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REVIEWS

Science and Society

Development and Regulation of Gene and Cell-Based Therapies in Europe: A Quantification and Reflection

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Gene and cell-based therapies (GCTs) are said to hold great promise as treatments for previously untreatable and high-burden diseases. Here, we provide insight into GCT development and regulation activities in Europe, quantify clinical and regulatory success, and compare these with other medicinal products in order to reflect on regulatory changes and challenges.

The European Gene- and Cell-Based Therapy Landscape

Gene and cell-based therapies (GCTs) are said to hold promise for previously untreatable and high-burden diseases. The development of GCTs, however, faces translational challenges due to their novelty and apparent misfit with existing healthcare delivery and regulatory systems. In Europe, the European Commission (EC), in close collaboration with the European Medicines Agency (EMA), has been active in mitigating these challenges by adapting the regulatory environment to accommodate and regulate GCTs as medicinal products. In 2008, the enactment of the advanced therapy medicinal product (ATMP) regulation[i] subjected GCT products to the EMA's centralized authorization procedure and a combined marketing authorization assessment by the Committee for Medicinal Products for Human Use (CHMP) and Committee for Advanced Therapies (CAT)[i]. Other examples of regulatory change include: the drafting of GCT-specific good manufacturing practice (GMP) guidelines[ii], a classification procedure for GCTs[iii], and enhanced possibilities for dialogue and deliberation between GCT developers and authorities[iv,v]. Additionally, non-GCT-specific regulatory pathways are in place, for which GCT developers are often eligible. These include conditional marketing authorization[vi] and formal commitments between developers and authorities in the priority medicines (PRIME)[vii] scheme. Most GCT developers can also benefit from incentives provided for orphan[viii] and pediatric products[ix], and those for small and medium-sized enterprises (SMEs)[x]. Never before have so many incentives and schemes to facilitate medicinal product development in Europe coexisted.

Effects of New Regulations

During the initial years of the implementation of new regulations, concerns among the stakeholders regarding the effect of regulatory change emerged, particularly after negative opinions and withdrawal of marketing authorization applications (MAAs) were noted and GCT marketing authorization holders withdrew four regulatory approved GCTs from the EU market (Figure 1) [1].

In response, several multistakeholder initiatives[xi,xii] were undertaken to inform and improve GCT development and discuss learnings with respect to the implementation of the regulatory instruments. Initiatives consisted, amongst others, of consultation and a concept paper[xi] by the Innovative Medicines Initiative (IMI) to facilitate translation of GCTs to patients in Europe as well as stakeholder workshops organized by the EMA and CAT[xii]. Regulatory challenges figured prominently in these meetings and stakeholders actively engaged with each other to exchange views and practices about GCT development in the new regulatory environment[xi].

If we look at the cumulative number of MAAs submitted from 2009 to 2018[xiii] (Figure 1), we roughly observe two phases of regulatory GCT activity. In the initial years following the enactment of the ATMP regulation (roughly 2009–2013), we not only observe an upward trend in GCT MAAs being submitted but also a similar upward trend in negative opinions and applicant withdrawals (Figure 1). This could have been caused by more developers entering the field (leading to more initial MAAs) and reaching regulatory milestones (probably leading to similar negative opinions and withdrawal by applicant). During these initial years we also see an overlap in the cumulative number of positive opinions, negative opinions, and withdrawals by applicants. However, from 2013 onwards, while the number of initial MAAs continues the upward trend, the number of negative opinions and applicant withdrawals does not follow similarly (Figure 1). This may imply that GCT developers started to benefit from the clarity provided by the new regulations and guidance, and might also signal a positive learning curve for CAT with regard to evaluation of submissions.

Factors Influencing European GCT Development

Literature and conference discussions on GCT development express concerns that the number of centrally marketed GCTs in Europe so far is disappointing when compared with clinical trial activity [2,3][xiv]; it is unclear whether such claims are supported by data. These concerns might also signal unrealistically high expectations surrounding GCT development and approval.

