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Journal of Regulatory Science

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Journal of Regulatory Science 04 (2016) 1–9

Regulatory Science

Comparison of Regulations for the Development of Oncolytic Virus Therapy in the United States, the European Union, and Japan

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Abstract

Oncolytic Viral Therapy (OVT) is one of the novel approaches for treating cancer and has a preferable safety profile. If a response to the therapy can been demonstrated, it can become one of the main therapies for cancer. We conducted a comprehensive comparative analysis of regulations for OVT development in the United States (US), the Europe Union (EU) and Japan to confirm a perceived lag in OVT development activities in Japan and explore its regulatory basis.

Clinical development of OVT has begun all over the world. However, most of the development has been conducted outside of Japan. The lack of OVT development was not caused by scientific reasons but rather regulatory reasons. In this context, this article focuses on the regulatory differences surrounding OVT throughout the developed world. In Japan, unlike the US, data from clinical development are required to obtain regulatory approval from Pharmaceuticals and Medical Devices Agency (PMDA); in other words, data from clinical research are not enough. However, in the US, data from either clinical development or clinical research can be utilized for new drug applications. In addition, Japan ratified the Cartagena Protocol, which demands special procedures for the use of viruses, which are key to OVT; the US need not follow these procedures as it did not ratify the Protocol. In short, in order to stimulate the development of OVT in Japan, we should harmonize our regulations on OVT with those of the US and EU.

Keywords: drug development, oncolytic virus therapy, oncology, drug lag, regulatory science

1. Introduction

Recent advances in medicine have enabled us to largely overcome some kinds of cancers. However, there are still numerous medical shortfalls in this area, and the number of novel anticancer compounds in the stage of clinical development has risen drastically over the past decade[1].

The traditional anticancer therapies include chemotherapy, surgical treatment and radiotherapy. Most of the traditional chemotherapeutic anti-cancer agents are cytotoxic; i.e., they kill both cancer and normal cells. This means that chemotherapy also harms cells that divide rapidly under normal circumstances, in addition to cancer cells: cells in the bone marrow and hair follicles, etc. This leads to a decrease in both the health and Quality of Life (QOL) of cancer patients, with side effects like neutropenia and alopecia. Recently, however, cancer treatment has been changing with the advances in molecular targeting brought about by several innovations in basic research and the utilization of pharmacogenomics and pharmacogenetics. Using these tools enables us to identify patients who are at increased risk for toxicity and those more likely to respond to specific chemotherapeutic agents as well. This is called "tailor-made" medicine or personalized medicine. Therefore, the current trend of cancer pharmacology is both to identify new classes of molecules or proteins that block pathways that are critical for the cancer cells to survive and to develop agents that inhibit these critical signal transductions with favorable toxicity profiles. Indeed, a number of new approaches are being used in clinical trials of molecularly targeted agents, in order to evaluate response rates, monitor toxicity, and identify potentially active drugs. In this way, more and more novel approaches to cancer therapy are being developed all over the world.

OVT is known to be one of the promising new approaches to cancer treatment. Indeed, the drug in this concept has been already approved and launched in the pharmaceutical market[2]. In this therapy, genetically modified Deoxyribonucleic Acid (DNA) or Ribonucleic Acid (RNA) viruses selectively enter the cancer cells and kill them by replicating themselves. Notably, the viruses can exert their efficacy without causing damage to nor-

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Table 1. Related guidelines issued by regulatory authorities in US, EU and Japan.

Table 1A. US

Section	Guidance	Issue
Preclinical	Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy	March 1998
Clinical	Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors	November 2006
Clinical	Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events	November 2006
CMC	Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	April 2008
CMC	Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products	February 2008
CMC	Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products	January 2011
Preclinical	Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products November 2013. (This guidance finalizes the draft guidance entitled "Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products" dated November 2012)	November 2013
Clinical	Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products 7/2013. (This guidance document is for comment purposes only.)	July 2013

mal cells. In addition to the killing of infected cells, they can mediate the killing of uninfected cancer cells indirectly through the destruction of tumor blood vessels, initiation of specific immune responses to cancer cells or production of specific anti-cancer proteins expressed from their DNAs[3, 4]. There are a lot of OVTs in clinical development throughout the world[5]. China was the first country in the world to approve OVT[6] and the United States' Food and Drug Administration (FDA) approved T-VEC (Imlygic) as the first-in-class OVT targeted for melanoma in 2015[7]. In 2016, Japan designated its first OVT as a breakthrough therapy called Sakigake, and we can verify that the Japanese regulatory agency has started to pay attention to this novel approach. Progress in basic research has been confirmed as well, and the types of viruses available for this novel therapy has been increasing significantly; as of today, more than 10 types of viruses have been identified as viruses applicable to OVT[8].

