

# Outcomes based pricing and reimbursement of innovative medicines with budgetary limitations

Discussion document for the multistakeholders meeting on pharmaceuticals ( Meeting DG GROW 12<sup>th</sup> September 2017)

## 1. Introduction

Health policies in the EU aim to increase the healthy life expectancy of citizens within the limits of the available public resources. In order to achieve this objective, there is a need to improve the quality, effectiveness, and efficiency of EU health systems.<sup>1</sup>

In addition, there is a continuous need for innovative health technologies, such as medicines, that help to substantially reduce morbidity and mortality, and improve quality of life.<sup>2</sup> However, these truly innovative technologies<sup>3</sup> usually come at an extra cost, and – given the requirement for efficiency and sustainability – it is of key importance to establish appropriate methods and procedures for pricing and reimbursement (P&R) of these technologies.

The increasing focus in our healthcare systems on outcomes that matter for patients may create new opportunities in this regard. P&R decisions for innovative technologies that account for the added value that those technologies deliver for patients and society overall, will encourage the continued search for truly innovative technologies. Value can thereby be defined as “the importance, worth, or usefulness of something”.<sup>4</sup> It is recognised that the value of a new medicine is determined by both disease and treatment related characteristics.<sup>5</sup> Indeed, if the impact of a disease on patients is high (severe symptoms, disability, reduced life expectancy etc.) and the medicine provides a substantial impact in reducing morbidity, improving quality of life or life expectancy, it can be considered of high value.

Furthermore, value does not necessarily mean “value for money”. The challenge for policy makers is to spend healthcare money wisely. Therefore, price and reimbursement levels of medicines should correspond with an acceptable “value for money” from a societal perspective.

<sup>1</sup> EU [Communication](#) on effective, accessible and resilient healthcare systems April 2014

<sup>2</sup> [Council Conclusions](#) on Innovation for the Benefit of Patients, December 2014

<sup>3</sup> Annemans L et al. Valorising and creating access to innovative medicines in the European Union. *Frontiers in Pharmacology*, 2011.

<sup>4</sup> <https://en.oxforddictionaries.com/definition/value>

<sup>5</sup> Moreno S and Ray J. The value of innovation under value-based pricing. *Journal of Market access and health policy*. 2014

Currently, the assessment and appraisal of value and “value for money” of innovative medicines show differences between EU Member States.<sup>6</sup> Decisions are hampered by the uncertainty related to the clinical and financial outcomes of these medicines at the time of market access. It is often not clear at that time to which extent their expected benefits will be observed in daily practice.

At the OECD Ministerial Meeting on ‘Next Generation of Health Reforms’ (17 January 2017), Ministers concluded that innovations can create opportunities to tackle waste and improve the efficiency of health systems, raise clinical standards, facilitate surveillance and boost research, and improve patient outcomes. However, they can also pose novel challenges: “Some effective and very costly new generation treatments change the treatment paradigm but have significant budget impact and wider implications for our health systems”. The Ministers stressed that health technology assessments can be a key instrument to provide evidence-based information on the impact of new technologies, such as on therapeutic value, other benefits, and cost.<sup>7</sup>

According to the EU subsidiarity principle, individual Member States have competence regarding P&R decisions. Yet, a set of common principles, together with a range of innovative pricing approaches and alignment on processes can contribute to improved patient access to innovative medicines in the EU. Co-operation amongst Member States and stakeholders is indeed of utmost importance to tackle health inequities and to reduce the divergence in health system outcomes.

This paper outlines an overview of the principles of “value based pricing” and reimbursement, followed by a discussion of the current uncertainty regarding clinical and financial outcomes at time of market access of innovations; this uncertainty is partly explained by the characteristics of the innovations themselves and the diseases for which they are developed but also partly by features of the healthcare system (financial incentives, and factors influencing physician and patient behaviour). Subsequently, a proposal is presented for outcomes based agreements that deal with this uncertainty and its causes. Such agreements, as part of a more comprehensive outcomes based approach to healthcare systems, require the co-operation of all stakeholders. The paper concludes with ten recommendations to realise this approach. These recommendations will hopefully form the basis for further discussion between all stakeholders on this crucial topic.

