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IN NEED FOR A MODERN DAEDALUS? THE CHALLENGING REGULATORY PATH FOR MARKETING GENE THERAPY MEDICINAL PRODUCTS IN CHINA AND EUROPE

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Abstract: This article highlights the regulatory challenges of the assessment process of Gene Therapy Medicinal Products. It also addresses the puzzling institutional maze that influences the regulatory path for the marketing of these products as shown through various examples in the European Union and in China.

Main text:

Advanced therapies raise critical questions, especially concerning their pre-market evaluation, which could differ greatly between regions worldwide, and in particular between Europe and China.

After years of hopes and disappointments in the field of gene therapy where failures gave rise to high effervescence widely relayed by the media at the detriment

of rare successes, few Gene Therapy Medicinal Products (GTMP), (the use of genes to treat or prevent a disease), have ever reached the market. In 2003 Gendicine was approved by the Chinese State Food and Drug Administration (SFDA). It became the first GTMP to be marketed in the world. Its European counterpart, Advexin, as well as Cerepro did not obtain European marketing authorization. Almost ten years later, in October 2012, Glybera was finally granted marketing authorization by the European Commission after scientific assessment by the European Medicines Agency (EMA) (Table). After a complex regulatory process it became the first GTMP to be approved in Western countries. Finally, two new GTMP have obtained a marketing authorization in the European Union (EU), Imlygic in December 2015 and Strimvelis in May 2016. Although approvals of these GTMP have mainly been presented as a huge step forward for patients' treatments and for the development of GTMP in general, no publication has addressed the major challenges present in the regulatory processes as revealed by the examples of these products both in China and in the European Union.

Table: GTMP regulatory assessment in the world

	Gendicine®	Oncorine®	Glybera®	Imlygic®	Strimvelis®	Advexin®	Cerepro®
(expected) Use	Head and neck cancers	Head and neck cancers	Lipoprotein lipase deficiency	Skin cancer (melanoma)	Severe combined immuno-deficiency	Li- Fraumeni cancer	High- grade glioma
Marketing authorisation holder or applicant	SiBiono GeneTech Co.	Shanghai Sunway Biotech Co. Ltd.	Amsterdam Molecular Therapeutics B.V.> UniQure Biopharma B.V.	Amgen Europe B.V.	GlaxoSmith-Kline (GSK)	Gendux Molecular Ltd.	Ark Therapeutics
Targeted market	China	China	EU	EU	EU	EU	EU
Regulators	SFDA	SFDA	EMA	EMA	EMA	EMA	EMA
Marketing assessment results	"Production permit" 2004 (Regularly renewed)	"Production permit" 2006 (Regularly renewed)	Marketing authorisation under exceptional circumstances October 2012	Marketing authorisation December 2015	Marketing authorisation May 2016	Application withdrawal December 2008	Application withdrawal March 2010

Regulatory paths for new drug approval

In the EU, the commercialization of GTMP relies on a marketing authorization which involves both the European Medicine Agency (EMA) and the European

Commission. As part of a specific regulation[1], the EMA, in charge of the evaluation process of new drugs, has set up a new specific and multidisciplinary committee to assess advanced therapy medicinal products, including GTMP, called the Committee for Advanced Therapies (CAT). In the EU, a regulation is a powerful legal harmonization instrument; it directly applies "as is" in the various EU Member States and unlike EU directives, it does not require a specific transposition into national legal systems. One of the CAT tasks is to formulate draft opinions on the quality, safety and efficacy of GTMP for final opinion by the Committee for Medicinal Products for Human Use (CHMP). Scientific experts have a main role in the assessment of risks and benefits linked to the use of the products. The final decision of granting marketing authorization is in the remit of the European Commission. This political body takes the final decision integrating other dimensions above and beyond the scientific evaluation.

In China, the SFDA is the only competent organization to evaluate the safety, efficacy and quality of drugs for marketing, and has the power to decide whether or not a product is approved[2]. A registration approval for the manufacture of the new drug is needed for market access. It involves obtaining the following approvals by the SFDA: new drug certificate, new drug registration certificate and drug Good Manufacturing Practice certificate[3]. Within the SFDA, the Center of Drug Evaluation which organizes panels of experts is in charge of the technical assessment of applications but the final decision is taken by the SFDA. Since February 22nd, 2013, the SFDA has been restructured and renamed the China Food and Drug Administration (CFDA). It became a ministerial- level agency to improve food and drug safety[4], and included several proposals "to boost confidence in the drug review and approval process as well as help promote regulatory oversight"[5], as deemed necessary[6].