In spite of the present trend of the accelerated development of OVT at the global level, Japan currently lags in the development of OVT[9]. Indeed, clinical trials for regulatory approval on oncolytic adenoviruses (OBP-301) for liver cancer has been initiated outside of Japan, but not in Japan even though the development company is headquartered in Japan[10]. Oncolytic herpes simplex viruses (G47b) for brain cancer and oncolytic herpes virus (HF10) for advanced cancer have only recently entered the clinical development stage in Japan. Given these facts, it is clear that clinical development of OVT has been waylaid in Japan, leading to the country's considerable lag in OVT development. This trend has consistency with the previous research that found a notable drug lag in anti-cancer drugs in Japan; the initiation of drug development in this therapeutic area may contribute to the longer anti-cancer drug lag[11]. However, there has been little research to clarify the main cause of this drug lag, especially related to OVT.

The primary objective of this research was to detect the regulatory differences between Japan and the US and EU that affect the development of OVT. To the best of our knowledge, this is the first comprehensive study to examine the regulation of OVT development in the US, EU and Japan. The perspectives obtained from this research may encourage global pharmaceutical companies and local companies as well to develop OVT at the global level, recognizing the regulatory differences in different regions. This will accelerate the OVT development globally and effectively, which can deliver this innovative therapy to the patients suffering from cancer all over the world.

2. Materials and Methods

Comparison of regulations related to OVT development.

The dataset used in these tables and the figure was generated from publicly available information on the FDA website (http://www.fda.gov/), European Medicines Agency

Table 1B. EU

Section	Guidance	Issue
Preclinical & clinical	Development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (concept paper)	concept paper, released for consultation December 2009
Preclinical & clinical	Questions and answers on gene therapy	December 2009
Preclinical & clinical	Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors	June 2010
Preclinical & clinical	ICH Considerations - Oncolytic Viruses	October 2009
Preclinical & clinical	Development and Manufacture of Lentiviral Vectors	May 2005
Preclinical	Non-clinical studies required before first clinical use of gene therapy medicinal products	May 2008
Preclinical & clinical	ICH Considerations General Principles to Address Virus and Vector Shedding	July 2009
Clinical	Follow-up of patients administered with gene therapy medicinal products	November 2009
Preclinical	Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products	May 2008
Preclinical	Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors	December 2006
Preclinical & clinical	Revision of the note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products (concept paper)	release for consultation December 2009
Preclinical & clinical	Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products	April 2001

(EMA) website (http://www.ema.europa.eu/ema/) and PMDA website (http://www.pmda.go.jp/english/). The data on regulations relevant to OVT—particularly non-clinical / clinical distinctions—were collected for each country or region, and the differences were investigated through comparative analysis by generating an itemized comparison table.

The development status of OVT categorized by year and region and the type of viruses utilized for OVT categorized by region.

The ClinicalTrials.gov website (https://clinicaltrials.gov/) was surveyed and analysis of clinical trial-related information on OVT (development status) was conducted. Regarding the development status, both overall development status and regional development statuses between 2001 and 2015 were investigated.

3. Results

Guidelines related to OVT development.

The summary of the related guidelines on OVT in the US, EU, and Japan issued by the relevant state regulatory agencies (FDA, EMA and PMDA) are listed in Tables 1A, B and C. We can verify that there are a lot of differences in guidelines between regions, especially in requirements for executing clinical trials of OVT.

Clinical or non-clinical regulations in developing OVT in the US, EU and Japan.

The regulations for clinical and non-clinical study in Japan, the US, and EU are chronologically shown in Table 2. Overall, we can verify that the missing items are fewer in the US and EU compared to those in Japan, and in these regions the regulations appear more systematic than those in Japan, suggesting that regulations on OVT development vary from region to region and that there is a "regulatory lag" in Japan. In addition, there are critical differences in the number of regulations between each requirement, especially in Japan, suggesting that the US and EU set similar requirements in clinical and non-clinical trials for developing OVT whereas Japan's are different. We also verified that this "regulation lag" in Japan may be the main cause of the development lag in OVT.

The requirements in non-clinical tests for FIH.

