorisation to the second medicinal product, provided that its quality, safety and efficacy are shown. Since the second medicinal product is designated as an OMP, the MAH of such a product will then benefit from a 10-year period of market exclusivity for that product for the approved indication. As stated earlier, this period will be extended to 12 years if a paediatric investigation plan is completed.

If, however, the CHMP considers the overlap of the target populations significant and thus that the two products are *similar*, the situation is very different. Then, the second applicant may only place the second medicinal product on the EU market if able to rely on one of the derogations from market exclusivity.

Article 8(3) of Regulation 141/2000 contains *three derogations* from the market exclusivity: (a) consent of the MAH for the original OMP to the second applicant, (b) the inability of the MAH for the original OMP ‘to supply sufficient quantities of the medicinal product’, and (c) the second applicant can demonstrate that the second medicinal product,

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<sup>74</sup> See also EMA, *supra* note 69, p. 66.

<sup>75</sup> *Supra* note 56, s. 2.3, para. 2.

<sup>76</sup> *Ibid.*, ss. 3.1, 3.4.

though similar to the authorised OMP, is ‘safer, more effective or otherwise clinically superior’.<sup>77</sup>

In the case under discussion, the second applicant will have difficulty establishing any of these. The first two options are in the sphere of influence of the MAH, rather than the second applicant. The third, (c), is hard to prove in practice. ‘Clinically superior’ is defined to mean that a second medicinal product is shown to have a significant diagnostic or therapeutic advantage over an authorised OMP in at least one of three specified ways: (i) ‘greater efficacy’; (ii) ‘greater safety in a substantial portion of the target population(s)’; and (iii) in exceptional circumstances, where neither (i) nor (ii) has been shown, a demonstration that the second ‘medicinal product otherwise makes a major contribution to diagnosis or to patient care’.<sup>78</sup> Demonstrating a significant diagnostic or therapeutic advantage over and above that provided by Holoclar (such as greater efficacy or greater safety in a substantial portion of the target population) usually requires direct comparative clinical trials.<sup>79</sup> But the small patient population poses practical hurdles for conducting clinical trials on OMPs, for example, they must often be carried out in multiple centres in multiple countries.<sup>80</sup> At the time of Holoclar’s designation as an OMP, its target population was estimated to be ‘approximately 0.3 in 10,000 people’ in the EU, which is considerably below the threshold of five in 10,000 people set by Regulation 141/2000 and amounts to only around 15,000 people in the entire European Economic Area.<sup>81</sup> Moreover, although the manufacturing process of Holoclar includes the use of material from animals (lethally-irradiated murine 3T3 fibroblast cells and foetal bovine serum), it will be difficult – even for a second applicant whose product is totally animal free and manufactured in compliance with Good Manufacturing Practice – to show ‘greater safety in a substantial portion of the target population(s)’, since no adverse effects derived from the use of such material have been reported over the last 30 years.<sup>82</sup>

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<sup>77</sup> Regulation 141/2000, Art. 8(3).

<sup>78</sup> Commission Regulation 847/2000, Art. 3(3)(d).

<sup>79</sup> *Ibid.*

<sup>80</sup> For further information see EMA, ‘Guideline on Clinical Trials in Small Populations’, Doc. Ref. CHMP/EWP/83561/2005, 27 July 2006.

<sup>81</sup> The EEA encompasses all EU Member States and Iceland, Norway and Liechtenstein. EMA, ‘Public Summary of Opinion of Orphan Designation’, EMA/COMP/482413/2008 Rev.1, 13 April 2015.

<sup>82</sup> Commission Regulation 847/2000, Art. 3(3)(d)(2). For Holoclar’s ingredients see EMA, ‘EPAR Product Information’, p. 4, online at [www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002450/WC500183404.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002450/WC500183404.pdf), retrieved 11 January 2017.