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[1] Regulation (EC) N°1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) N°726/2004 OJ L324, 10/12/2007, p.121.
[2] Article 3, SFDA Order N° 28, Provisions for drug registration, 01/10/2007.
[3] H. Yin, Regulations and procedures for new drug evaluation and approval in China, Hum. Gene Ther. 17, 970-974 (2006).
[4] China State sponsored news-site 'xinhuanet': Bi Mingxin, China gets stronger food, drug regulator, March 22nd, 2013: http://news.xinhuanet.com/english/china/2013-03/22/c_132253914.htm (Access date 6th October 2014).
[5] H. Jia, China overhauls drug regulation agency, Nature Biotechnol. 31, 5: 375 (2013).
[6] Gareth Macdonald, SFDA aims to stimulate R&D, accelerate approvals and improve distribution practices, 5 March 2013, in- Pharma Technologist. Com website: http://www.in-

Assessment process of GTMP

Among the GTMP that have been assessed at this time, we target our analysis on those that aimed to reach the European or Chinese markets (although it should be noted that Rexin reached the Philippines' market in 2007 to treat all chemotherapy resistant solid tumors).

Gendicine and Oncorine

Since 1999, the development of Gendicine and Oncorine was has been financially supported through several Chinese government plans. For Gendicine, the SFDA delivered the Biological type I New Drug Certificate in October 2001, the Production Permit in January 2004, and the Drug GMP Certificate in March 2004. Gendicine also obtained the National Key New Product Certificate in 2005 issued jointly by the Ministry of Science & Technology, the Ministry of Commerce, the General Administration of Quality Supervision, Inspection & Quarantine and the Bureau of Environmental Protection. Oncorine obtained the Biological type I New Drug Certificate in November 2005, the Drug GMP Certificate and the Production Permit in 2006. Since 2004 and 2006, the Production Permits of Gendicine and Oncorine have been regularly renewed.

Glybera

Amsterdam Molecular Therapeutics B.V. applied for marketing authorization at the EMA in October 2009. Before the process was completed the applicant changed from Amsterdam Molecular Therapeutics to UniQure Biopharma. In June 2011, the CAT and CHMP adopted negative opinions because of a lack of evidence of long-lasting benefit in the patients studied and a lack of reduction in the rate of pancreatitis (the clinically relevant endpoint). Additionally they had concerns over the risks linked to the associated immunosuppressive treatment. The company requested a re-examination. After several procedural steps, the CAT adopted in October 2011 a positive opinion conditioned by the restriction of the indication. But, the CHMP maintained its previous negative opinion concluding that benefits did not outweigh the risks. In January 2012, the European Commission requested a re-evaluation in a restricted group of patients with severe or multiple pancreatitis episodes. In April

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pharmatechnologist.com/Regulatory-Safety/SFDA-Aims-to-Stimulate-R-D-Accelerate-Approvals-and-Improve-Distribution-Practices (Access date 6th October 2014).

2012, the CHMP gave a third negative opinion. However, for procedural reasons it was invalidated and a new examination was performed; it was conducted in June 2012 and resulted in a final positive opinion. However, 15 CHMP members (out of 32) had a divergent opinion and considered that efficacy and safety had not been sufficiently demonstrated. Finally, the European Commission granted a marketing authorization under exceptional circumstances to Glybera; these include specific obligations for post-authorization measures (such as the setting up of a long term surveillance of patients) to be conducted in a specified timeframe[7].

Advexin and Cerepro

Both Gendux Molecular Ltd for Advexin and Ark Therapeutics for Cerepro withdrew their applications for marketing authorization at the EMA. The former specified that the company's marketing strategy had changed[8] while the latter admitted it was not able to provide meaningful evidence of benefits compared to the risks[9]. At that time, the CHMP was about to give a negative provisional opinion for Advexin as it had concerns about the lack of evidence regarding the benefits and safety of the product for patients, for people in close contact with them and for the environment[10]. Regarding Cerepro, the CHMP had already delivered a negative opinion. Following a request of re-examination by the company, the CHMP was about to give a new negative opinion due to the lack of effectiveness which caused an emphasis on the concerns regarding side effects[11].

Imlygic and Strimvelis

On 28 August 2014, Amgen Europe B.V. submitted a marketing authorization application to the EMA for Imlygic. Its indication is the treatment of adults with

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[7] Glybera European Public Assessment Report, European Medicines Agency (EMA/882900/2011, 2012; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002145/WC500135476.pdf).

[8] Letter of withdrawal for Advexin (Gendux Molecular Limited, 2008; http://www.emea.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500063082.pdf).

[9] Letter of withdrawal for Cerepro (Ark Therapeutics, 2009; http://www.ema.europa.eu/docs/en_GB/document_library/Other/human/001103/WC500076159.pdf).

[10] Withdrawal Assessment Report For Advexin, European Medicines Agency (EMEA/692328/2008; http://www.emea.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500063080.pdf).