The regulations for the initial non-clinical testing in humans in Japan, the US, and EU are shown in Table 3. There are a few missing parts in the US and Japan compared to the regulations of the EU. However, considering the regulations in non-clinical testing, there was no critical difference among regulations, suggesting that the difference lies in the clinical trial regulations.

Table 1C. Japan

Section	Guidance	Issue
Preclinical & CMC	Guidance on quality and safety securing of pharmaceutical products for gene therapy (Yakushokushinsahatsu Notification No. 0701-4 of July 1, 2013)	July 2013
Clinical	Guidance on clinical research with human stem cells (MHLW Notification No. 317 of September 30, 2013)	September 2013
Clinical	Guidance on clinical research for gene therapy (MEXT* and MHLW** Notification No. 2 amendment of December 1, 2008) *Ministry of Education, Culture, Sports, Science and Technology ** Ministry of Health Labor and Welfare	December 2008
Preclinical	Law to maintain the diversity of Organisms through Control of the Use of Genetically-modified Organisms (Law No. 97 of 2003; Cartagena Law)	February 2004
Preclinical	For procedures of type 1 [regulations] approval application based on clinical research for gene therapy (law to maintain the diversity of Organisms through Control of the Use of Genetically-modified Organisms) of MHLW'S Secretariat Health Science Division Notification No. 0219001 of February 19, 2004	February 2004

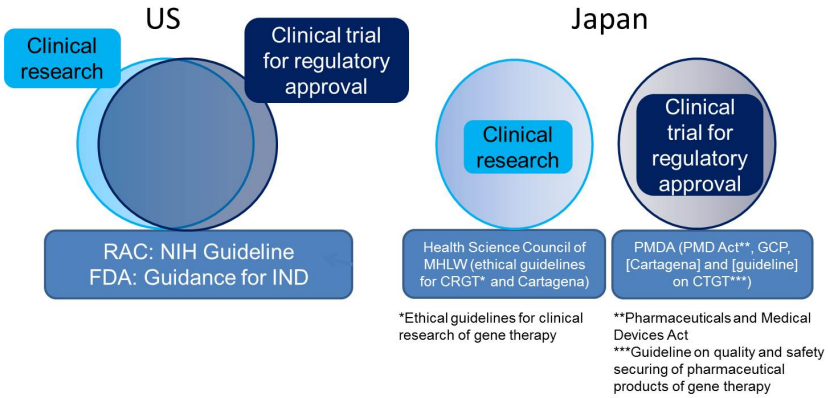


Figure 1: Regulatory review process for OVT in the US and Japan.

Regulatory review process on OVT

The initiation procedures for the clinical trial review in OVT in the US and Japan are shown in Figure 1. When starting a clinical trial for OVT, the quality and safety of the produced genetically modified virus and the protocol of the clinical trials are reviewed in each county. There is a separate and independent review process in clinical research and clinical trials for regulatory approval in Japan. Meanwhile, in the United States, any case clinical study protocols are reviewed by the Recombinant DNA Advisory Committee (RAC) and the evaluations of produced genetically modified viruses are performed by the FDA. Therefore, it is possible for the late phase of clinical trials for regulatory approval to be initiated based on data from any clinical study in the US.

This difference in the review process may contribute to the development lag in Japan.

The regional development status on OVT

The number of clinical trials of OVT categorized by region is shown in Figure 2. Most OVTs have been developed in the US. In contrast, Japan has only one OVT at the development stage. Considering that the development of OVT has been encouraged recently, these data confirm the existence of a development lag for OVT in Japan.