If the CHMP concludes that the second medicinal product is similar to Holoclar and that none of the three options arise, it will recommend the refusal of marketing approval. This seems to us to be a real possibility, because there is a clear overlap of target populations and the derogation provisions are either outside the control of the second applicant or present an almost insurmountable hurdle in practice. This example supports our contention that the marketing authorisation of an OMP, or more precisely, the market exclusivity provision laid down in Article 8 of Regulation 141/2000, has a huge potential impact on related research. In practice, it will be extremely difficult for some researchers/sponsors to obtain a marketing authorisation for their product.

## 4 Amending Proposals

The laudable aim of orphan incentives is to promote investment in the research and development of OMPs in order to ensure that patients suffering from rare diseases have the same quality of treatment as other patients.<sup>83</sup> We maintain that the problems we have identified can be addressed in a way that is consistent with this aim without repeal of the 10-year market exclusivity provision. Before advancing our suggestions for amending proposals, we will first explain why the solution cannot rest with national exemptions from the central authorisation.

### 4.1 *Harmonisation of the National Exemptions*

There may be the option for some researchers/sponsors of an ATMP to apply for a national exemption in the respective EU country. Article 28(2) of Regulation 1394/2007 introduces the so-called ‘hospital exemption’, whereby it is permissible under specific conditions to manufacture and supply an ATMP without an EU marketing authorisation by the European Commission.<sup>84</sup> The hospital exemption

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For an example of a product that is totally animal free and manufactured in compliance with GMP see *supra* note 72. For further information on the issue of xenogeneic components and a defence of their use see G. Pellegrini, P. Rama and M. De Luca, ‘Vision from the Right Stem’, *Trends in Molecular Medicine* 17(1) (2011) 1–7; G. Pellegrini et al., ‘Concise Review: Hurdles in a Successful Example of Limbal Stem Cell-Based Regenerative Medicine’, *Stem Cells* 32(1) (2014) 26–34. Safety concerns have been expressed, e.g., by M. Haagdorens et al., ‘Limbal Stem Cell Deficiency: Current Treatment Options and Emerging Therapies’, *Stem Cells International* (2016) 1–22.

<sup>83</sup> *Supra* note 3, p. 2.

<sup>84</sup> See also Directive 2001/83/EC, Art. 3(7). ATMPs are usually subject to the centralised procedure: Regulation 726/2004, Art. 3(1) and Annex 1a.

scheme is regulated on a national level and effectively applies to products that are produced on a one-off *ad hoc* basis for the treatment of an individual patient in accordance with a specific medical prescription. In Germany, for example, the hospital exemption is laid down in section 4b of the German Medicinal Products Act.<sup>85</sup> In contrast in the UK, there are two national schemes available for ATMPs: (1) the hospital exemption in regulation 171 of the Human Medicines Regulations 2012/1916 and (2) the ‘specials exemption’ in regulation 167 of the same Regulations, which allows for the supply of an ATMP under certain requirements to fulfil a patient’s ‘special needs’.<sup>86</sup>

In our view, however, the solution to the identified problems does not rest with national exemptions. First, the UK specials exemption, for example, will probably not apply to the cases under discussion, because the special needs test requires that there is no equivalent approved medicinal product available that can fulfil the special needs of the patient in question.<sup>87</sup> Secondly, the hospital exemption is exclusively for ATMPs and does not apply in cases of an OMP that is not designated as an ATMP at the same time. Thirdly, even if the requirements of a hospital (or specials) exemption in the respective EU Member State are met, an ATMP under such a national scheme would only be available to a small number of patients instead of all patients in Europe (as in the event of an EU marketing authorisation). Thus, even though the national exemptions would certainly benefit from harmonisation (cf. German hospital exemption with the UK hospital and special exemptions),<sup>88</sup> such reforms could not address the problems identified.

#### **4.2 New Principles for Assessing Similarity**

Above we highlighted some difficulties with the concept of a ‘similar medicinal product’ in Article 3(3)(b) of Commission Regulation 847/2000, which requires consideration of whether the second medicinal product contains a *similar active substance* and is intended for the *same therapeutic indication*. It seems to us that both limbs would

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<sup>85</sup> Medicinal Products Act (The Drug Law; Gesetz über den Verkehr mit Arzneimitteln, Arzneimittelgesetz – AMG) of 12 December 2005, Federal Law Gazette (BGBl) I, 3394.