[11] Withdrawal Assessment Report For Cerepro, European Medicines Agency (EMA/CHMP/798830/2009; http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2011/02/WC500101545.pdf).

melanoma that is regionally or distantly metastatic. It obtained a marketing authorisation on 16 December 2015 after positive opinions of the CAT and the CHMP issued both in October 2015. The same month, on 27 October 2015, the US Food and Drug Administration have approved Imlygic for the US market.

Strimvelis was designated as an orphan medicinal product for the treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency in the EU on 26 August 2016. GlaxoSmithKline Trading Services submitted an application for Marketing Authorisation to the EMA for Strimvelis on 1 May 2015. One year later (on 26 May 2016), it obtained a marketing authorization after positive opinions of both the CAT and the CHMP, respectively issued in March and April 2016.

Contrary to the other GTMP, Imlygic and Strimvelis did not raise particular concerns during their scientific evaluation although one divergent position was expressed for efficacy and safety reasons regarding the marketing authoirsation of Imlygic[12].

All the other decisions relied on scientific evaluations which resulted in concerns that were greater regarding the drugs' efficacy than their safety. These decisions, both in Europe and in China, were also largely influenced by other types of variables, such as economic, political and ethical considerations.

The scientific evaluation of GTMP: what prevails efficacy or safety?

Both in China and in the EU, the scientific evaluation of GTMP based on the assessment of the quality, safety and efficacy of the product is difficult even though experts are involved in the process. Based on the media focus on negative outcomes of the use of GTMPs, one could think that the most important challenge of GTMP meeting evaluation criteria would be their safety, but in fact, showing the efficacy of these products has also been shown to be problematic. The approval of Gendicine has been criticized by Western countries as efficacy was based on tumor shrinkage rather than extension of patient lifetime[13]. A Greater emphasis may have been placed on

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[12] Annex 1, Imlygic European Public Assessment Report, European Medicines Agency, EMA/734400/2015, p. 150 ; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002771/WC500201082.pdf).

[13] M. L. Edelstein, M. R. Abedi, J. Winxon, Gene therapy clinical trials worldwide to 2007- an update, The Journal of Gene Medicine, 9: 833-842, DOI: 10.1002/jgm.1100 (2007).

safety than on efficacy. Meanwhile safety and lack of transparency on studies' results have also been challenged. Moreover in the EU, Glybera, Advexin and Cerepro suffered from several negative (provisional) opinions at the EMA's relevant committees also regarding the lack of proven efficacy. For all these GTMP, the concerns raised have been linked to the lack of data due to the low number of patients involved in clinical trials. Given that Advexin, Cerepro and Glybera, have been designated as orphan drugs in the EU, it is not surprising that they have this problem. The questioning on efficacy of GTMP challenged the benefits/risks balance: should GTMP considered safe be authorized if their efficacy is limited? Interestingly in the USA, the Advexin application file was refused as not complete while Glybera, in December 2015, abandoned its plans to win the US market after the US Food and Drug Administration indicated it would require additional clinical studies for the product[14]. It seems the acceptability threshold may differ according to the national agencies.

Other influences beyond the scientific evaluation of GTMP

When scientific assessments do not give a clear answer, other dimensions are taken into account and this is particularly true for GTMP. First, the marketing authorization is a *political decision* deemed to represent what is acceptable for society. Both in China and in the EU, the political decisions played a major role in the marketing authorization of Gendicine, Oncorine and Glybera. Second, *economics* is a main dimension. As "the global gene therapy industry has the potential to become a multi-million dollar industry by the end of 2017 as new products […] may enter the market to boost the growth."[15], the race is launched for the leadership in this field. Whereas China authorized the first gene therapy in the world, the EU adopted a specific regulation aiming to enhance competitiveness of European enterprises developing advanced therapies. The authorization of Glybera demonstrates that a marketing authorization can be obtained for GTMP in the EU[16]. But going through the whole regulatory process is complex, costly and time consuming. When withdrawing its application for Advexin, Gendux Molecular Ltd gave the argument of

[14] FDAnews Drug Daily Bulletin, UniQure Won't Seek U.S. Regulatory Approval for Glybera Gene Therapy Program, 9 December 2015 : http://www.fdanews.com/articles/174384-uniqure-wont-seek-us-regulatory-approval-for-glybera-gene-therapy-program
[15] Global Gene Therapy Market Anlaysis, Global Biological Therapy Industry (2013).
[16] Geoff Watts, Gene therapy to be authorised for first time in EU, BMJ 2012: 345.

limited resources to face the regulatory demand. After several negative opinions of the CHMP, Amsterdam Molecular Therapeutics stopped investment in Glybera and transferred gene therapy assets to Uniqure[17]. Moreover, the price of GTMP will be a high burden. Glybera "could cost as much as $1.6 million for the single injection necessary to confer lifetime therapy", a pricing that would be inappropriate for more common diseases[18]. Finally, *ethical considerations* may also influence marketing authorization of GTMP. Medical tourism is an issue for patients 'safety and for the environment. Despite the lack of clear data on its real extent, it seems that 300 to 600 patients travelled to China for Gendicine[19]. This very complex issue gives rise to large bioethical discussions that will not be developed in this paper notably as many countries, including the emerging ones, target the global health care market.