<sup>6</sup> Towards a harmonized EU assessment of the therapeutic value of medicines. European Parliament. Directorate General for internal policies, 2015.

<sup>7</sup> Ministerial Statement ‘The next generation of health reforms’. OECD Health Ministerial Meeting 17 January 2017

## 2. “Value based pricing”

In value based healthcare, the underlying premise is that healthcare interventions are rewarded according to the value they provide. This principle is based on the general economic concept that prices of new goods indicate the difference between what currently available goods offer and the outcomes that the new goods can provide.<sup>8</sup>

It has been argued that prices should better reflect investments for Research and Development (R&D), a logic which is sometimes referred to as “cost plus pricing”. Although this approach might at first sight seem fair, it raises a number of issues. Firstly, it may lead to the wrong incentives, in that the higher the R&D costs, the higher the price which could be justified. Secondly, investment costs for medicines that eventually do not make it to the final stage (because of insufficient effect or due to toxicity, or other reasons) must be amortised and factored into the cost of R&D, which may then lead to a perverse situation where a company with many failures could justify a higher price for a few products that make it to market authorisation. Finally, this approach does not sufficiently encourage true innovation. Irrespective of the benefit to patients, reward will be according to R&D costs.

Therefore, the basis for pricing negotiations for innovative medicines should be the medicine’s additional value to patients and society. High value then originates from substantially better treatment outcomes versus the actual standard of care. However, better outcomes should not be the sole criterion. For instance, from the work of Erik Nord, it appears that societal willingness to pay for new treatments is dependent on the degree of severity or suffering associated with the current situation.<sup>9</sup> This has also been confirmed in more recent work, such as in Shiroiwa et al (2016)<sup>10</sup> and Richardson et al (2016) where the latter suggest that higher willingness to pay is especially relevant for very severe conditions.<sup>11</sup> Value should therefore be defined by both disease and treatment related characteristics.<sup>12</sup> Treatment related characteristics are, for example, the impact of the treatment on quality of life, morbidity or life expectancy, as well as the size of that impact. Disease related characteristics are, for example, the severity of the condition, its life threatening nature, current treatment alternatives, the wider societal impact of the disease etc., all together referred to as medical or therapeutic need.

<sup>8</sup> Taylor D and Craig T. Value based pricing for NHS medicines: magic bullet, counterfeit treatment or the mixture as before? *Health Economics, Policy and Law* (2009), 4: 515–526

<sup>9</sup> Nord E. Concerns for the worse off: fair innings versus severity. *Social Science & Medicine* 60 (2005) 257–263

<sup>10</sup> Shiroiwa T, Saito S, Shimosuma K, Kodama S, Noto S, Fukuda T. Societal Preferences for Interventions with the Same Efficiency: Assessment and Application to Decision Making. *Appl Health Econ Health Policy*. 2016 Jun;14(3):375-85.

<sup>11</sup> Richardson J, Iezzi A, Maxwell A. How important is severity for the evaluation of health services: new evidence using the relative social willingness to pay instrument. *Eur J Health Econ*. 2016 Jul 25.

<sup>12</sup> Annemans L et al. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases. *OJRD* 2017 accepted for publication.

It is obvious then that in the interpretation of value, societal values such as equity and solidarity play an inevitable role and may also partly explain the differing approaches among Member States.

“Value based pricing” provides the benefit that innovation leading to true added value is encouraged, but several policy makers point to the risk that it could lead to unreasonable prices that endanger the sustainability of healthcare systems and access to patients. “The higher the value, the higher the price” principle does not contain any built-in limits of our society’s capacity to invest in health. In some disease areas such as cancer and hepatitis C, where very high value is obtained by new generations of innovative medicines and even more is expected from combination therapies, the risk of unsustainable prices is very apparent.<sup>13</sup>

Therefore, P&R decisions should also take into consideration the budget impact and affordability for the healthcare system and the individual patient. As medicines are not goods like any others, pricing of medicines requires a framework to balance incentives for innovative research with access for patients and long-term sustainability of healthcare systems based on solidarity.