<sup>86</sup> See also Directive 2001/83/EC, Art. 5(1).

<sup>87</sup> See MHRA, ‘The Supply of Unlicensed Medicinal Products (“Specials”)', s. 2.2, online at [www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/373505/The\\_supply\\_of\\_unlicensed\\_medicinal\\_products\\_\\_specials\\_.pdf](http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf), retrieved 11 January 2017.

<sup>88</sup> See also European Commission, ‘Report from the Commission to the European Parliament and the Council’ 28 March 2016, COM(2014) 188 final, ss. 4.2 and 5. See also *supra* note 21, pp. 7 and 8.

benefit from revision of their respective definitions.

#### 4.2.1 Similar Active Substance

The European Commission, in a consultation document released on 29 July 2016, has itself recognised the need to revisit the first limb of the definition. It proposes two amendments to Commission Regulation 847/2000: the first is to repeal the definition of ‘active substance’ in Article 3(3)(a) and the second is to revise the definition of ‘similar active substance’ in Article 3(3)(c).<sup>89</sup>

In principle, we welcome the first proposal. Since ‘active substance’ now has a more precise and detailed definition in Article 1(3a) of Directive 2001/83/EC, there is no need for the definition in Article 3(3)(a) of Commission Regulation 847/2000. The consultation document argues that Article 8(4) of Regulation 141/2000 expressly empowers the Commission to adopt definitions of ‘similar medicinal product’ and ‘clinical superiority’ in an implementing Regulation, but ‘does not empower the Commission to define the term “active substance”’.<sup>90</sup> With respect, it seems to us that such a power is implied. If it is permissible for the Commission to define ‘similar medicinal product’ by reference to an ‘active substance’, then it must be permissible for the Commission Regulation to provide or refer to a definition of ‘active substance’. The drawback of the Commission’s proposal is that since Directive 2001/83/EC is transposed into national law, EU Member States have a degree of leeway as to the exact definition to be adopted. This creates the possibility of divergence in the ambit of market exclusivity that is not tied to its rationale. In our view, it would be better if Article 3(3)(a) of Commission Regulation 847/2000 is not repealed but revised. Instead of providing its own definition of ‘active substance’, Article 3(3)(a) should define the term by reference to Article 1(3a) of the Directive. This approach has the advantage that the Commission Regulation is directly applicable in all EU Member States. A single definition among all Member States would contribute to a greater level of consistency and legal certainty. This proposal does not, as it might appear, undermine the decision of the European Parliament and the Council to place the definition on active substance in a Directive, rather than a Regulation, because our proposal would mean that the Directive’s definition is only directly applicable within the scope of Commission Regulation 847/2000.

We fully support the European Commission’s second proposal for

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<sup>89</sup> *Supra* note 9, pp. 2–4.

<sup>90</sup> *Ibid.*, lines 3 and 4.

change. The definition of ‘similar active substance’ in Article 3(3)(c) of Commission Regulation 847/2000 requires adaption to technical progress.<sup>91</sup> We do not propose to review the specific recommendations of the Commission here beyond noting that the proposed updates will address advances in the field of biological medicinal products including ATMPs and, by contributing to greater legal certainty, will make it easier for researchers/sponsors to predict whether an active substance will be considered similar under the current definition. We therefore welcome the Commission’s effort to consult the public and stakeholders on its proposal regarding the highly technical definition in Article 3(3)(c).

#### 4.2.2 Same Therapeutic Indication

We saw above (in 3.2) that in cases of related research where a second medicinal product contains a *similar active substance* to that contained in an authorised OMP, the *therapeutic indication* will be decisive to the assessment of whether two related medicinal products are similar. We sought to demonstrate the difficulties presented when applying the Commission Guideline to the effect that, in the event of an overlap of the target populations, the extent of that overlap will be a crucial factor to conclude that two medicinal products are intended for the same therapeutic indication.<sup>92</sup> It remains unclear *when* such overlap should be considered significant, i.e., *when* the competent assessing body is likely to come to the conclusion that a second medicinal product is intended for the same therapeutic indication. Such uncertainty as to whether researchers/sponsors will, after investing considerable time and effort in developing an OMP, be allowed to bring their product on the EU market does not promote the development of OMPs and is thus contrary to the aim of orphan incentives.