A new era for the regulatory support to GTMP development?

While no new GTMP seems to have been approved in China from the approval of Gendicine and Oncorine, it appears the two new GTMP authorised in 2015 and in 2016 in the EU did not raise so much concern during their assessment. Moreover, the main issue seems to have been redirected towards the effective access to innovative drugs, on the basis of cost-effectiveness in the context of Healh Technology Assessment[20]. Indeed, although Glybera was authorized in 2012, it has been administered to one patient only in September 2015 in Germany and it is not reimbursed by national insurances in the EU. Known as the 'one million drug'[21], the Glybera's cost- effectiveness ratio has not been considered acceptable by the French, German and Dutch authorities.

That is why, the current trend is to develop new regulary tool to support medicines development as well as early access. Chinese reforms aim notably to emphasize the clinical value of innovative drugs, to encourage the development of

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[17] N. Moran, First gene therapy nears landmark European market authorization, Nature Biotechnol. 30, 807–809 (2012).

[18] J. Whalen, Gene-therapy approval marks major milestone, Wall Street Journal (November 3, 2012), p. B3. Cited in Christopher H. Evansa, Steven C. Ghivizzanib, Paul D. Robbins, Arthritis gene therapy and its tortuous path into the clinic, Translational Research, Volume 161, Issue 4, p. 205-216.

[19] L. C. M. Kaptein, Y. Li and G. Wagemaker, Gene Therapy in China from a Dutch perspectives (report commissioned by the Netherlands Commission on Genetic Modification, 2010).

[20] A. Mahalatchimy, Reimbursement of cell- based regenerative therapy in the UK and France, Medical Law Review, Vol. 24, Issue 2 (Spring 2016), pp. 234-258, doi: 10.1093/medlaw/fww009, First published online: April 15, 2016.

21 Morrison C., $1-million price tag set for Glybera gene therapy. Nat Biotechnol. 2015 Mar;33(3):217-8. doi: 10.1038/nbt0315-217.

drugs that answer clinical needs and have a better therapeutic effect, through a speed-up review[22]. Similarly, the EMA adopted the PRIority Medicine scheme, an enhanced early dialogue to facilitate accelerated assessment for PRIority Medicines[23]. It is also developing the Adaptive Pathways concept: "a prospectively planned, iterative approach to bringing medicines to market. The iterative development plan will initially target the development to a well-defined group of patients that is likely to benefit most from the treatment. This is followed by iterative phases of evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available"[24]. The latter aims notably to reduce the gap between market approval and reimbursement decision for patients to have real and earlier access to these new medicines. However, here again, safety seems to appear as a secondary criterion as long as "safe access" could be claimed instead of "early access".

The development of gene therapy medicinal products is clearly a race as it is shown with Chinese scientists being, again in the field of gene therapy, the first to use the CRISPR- CAS9 gene- editing technique in humans[25].

Thus, it is clear that approvals do not rely only on scientific assessment and include other factors. If a country approves a GTMP, patients will benefit from new treatments which could lead toward less medical tourism out of that country. However, the question remains: will these patients really have access to effective drugs? Regarding the efficacy criterion, collaboration between EMA and CFDA is necessary for the benefits of patients. For drugs focused on rare diseases, it would permit to have a higher number of patients to assess the therapeutic effect. Moreover, a lot of data are generated from Gendicine in China that would be useful worldwide for the future of gene therapy if transparency is improved. Even though the EMA supports the European Commission's collaboration with China, regulators agreements are not yet developed at a scale and place that would match the level of scientific

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[22] CFDA, [Ideas on deepening the reform of pharmaceutical review and approval and further encourage innovation], 26 February 2013 (In Chinese; http://www.sfda.gov.cn/WS01/CL0051/78609.html).
[23] EMA, Enhanced early dialogue to facilitate accelerated assessment for PRIority MEdicines, 25 February 2016, EMA/CHMP/57760/2015.
[24] EMA, Final report on the adaptive pathways pilot, 28 July 2016, EMA/276376/2016.
[25] David Cyranoski, Chinese scientists to pioneer first human CRISPR trial, Nature 535, 476–477 (28 July 2016) doi:10.1038/nature.2016.20302.

collaboration. To achieve translational medicine, all dimensions at stake including the regulatory ones needs to be collaboratively developed[26].

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[26] E. Meslin, A. Blasimme, A. Cambon-Thomsen Mapping the Translational Science Policy 'Valley of Death', Clin Transl Med. Jul 27, 2(1):14 (2013).