Two additional elements are therefore of crucial importance in addition to value, as such:

- a. The cost-effectiveness in terms of a ratio between the net cost of the treatment and the net health benefits. Net cost means that predicted savings or additional costs elsewhere in the system or in society are explicitly taken into account, and that budget silos that prevent effective spending are removed. In the interpretation of cost-effectiveness it is important to have societal thresholds as well as benchmarks (i.e. other products offering a similar level of value). This is a first instrument against the limitless interpretation of “value based pricing”.
- b. The net impact on the healthcare budget. Even if a treatment is cost-effective, it does not mean automatically that it is affordable, either in the short or the long term.<sup>14</sup> The case of direct antiviral agents in the management of hepatitis C illustrates this. Even being cost-effective, the impact on the healthcare budget in countries with high prevalence of the disease inevitably influences the P&R decision. This is undoubtedly a matter of opportunity cost. Putting too much money in one basket, i.e. one disease, takes away the opportunity to help other patients. Horizon scanning and budget impact analyses are therefore required to assess the extent to which the healthcare system can afford to pay for the innovation. In this

<sup>13</sup> Vogler S et al. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. *Lancet Oncol* 2016; 17: 39–47

<sup>14</sup> Birch S, Gafni A; Information created to evade reality (ICER): things we should not look to for answers. *Pharmacoeconomics*. 2006;24(11):1121-31.

scenario, the possible offsets elsewhere in the system are to be taken into account as well.<sup>15</sup> Again, as with cost-effectiveness thresholds, a limit to society's ability to pay for innovation is built-in. It should also be acknowledged that several innovative medicines may have different indications and their value may differ between indications. In such a situation the total budget impact across indications should be considered.

The societal willingness to pay thresholds can differ between Member States, and they can be modulated depending on the disease burden<sup>16</sup> and the budget impact of the innovative medicine.<sup>17</sup> Hence, for a treatment in an area with a high burden, and with a low budget impact, the societal willingness to pay for additional health outcomes may be higher.<sup>18</sup> Again, specific characteristics of each country, such as ability to pay, epidemiological and cultural factors and societal values play a prominent role here.

When healthcare payers communicate explicitly about the societal limits of "value based pricing", it should be possible to reward value and at the same time account for affordability, strategic planning and investment. The industry should show that the value created through innovative medicines is beneficial to both industry and society, and that this is realised in a sustainable and affordable way.

### 3. Uncertainty

The above-mentioned criteria (treatment outcomes, disease burden, cost-effectiveness, and budget impact) are the typical criteria that are used to support P&R decisions in many countries.<sup>19</sup> In fact, they form the core criteria of Health Technology Assessment (HTA). In a typical process, HTA helps healthcare payers to make decisions based on HTA criteria, while the latter make the decisions based on an appraisal of all elements and following established procedures.

However, the challenge is that most of the outlined criteria are subject to uncertainty at the time of market access. There may be different reasons for such uncertainty. For instance, the absence of long term evidence at the time of launch, or the fact that patients in clinical trials do not fully correspond with patients in daily practice. However, also the way in which healthcare providers will apply an innovation in daily practice

<sup>15</sup> Niezen et al. Finding legitimacy for the role of budget impact in drug reimbursement decisions. *Int J Technol Assess Health Care*. 2009 Jan;25(1):49-55

<sup>16</sup> Zorginstituut Nederland (ZIN). *Kosteneffectiviteit in de praktijk (cost-effectiveness in practice)*; 26 June 2015

<sup>17</sup> Griffiths EA et al. Acceptance of health technology assessment submissions with incremental cost-effectiveness ratios above the cost-effectiveness threshold. *Clinicoecon Outcomes Res*. 2015 Aug 31;7:463-76

<sup>18</sup> Paulden M et al. Value-Based Reimbursement Decisions for Orphan Drugs: A Scoping Review and Decision Framework. *PharmacoEconomics* (2015) 33:255–269

<sup>19</sup> Franken M. Decision making in drug reimbursement. PhD Thesis. Erasmus University Rotterdam, 2014

(patient selection, modalities of use etc.) and the presence or lack of incentives for correct use can substantially impact outcomes.<sup>20</sup>

Generally, uncertainty can be divided into uncertainty about the expected health outcomes and uncertainty about the financial outcomes. Both types of uncertainty can be due to either factors related to the medicine and the way it was developed, as well as factors related to the performance of the healthcare system.