One way to decide whether expectations are too high for GCT therapies would be to compare the emergence of this field with previous waves of change in drug development, such as the emergence of biopharmaceuticals. A lesson we have learned from biopharmaceuticals is that although expectations are often high in

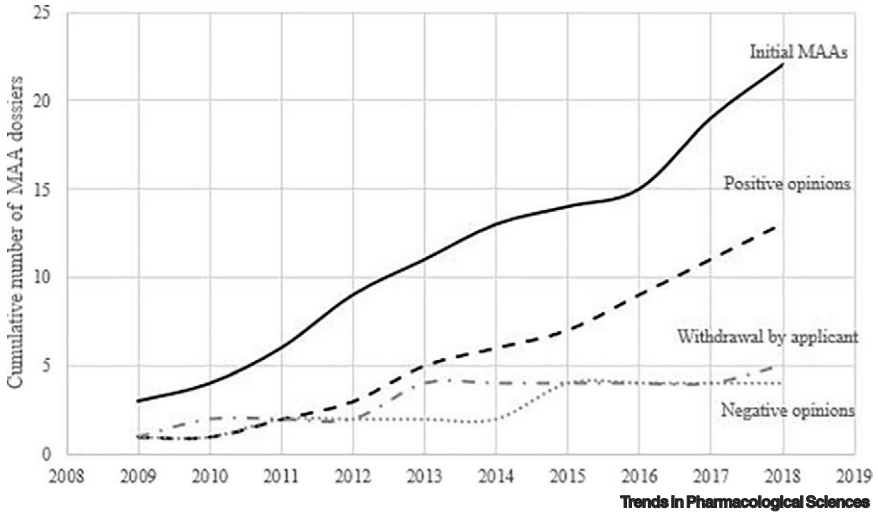

Figure 1. Trends in Gene and Cell-Based Therapy (GCT) Regulatory Activity in the EU between 2009 and 2018. The graph shows the cumulative number of initial marketing authorization applications (MAAs), positive and negative opinions by the Committee of Advanced Therapies (CAT) leading to approval or rejection of centralized marketing authorization by the European Commission (EC), and withdrawal by applicant from 2009, the year after regulatory policies were put in place in the EU, onwards. The numbers were obtained from 'the CAT monthly report of application procedures, guidelines, and related documents on advanced therapies' dated December 2018[xiii].

early phases of emergence, 'revolutionary' models of innovation result in overestimation of the speed and extent of improvement in therapeutic value that can be reasonably expected [4]. Similar to the emergence of biopharmaceuticals, it is likely that the introduction of GCTs will follow an incremental pattern of technological and regulatory change, building on existing drug development and regulation heuristics and experiences [5]. As the medicinal product field is strictly regulated and GCTs have only recently been accommodated within the regulatory medicinal product framework, it will take time for developers and authorities to learn how to bring these products to market.

We should also consider that complexities and challenges described by developers are often not scientific and technical but arise from their lack of familiarity with both the regulatory frameworks as well as the development of products for indication areas where needs are challenging to serve. Key developers in the GCT field are not large pharmaceutical companies but SMEs, hospitals, and academic researchers [6]. These SMEs are often founded around a technology or product discovered in academic or hospital settings [7]. These parties cannot draw on resources, experiences, and capabilities from prior development trajectories, and experience more difficulties in navigating the regulatory landscape than pharmaceutical companies [8]. Moreover, most developers develop GCTs for niche areas where competition is limited and markets uncertain. Small patient populations and unfeasibility of large and repeated trials limit learning opportunities about the benefits and risks of GCTs in these patient populations.