Encouraging investment in the research and development of OMPs requires transparency, consistency and appropriate predictability in the procedure for assessing similarity. If the principle for assessing the ‘same therapeutic indication’ criterion is retained, so the focus in cases of an overlap of the target populations remains on the extent of such overlap, clear guidance on when the competent assessing body should consider an overlap significant is needed. Indeed, for clarity, the European Commission should provide specific examples of significant overlaps of the target populations in the Commission Guideline. These examples should be updated at regular intervals to take account of scientific and technical developments.

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<sup>91</sup> *Ibid.*, p. 1.

<sup>92</sup> *Supra* note 56, s. 2.3, para. 2.

Clarifying statements of this type would contribute to a more transparent and consistent procedure for assessing similarity, but would not address the underlying problem. Applicants for a marketing authorisation for a second medicinal product would still depend on the interpretation by the competent assessing body as to whether it considers the overlap significant. Consequently, our preferred proposal is to abandon the need to assess the extent of the overlap of the target populations. Instead, we recommend that market exclusivity should be strictly tied to the approved target population of the OMP. That is to say, two medicinal products should only be regarded as intended for the same therapeutic indication in the area of overlap of the target populations. This would mean that where there is no overlap of the target populations, the two medicinal products would be regarded as having different therapeutic indications. We will now explain this further by applying it to the example above.

Holoclar and the second medicinal product have an overlap of target populations because both are intended to apply to adult patients with total unilateral LSCD due to physical or chemical ocular burns. Consequently, these two medicinal products would be regarded as having the same therapeutic indication with regard to that target population. This would mean the second medicinal product is, in this respect, similar to Holoclar. It follows that the second medicinal product could not be placed on the EU market during the 10-year period of market exclusivity for Holoclar for the treatment of adult patients with total unilateral LSCD due to physical or chemical ocular burns, unless one of the three derogations in Article 8(3) of Regulation 141/2000 applied.

Where there is no overlap of the target populations – i.e., for the treatment of patients with total unilateral LSCD due to causes other than physical or chemical ocular burns – the two medicinal products would be regarded as having different therapeutic indications. Since it is assumed that, in the present case, the second medicinal product is intended to be used to treat both adults and children (i.e., patients under the age of 18 years) with total unilateral LSCD, the second medicinal product also has a different therapeutic indication to Holoclar with regard to the treatment of children with total unilateral LSCD due to physical or chemical ocular burns. It follows that the CHMP would consider the second medicinal product – in this regard – as *not similar* to Holoclar. Consequently, provided that the quality, safety and efficacy of the second medicinal product could be shown, the European Commission could grant a marketing authorisation to the second medicinal product for the following therapeutic indication: Treatment of adult patients with total unilateral LSCD due to causes other than physical or chemical ocular

burns and treatment of children with total unilateral LSCD, including such due to physical or chemical ocular burns. The marketing authorisation holder (MAH) of the second OMP would then benefit from market exclusivity for that product for that approved indication.

This proposal has three main advantages compared to the current criterion for assessment of ‘same therapeutic indication’. *First*, it ensures a transparent and consistent assessment procedure. The clear division between overlap (= same therapeutic indication) and no overlap (= different therapeutic indications) simplifies the process. It makes the outcome predictable and thus contributes to greater planning security for researchers and sponsors of OMPs. *Secondly*, it produces a ‘win-win situation’: the MAH of the authorised OMP, the researcher/sponsor of the second medicinal product and the patients in Europe would benefit from our proposed approach. Applied to the example, the MAH for Holoclara would retain the benefit of market exclusivity for the approved indication until 19 February 2025.<sup>93</sup> In addition, the second medicinal product could be placed on the EU market to treat adult patients with total unilateral LSCD due to causes other than physical or chemical ocular burns and to treat children with total unilateral LSCD, including such due to physical or chemical ocular burns. The MAH of the second OMP would benefit himself from market exclusivity for that product for that approved indication. In contrast, there is only an ‘all or nothing’ solution under the current approach. Either the second medicinal product can be put on the EU market to treat patients with total unilateral LSCD (including such due to physical or chemical ocular burns) or not, depending on whether the CHMP considers the overlap of the target populations significant. Moreover, patients (adults and children) in Europe suffering from total unilateral LSCD due to causes other than physical or chemical ocular burns and children suffering from total unilateral LSCD due to physical or chemical ocular burns would gain access to the second product/treatment, which could cure their rare disease. *Thirdly*, our proposal is consistent with the aim of orphan incentives, because it encourages investment in the research and development of OMPs.