### ***Uncertainty about expected health outcomes***

At the time of market access, there is generally evidence on efficacy and safety, often also on relative efficacy, and rarely on relative effectiveness. The latter can be defined as the extent to which an intervention does more good than harm, compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of healthcare practice.<sup>21</sup>

Given that definition, it is no surprise that at the time of market access effectiveness is often *predicted*. For instance, there can be a predicted effect on morbidity or mortality while not yet shown in a trial, because the latter was focussing only on an intermediate endpoint. Or, there can already be an observed impact on morbidity/mortality in a one-year trial but no evidence on the sustainability of that effect, or the need for further treatment to maintain the effect. Or the medicine seems to work only in a proportion of patients in the trial, but it is difficult to clearly define how many patients will respond in real life. Other examples refer to uncertainty about compliance and persistence on treatment in daily practice.

### ***Uncertainty about financial outcomes***

At the time of market access, it is very difficult to forecast how many patients will be treated with the innovative medicine, and how long they will stay on the medicine. For instance, more/less patients than expected may receive the medicine which will increase/decrease the volume of sales. Or it may be used for a longer/shorter period of time and at an average higher/lower dosage than was originally estimated.

Note that the uncertainty described above about health outcomes may also lead to financial uncertainty. Indeed, if the savings in the healthcare system are not as large as predicted, the total financial impact of the medicine will be higher than predicted.

At the time when the initial decisions on P&R and coverage of medicines need to be made, many health and financial outcomes of these medicines are thus *predicted*. The

<sup>20</sup> Ferraro and Kanavos. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med. 2015 Jan;124:39-47.

<sup>21</sup> High level Pharmaceutical Forum 2005 – 2008 Final Report

challenge is to deal with this uncertainty. Outcomes based managed entry agreements (OBMEA) have been proposed as one solution for this challenge.

It should also be clear from the above that not only the features of the innovation and of the disease for which it has been developed affect uncertainty, but also the way clinicians, institutions, patients etc. use the medicine in daily practice will affect its outcomes. Prescribers have the decision-making power in respect of prescribing patterns, hospitals and prescribers may not have the right incentives for correct use, and patients may influence outcomes through their behaviour (e.g. lack of compliance and persistence on therapy).

Hence, proper solutions towards dynamic outcomes based approaches to pricing and reimbursement of innovative medicines should explicitly include health system reforms so that the right incentives are in place to enable the correct use of value adding medicines.

#### 4. Outcomes based managed entry agreements

Outcomes based managed entry agreements (OBMEA) allow the price and reimbursement conditions of medicines to change over time in function of follow up data of the original trials or observed health and financial outcomes in daily practice.<sup>22</sup>

Practically this would mean that if a price and coverage level is accepted and agreed upon at the first submission, this level can be reviewed later based on evidence from daily practice. Hence, at some time point (or time points – see below) in the future a *verification* of the predicted outcomes will be required. For some diseases the first of these points in time (the first “point of verification”) may be less than one year from the time of launch, while for other situations (such as adjuvant treatment for cancer) the effectiveness in real practice will only be available many years later. In the latter situation, intermediate time-points and end-points could be defined to obtain at least some evidence of effectiveness. The basic idea behind outcomes based agreements is that in function of the results at the “point of verification”, the initial price and reimbursement conditions will be affected. This of course requires that there is a clear definition of which results are expected, taking into account the nature of the real life population and its difference with the trial population.

Several proposed taxonomies on outcomes based managed entry agreements have been published.<sup>23 24</sup> Basically there are two types of such agreements:

<sup>22</sup> Carlson JJ et al. Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers. *Appl Health Econ Health Policy*. 2014 Jun;12(3):231-8

<sup>23</sup> Carlson JJ et al. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*. 2010 Aug;96(3):179-90.

### ***Coverage upon evidence development (CED)***

In this type of agreement, the medicine is covered from the start, at a negotiated P&R level, and for a well-defined patient population. The coverage is temporary, up to the point of verification. At that point, the originally predicted outcomes on a population level are compared with the actually observed outcomes in daily practice, or with follow up data and hence long term evidence from clinical trials. As from that point P&R conditions can be modified. Hence, the consequences of this type of agreement occur beyond the point of verification.