Quantifying Clinical Trial and Regulatory Success of GCTs

In an effort to quantify whether expectations are high for GCTs, we provide insights into the development success of GCTs and where possible, make a comparison with other medicinal product groups. While reconstructing the success rates of GCT development is difficult because of limited historical data and small sample sizes, we are aware of two publications that give a useful overview of clinical GCT activity in the EU. Maciulaitis *et al.* found that between 2004 and 2010 clinical trials were performed for 250 different GCTs using the EU clinical trial database (EudraCT)[xv], 100 of which were privately sponsored [9]. de Wilde *et al.* identified 198 GCT products in clinical trials during the period from 2004 to 2014 using the EU Clinical Trials Register[xvi], 80 of which were conducted by private sponsors [10]. We evaluate the success of GCT drug development with two measures;

(i) clinical trial success rate, obtained by dividing the number of products accepted by the EMA for initial MAA by the number of unique products in clinical trials (Table 1), and
(ii) regulatory success rate, obtained by dividing the number of products receiving an initial positive opinion by the EMA's CAT leading to approval by the EC, by the number of products submitted for initial MAA (Table 2).

Clinical Success Rate

As a benchmark for clinical trial success, we take the rule of thumb suggested by Mullard *et al.* who posit that globally around 10% of drug projects in Phase I clinical trials receive market authorization (MA) [11]. This number does not consider product, jurisdiction, or disease variability, and therefore provides a generic benchmark. Based on the EMA CAT report, we find that 22 initial MAA evaluations for GCTs received a positive opinion by the EMA as of December 2018[xiii]. Hence, we estimate that the overall clinical success rate of GCTs lies between 8.8 and 11.1% (22/250, based on Maciulaitis *et al.* [9]; 22/198, based on de Wilde *et al.* [10]) (Table 1, Figure 2A).

Our estimate assumes that all products observed by Maciulaitis *et al.* [9] and de Wilde *et al.* [10] could have been submitted for MAA. While GCT MAAs are

Table 1. Estimated Clinical Success Rate per Medicinal Product Group[a]

	GCTs	GCTs	All products (non-GCTs)	NAS	Orphan products	Biologics
Time frame	2004–2010	2004–2014	2003–2011	2003–2011	2003–2011	2003–2011
Number of unique products in trial	250	198	–	–	–	–
Privately sponsored products	100	80	–	–	–	–
Number of unique initial MAAs[b]	22	22	–	–	–	–
% Clinical success rate (all)	8.8	11.1	12.5	9.8	40.6	16.4
% Clinical success rate private sector	22.0	27.5	–	–	–	–
Overall estimated clinical success rate (%)	8.8–22.0	11.1–27.5	12.5	9.8	40.6	16.4

[a]Clinical success rates of GCTs are estimated by dividing the number of unique products in clinical trials (obtained from [9,10]) by the number of GCTs submitted for initial MAAs[xiii]. Non-GCT clinical success rates were derived from [12] by multiplying phase success rates per clinical phase [(Phase I) × (Phase II) × (Phase III)].
[b]Denotes number of unique initial MAAs until December 2018. No distinction is made between indications.

reportedly submitted based on less evidence (such as a single Phase I or I/II clinical trial) than conventional medicinal products (such as small molecules or biologics), we realize that our estimation might be an overestimation. Our analysis also assumes that all GCT developers aim to apply for MA. Yet, it is known that a substantial number of nonprivate developers do not aspire to formal MA [6]. Only including trials that have private sponsors increases the success rate to 22.0–27.5% (22/100, based on Maciulaitis *et al.* [9]; 22/80, based on de Wilde *et al.* [10]) (Table 1, Figure 2A). Thus, combining the available data and considering the earlier assumptions, we estimate that the overall GCT clinical success rate is in the range of 8.8 to 27.5% (Table 1, Figure 2A).

To compare GCT clinical success rates with other medicinal products developed by companies, we relied on Hay *et al.* [12]. Although Hay's numbers are based on the US market, they are representative of European trends [13]. Without distinguishing between indications or different medicinal products, we derive a clinical success rate of 12.5% from this research tracking clinical trials between 2003 and 2011 (Table 1, Figure 2A). However, the success rates vary per indication and product type. Here, we focus merely on product types and disregard variance per indication due to lack of data to support this analysis. Analyzing the different product types, Hay *et al.* shows a success rate of 9.8% from Phase I to FDA submission for small molecule new active substances (NAS)