In order to implement our proposed approach, the Commission Guideline would need to be revised accordingly. In particular, we suggest that section 2.3 could be formulated as follows:<sup>94</sup>

The therapeutic indication of an orphan medicinal product is set by the marketing authorisation and must be subsumed under the

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<sup>93</sup> See *supra* note 69.

<sup>94</sup> The first sentence below draws on *supra* note 56.

(usually broader) designated orphan condition. If there is an overlap of the target populations, a medicinal product will be considered (compared to a currently authorised orphan medicinal product) as intended for the same therapeutic indication with regard to the overlap and otherwise considered to have a different therapeutic indication. This means that if the therapeutic indication of a currently authorised orphan medicinal product is A and the therapeutic indication of a medicinal product is A+B, then the two products will have the same therapeutic indication regarding A and different therapeutic indications regarding B.

Specific examples of various types of medicinal products (e.g., chemical medicinal products, biological medicinal products and radiopharmaceutical medicinal products) should additionally be provided.

#### **4.3 *Article 8(3)(c) of Regulation 141/2000 – Exception for Similar OMPs***

We also argued above (in 3.2) that a second applicant, whose medicinal product is a designated OMP and similar to an authorised OMP, will have difficulty establishing that one of the three derogations in Article 8(3) of Regulation 141/2000 applies. The first two derogations (consent or inability to supply sufficient quantities) are in the sphere of influence of the MAH for the original OMP, rather than the second applicant. The third derogation is hard to demonstrate in practice, even though it is in the hands of the second applicant to establish that the second medicinal product is more effective, safer or otherwise clinically superior. The derogation based on ‘clinical superiority’ in Article 8(3)(c) of Regulation 141/2000 has the potential to amount to an almost insurmountable hurdle for some researchers.

In line with the aim of supporting research, development and marketing with regard to OMPs, we thus recommend improved conditions for a demonstration of ‘clinical superiority’ for similar OMPs. Under Article 3(3)(d) of Commission Regulation 847/2000, ‘clinically superior’ is defined to mean that a second medicinal product is shown to have a significant diagnostic or therapeutic advantage over an authorised OMP in at least one of the three specified ways. Each of the three specified ways could be addressed to render the provision more suitable for the purpose of facilitating the developing and bringing OMPs on the EU market.

First, the specification of ‘greater efficacy’, in Article 3(3)(d)(1), refers to direct comparative clinical trials being ‘generally necessary’. This should, in our view, be further qualified by an explicit statement to

the effect that the nature of those clinical trials should take account of the particularities of the products in question, such as limitations on patient recruitment.

Secondly, ‘greater safety in a substantial portion of the target population(s)’, in Article 3(3)(d)(2), also refers to direct comparative clinical trials being ‘necessary’ in ‘some cases’. Our proposal, on which the Commission could usefully seek public and stakeholder input, would be to give the benefit of the doubt to a second OMP where (a) it is demonstrated to be at least as safe and (b) the CHMP consider it more likely than not, according to the standard of a prudently cautious and conscientious scientist in the relevant field of research, that the safety of the second product is greater. For example, it is generally recognised in the literature that a cell-based OMP that is totally animal free and manufactured in compliance with GMP is safer than a cell-based OMP with xenogeneic components, since the use of animal materials in tissue destined for human transplantation bears the risk of eliciting an immunologic response and producing interspecies pathogen transfer.<sup>95</sup> A prudently cautious and conscientious scientist in the relevant field of research would therefore probably assess an animal-free product that is manufactured under GMP conditions as more likely than not to be safer.<sup>96</sup> In other words, ‘greater safety’ based on the scientific literature might be presumed in this example once the second product is demonstrated to be at least as safe. This approach would give patient safety the highest priority, yet recognise that limitations on patient recruitment to clinical trials on OMPs can make it extremely difficult to demonstrate ‘greater safety in a substantial portion of the target population(s)’ statistically. If any risk to the patient can be minimised by using newly developed materials and/or methods to manufacture OMPs, it should be possible for such similar OMPs to be placed on the EU market to ensure, in accordance with the aim of orphan incentives, that patients suffering from rare diseases have access to the same quality of medicinal products as any other patient in the EU.