### ***Performance Linked Reimbursement***

In case of performance linked reimbursement the medicine is also covered from the start, at a given P&R level, and for a well-defined patient population. However, the comparison between predicted and observed outcomes has consequences for the P&R conditions already in the period between launch and the point of verification. Moreover, in this type of agreement, both the patient level and the population level can be the subject of observation. On a population level, if the outcomes at the point of verification are not as good as the predicted ones (and ideally accounting for patient characteristics), there will be a pay-back by the manufacturer of part of the money received within the period between launch and point of verification. Hence the consequences at the point of verification are retro-active.

On a patient level, for every patient for whom the medicine does not achieve a particular expected effect, some type of immediate pay-back is foreseen. Hence the consequences are immediate. This type of agreement is often referred to as “no cure no pay”.

As suggested earlier, in principle, there may even be more of such points of verification, which makes the decision-making process on pricing and reimbursement a continuously evolving and dynamic process.

Several issues have been observed with outcomes based managed entry agreements.<sup>25</sup> They refer to the quality of the data (including the presence of confounders), the quality of the contract, the burden of the entire process and data governance issues.

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<sup>24</sup> Launois R et al. Health economic value of an innovation: delimiting the scope and framework of future market entry agreements. *J. Mark Access Health Policy*. 2014 Jun 23;2.

<sup>25</sup> Ferrario A, Kanavos P. *Soc Sci Med*. 2015 Jan;124:39-47.



Regarding the quality of the *data*, there may be an issue of missing data, which leads to biased estimates of real world performance. Also, many confounders may influence the final outcomes in real life. Patient co-morbidities, patient behaviour (non-adherence), physician prescribing patterns etc. are just a few of these. Hence, the agreements need to build in exceptions, i.e. situations whereby the agreement is not valid. However, it also means that health system reforms and partnerships between stakeholders should aim at improving prescribing patterns and adherence via educational initiatives and/or financial incentives. Therefore, when dealing with patient access to value adding innovative treatments, policy makers should consider organisational changes, adapted healthcare processes, and financial incentives that allow the correct use of those innovations in the right patients.

The quality of the *contract* relates to the selection and clear definition of indicator(s) to be assessed, the clear communication about the consequences if expectations are not met, and the list of abovementioned exceptions and engagements from both parties to work together to improve prescriber behaviour and patient adherence. Physicians, hospitals and payers also have a risk of conflict of interest, when individual patient outcomes, as documented by them, are directly linked to financial consequences affecting them. This is an argument to include these other parties in the negotiations about these contracts. Finally, in chronic conditions, the nature of the outcomes in the long run does not match with the short term budgetary logic and concerns of payers. An agreement not accounting for this issue will lead to mistrust and will fail.

The administrative burden refers to the additional workload for physicians, hospitals, payers and manufacturers. However, it may also be argued that the firm collection of data will help to enable clinical practice and by consequence health system performance.

Finally, data governance issues refer to scientific rigour of data management and analysis, the lack of access to and availability of the data, the cost of collecting the data, integrity and privacy issues, and poor standards for collaboration on data access.

Outcomes based managed entry agreements may be promising to deal with the challenge of uncertainty at the time of market access, but it is also clear from the above that many practical issues hamper their use. Hence, these agreements are not supposed to become the new norm. Carefully balancing pros and cons, calculating the cost of the entire process and balancing this cost with the benefits of better dealing with the uncertainty is crucial. Techniques looking at the expected value of perfect information might be useful here, but their systematic approach has not yet been supported by evidence.

## 5. Discussion and recommendations on outcomes-based agreements

This paper started by describing how a decision framework for the assessment of innovative medicines for P&R purposes should be based on multiple criteria: added therapeutical value, therapeutic need, cost-effectiveness and budget impact. Decisions should be outcomes based in line with the trend towards outcomes based healthcare policies.