Table 2. Estimated Regulatory Success Rate for GCTs and Non-GCTs[a]

	GCTs[xiii]		All products (non-GCTs)[xiv–xxiii]		NAS[b,xvii–xxvi]		Orphan products[xvii–xxvi]	
Year	Initial MAAs	Positive opinions	Initial MAAs	Positive opinions	Initial MAAs	Positive opinions	Initial MAAs	Positive opinions
2009	3	1	93	117	–	–	–	–
2010	1	0	90	51	34	20	12	4
2011	2	1	98	87	48	38	14	4
2012	3	0	93	59	47	30	19	8
2013	2	2	78	77	48	46	18	9
2014	2	1	98	81	37	40	21	17
2015	1	1	110	94	36	40	25	18
2016	1	2	113	79	40	28	27	16
2017	4	2	86	90	32	30	19	15
2018	3	3	81	80	31	31	17	18
Total	22	13	940	815	353	303	172	109
Regulatory success rate (%)	–	59.1	–	86.7	–	85.8	–	63.4

[a]Regulatory success rate is estimated by dividing positive opinions by the number of initial MAAs.
[b]Excludes orphan products. No distinction is made between indications.

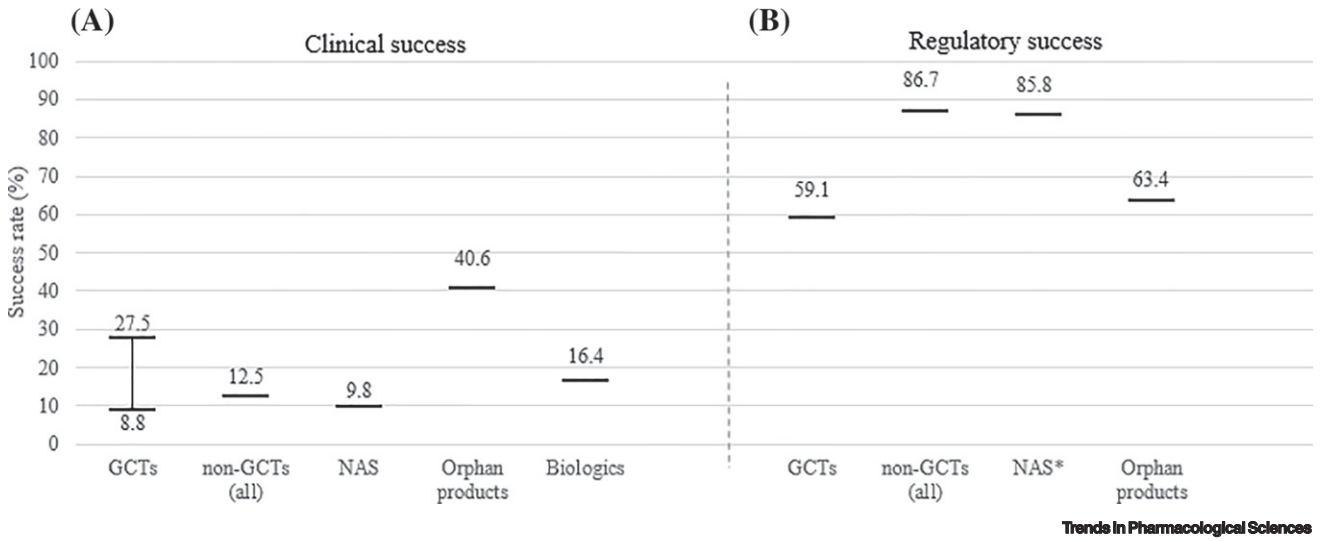

Figure 2. Comparison of Success Rates between Gene and Cell-Based Therapies (GCTs) and Non-GCTs. (A) Clinical success rate of GCTs compared with non-GCTs, new active substances (NAS), orphan products, and biologics. (B) Regulatory success rate of GCTs compared to non-GCTs, NAS, and orphan products. The estimate of regulatory success rate of NAS* includes orphan products that are a NAS. No distinction is made between indications.