Thirdly, Article 3(3)(d)(3) refers to ‘exceptional cases’, in which the second ‘medicinal product otherwise makes a major contribution to diagnosis or to patient care’. This would benefit from specific examples

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<sup>95</sup> See for example EMA, ‘CHMP Guideline on Xenogeneic Cell-Based Medicinal Products’, EMEA/CHMP/CPWP/83508/2009, 22 October 2009, p. 4; *supra* note 72, p. 598; S. M. Sharma et al., ‘Comparative Analysis of Human-Derived Feeder Layers with 3T3 Fibroblasts for the Ex Vivo Expansion of Human Limbal and Oral Epithelium’, *Stem Cell Reviews and Reports* 8(3) (2012) 696–705; Haagdorens et al., *supra* note 82, pp. 5, 10.

<sup>96</sup> *Ibid.*

for similar OMPs.

For the implementation of our suggestions, we recommend that the European Commission should amend Article 3(3)(d) of Commission Regulation 847/2000 where necessary and explain the details in the Commission Guideline (particularly in section 3.3.2.3). Incorporating the details in the Commission Guideline (rather than in the Commission Regulation) has the advantage that – in cases of unexpected difficulties or major technological advances – the Commission Guideline could be amended faster.<sup>97</sup>

## 5 Conclusion

This article has analysed the extent to which an EU marketing authorisation of an OMP has an impact on related research. We have explained the negative effects of the current 10-year market exclusivity provision for researchers/sponsors seeking to obtain a marketing authorisation for their product. While defending and retaining that provision we have made two proposals: (i) new principles for assessing similarity and (ii) improved conditions for a demonstration of ‘clinical superiority’ for similar OMPs.

With regard to the first issue, we have supported the aims of the European Commission’s proposals of 29 July 2016. We have, however, gone beyond the Commission’s proposals by highlighting specific issues arising with regard to the criterion of ‘same therapeutic indication’. We demonstrated that in particular in cases of related research where a second medicinal product contains a ‘similar active substance’ to that contained in an authorised OMP, the therapeutic indication is decisive in order to assess whether two medicinal products are similar under Article 3(3)(b) of Commission Regulation 847/2000. We argued that in cases where there is an overlap of the target populations, the current principle of looking at the extent of such overlap in order to establish whether two medicinal products are intended for the same therapeutic indication should be abandoned, or at least clear guidance on when the competent assessing body should consider an overlap significant should be introduced. Our preferred proposal is for the competent assessing body to focus on the overlap of the target populations itself (instead of the extent of the overlap) and conclude that: (i) the two medicinal products are intended for the same therapeutic indication where there is overlap of the target populations and (ii) the two medicinal products have different

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<sup>97</sup> For the procedures see Art. 8(4) and (5) of Regulation 141/2000.

therapeutic indications where there is no overlap of the target populations.

We also argued that it is difficult for a second applicant of a similar medicinal product designated as an OMP to establish that one of the derogations in Article 8(3) of Regulation 141/2000 applies. In particular, the third derogation based on 'clinical superiority', although in the sphere of influence of the second applicant, is hard to demonstrate in practice. In accordance with the aim of orphan incentives, we have proposed clarification to provide improved conditions for a demonstration of 'clinical superiority' in relation to Article 3(3)(d) of Commission Regulation 847/2000.