It was further shown that in an outcomes based assessment of new medicines, there is significant uncertainty regarding these outcomes (both health related and financial) at the time of initial assessment, which may be explained by characteristics of the healthcare system, prescribers and patients. Most outcomes at that point in time therefore rely on predictions. The challenge for health policy makers is to deal with this uncertainty, and outcomes based managed entry agreements have been put forward as a possible solution for this challenge, though it was also argued that it would not become the new norm. These agreements, when considered useful, allow the price and reimbursement conditions of medicines to change over time in accordance with observed health and financial outcomes in daily practice. They may be helpful in accelerating access to valuable innovative medicines while at the same time improving health system performance.

However, these agreements are subject to several issues related to the quality of the real world data, the quality of the contract, the burden of the entire process and data governance issues. As a consequence, there is a risk that they will increase instability rather than solve it.

Partnerships can play a critical role in addressing the challenges with outcomes based agreements, in particular to collect and understand the data and the drivers of variation and then define a relevant set of interventions for an integrated solution.

At the OECD Ministerial on Next Generation of Health Reforms (17 January 2017), Ministers indeed concluded “that we should work together to generate evidence on the effectiveness of treatments taking into consideration the real world, so that we can make informed decisions about the adoption and use of new technologies.”<sup>26</sup>

Therefore, to move forward, we have developed the following recommendations to outline general principles which if adhered to by policy makers in different Member States, can help achieve more efficiency and consistency in the outcomes based assessment of new health technologies and avoid duplication of efforts. Ultimately, the aim must be to realise better patient access to value adding innovations at affordable prices. The following principles/recommendations are proposed.

<sup>26</sup> Ministerial Statement ‘The next generation of health reforms’. OECD Health Ministerial Meeting 17 January 2017

1. Outcomes based managed entry agreements are not the new norm. The level of uncertainty should determine the usefulness of an agreement as well as the resulting benefit for the healthcare system. Techniques such as 'Expected Value of Perfect Information' can be used to assess the balance between the costs and benefits of these agreements.
2. For those situations where an agreement is considered useful, an appropriate study and research design is needed to address the specific uncertainties of each case. The question should not be 'we have data, what shall we do with it?', but 'we have a research question, which data do we need to answer that question?'
3. For outcomes based approaches in healthcare to be effective, it is crucial to have well worked out common standards for efficient and high quality data collection and analysis, which requires high performing IT systems. Although not the key topic of this paper, it is clear that more governance is required for the collection and use of real world data.
4. The process to come to an outcomes based managed entry agreement should begin with the use of early dialogues between payers, regulators and manufacturers. Early dialogues need to start before medicines enter into Phase III of development and should make clear what evidence will be available at time of launch and identify the level of uncertainty. The appropriate format of these early dialogues is currently a matter of debate. The EU and Member States can learn from the current pilot projects to propose a systematic application of early dialogues informing value based decisions.
5. The process of outcomes based managed entry agreements should be a dynamic one with a continuum of evidence generation, and it should be made clear at each stage what evidence is required for the next stage. This will of course depend on the degree and type of initial uncertainty that has been identified. P&R levels can also be adjusted to better account for the use of a medicine in different indications.
6. In each step of this process, the implications of failing to meet the requirements and expectations should also be agreed in advance.
7. It is important that the agreements describe as clearly as possible which, and how many, patients can and will be treated once the medicine is on the market.
8. In such outcomes based agreements, it should also be envisaged that P&R levels may initially be low compared to the anticipated value, and may only increase when more evidence comes in. However, it should be noted that in the current system International Reference Pricing frustrates this approach.
9. It is important that the agreements go hand in hand with training and education of healthcare providers, promote stakeholder partnerships and incentivise health

system reforms to allow the right financial incentives to make sure that the medicines are used correctly and to guide health system performance evaluation. This means that besides payers and industry, prescribers and patients should also take part in the discussions preceding the contract.

10. Agreements should not only be considered on an individual country level. There are opportunities for multi-country agreements, even with differential price levels. We refer with this regard to the literature on differential pricing.

The principles for outcomes based agreements outlined above rely on systematic cooperation and partnership between different stakeholders (patients, prescribers, regulators, payers and industry). By following these recommendations, we believe that outcomes based approaches, including managed entry agreements when appropriate, can play a role in improving and possibly accelerating access of valuable innovative medicines to patients in need and improving the healthcare system performance.

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