[known as new molecular entities (NMEs) in the USA], 40.6% for orphan products, and 16.4% for biologics (Table 1, Figure 2A). The range reported by Hay *et al.* for clinical success of non-GCTs (9.8–40.6%) thus largely overlaps with our estimates for GCTs (8.8–27.5%) (Table 1, Figure 2A).

Regulatory Success Rate

To estimate regulatory success rates of GCTs, all non-GCT medicinal products, NAS, and orphan products, we collated the number of initial MAAs and positive opinions for each group from the EMA annual[xvii] and CAT reports from 2009 to 2018[xiii] (Table 2). These reports did not include specific information for biologics; hence they were excluded from further analysis. Regulatory success rate was calculated by dividing the total number of positive opinions by the number of submitted initial MAAs. We found that the regulatory success rate for GCTs (59.1%) was lower than for non-GCTs (86.7%) (Table 2, Figure 2B). However, regulatory success rates varied by product type, with NAS (85.8%) having similar rates to non-GCTs (86.7%) and orphan products (63.4%) having similar rates to GCTs (Figure 2B).

Ultimately, we obtained an overall estimate of GCT development success in the EU (obtained by multiplying clinical success rate with regulatory success rate) as ranging between 5.2 and 16.3% [(8.8–27.5%) × 59.1%]. This estimate falls within Mullard's 10% rule of thumb, suggesting no indication of lower success rates for GCTs compared with other medicinal products.

Concluding Remarks

A decade of GCT development and regulatory approval in Europe demonstrates that constructive engagement of stakeholders and an active approach towards policy learning is crucial in making implementation of regulation a success. Even in the short time period where GCTs have been regulated as medicinal products in Europe, it is encouraging to observe, as is clear from our analysis, that the implementation of the regulatory policies has not slowed the development and success rates of GCTs compared with conventional medicinal products. It is likely that this can be, at least partially, attributed to the active approach to regulatory change taken by the EMA and EC, although mitigation of other translational challenges might also play a role, such as a reduction in technological and scientific uncertainties and an increase in clinical adoption and experience. Continued success is dependent on regulation and regulators being adaptive to rapid technological advancement and new information about benefits and risks accruing over the drug life cycle. In so doing, regulation can simultaneously contribute to minimizing risks for patients, balancing the values and interests of stakeholders, and enabling further GCT innovation.

Acknowledgments

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Resources

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[ii]https://ec.europa.eu/health/documents/eudralex/vol-4_en

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Spotlight

Drug Screen Tugs at Common Thread for Repeat Disorders

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Repeat-associated non-ATG (RAN) translation is emerging as a driver of pathogenesis in microsatellite expansion disorders. Green and colleagues recently identified several candidate RAN translation inhibitors from a high-throughput small-molecule screen for fragile X tremor ataxia syndrome. Their study establishes a path forward for identifying inhibitors of RAN translation for multiple disorders.

Repeat-associated non-ATG (RAN) translation of microsatellite expansions is an important pathogenic process in a growing number of neurodegenerative disorders. As the name implies, RAN translation is a noncanonical form of translation where protein synthesis initiates in all three reading frames in the absence of an AUG start codon, either upstream or within the microsatellite repeat, to produce aggregate-prone peptide repeats [1]. RAN translation, originally discovered by the Ranum laboratory in spinocerebellar ataxia type 8, has now been reported in myotonic dystrophy types 1 and 2, fragile X tremor ataxia syndrome (FXTAS), Huntington disease, and *C9orf72* amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), among other disorders (reviewed in [1]). Despite the distinct clinical and genetic aspects of each disorder, the production of toxic RNA containing the repeat expansion and RAN translation appears to be a common feature of various microsatellite expansion disorders. While there are many unanswered questions regarding the mechanism and the specific contributions of RAN translation to pathogenesis, a growing body of evidence supports targeting RAN translation as a viable therapeutic strategy.

A recent publication by the Todd laboratory reported a high-throughput chemical screening strategy to identify modulators of RAN translation for FXTAS involving a