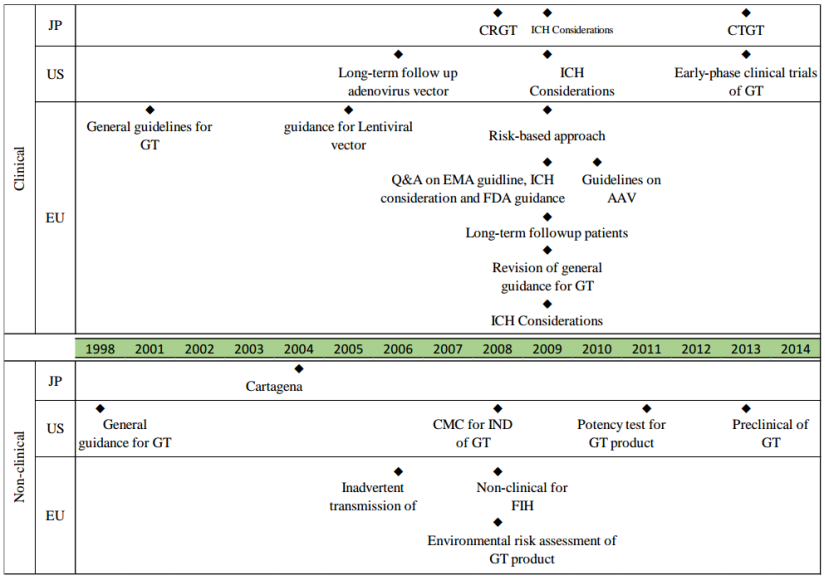
The overtime development status of OVT

The annual development status and the numbers of OVTs in development in each region for each year are shown in Figure 3. Development has been encouraged especially in the US whereas Japan has a wide development lag in OVT development, which is consistent with Figure 2.

Viruses used for OVT categorized by region.

The types of viruses utilized for OVTs which are in the clinical development stage are described in Table 4. Clinical trials

Table 2. Clinical / non-clinical regulations in OVT in the US, EU and Japan categorized by year.



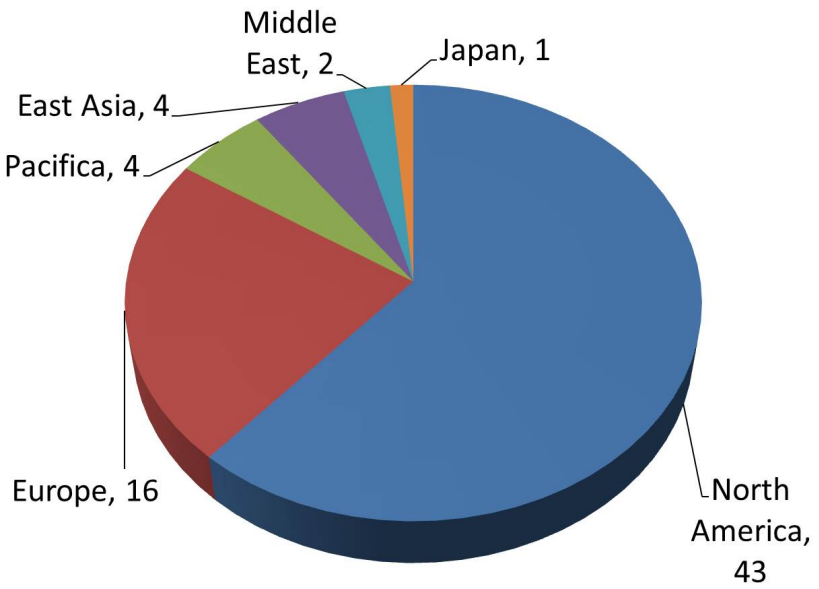


Figure 2: The development status of OVT categorized by region.

have been conducted all over the world, using a wide range of viruses, indicating that almost any virus can be used for OVT.

The ideal development process for OVTs

In the US the clinical data obtained from clinical researches can be extrapolated into clinical trials for the regulatory approval process in Figure 4. On the other hand, in Japan, these extrapolations are impossible because of immature regulation settings in Japan, suggesting that the collection of clinical data can be redundant, and the clinical development may have to be initiated from scratch even though sufficient data have been accumulated through various clinical researches.

4. Discussion

Overall, there are a lot of challenges facing this field at the current time. Technically, there are few solutions for quality control of viruses, virus delivery methods, and the evaluation method of clinical efficacy. The clinical testing of each new virus modification is also one of the biggest issues due to the enormous amount of time and expense required for the manufacture, pharmacokinetic / pharmacodynamics testing, toxicology testing, protocol development and regulatory approval to initiate clinical development. Japan's regulatory agency (PMDA) has at last established regulations for development of OVT. However, this action took a long time compared to the US and EU, and this delay informs some of the differences between

Table 3. The requirements of non-clinical tests for FIH in the US, EU and Japan.

	Japan	EU	US
Selection of animal	√	X	√
Experimental pathological animal model	X (written in selection of animal section)	X (written in objective section)	√
POC	√	√	√
Amount of dosage and route of administration	√	√	√
Viral disposition and ADME	√	√	√
TOX	√	√	√
Gene integration	√	√	√
Gene transfer into germ cell	√	√ ICH consideration	√ ICH consideration
Target cell selectivity	√	√	X
Immunogenicity and immunotoxicity	√	√	√
Reproductive and developmental TOX	X	√	X
Genotoxicity	X	√	X
Shedding of vector	√	√	X
Cartagena	√	X	X

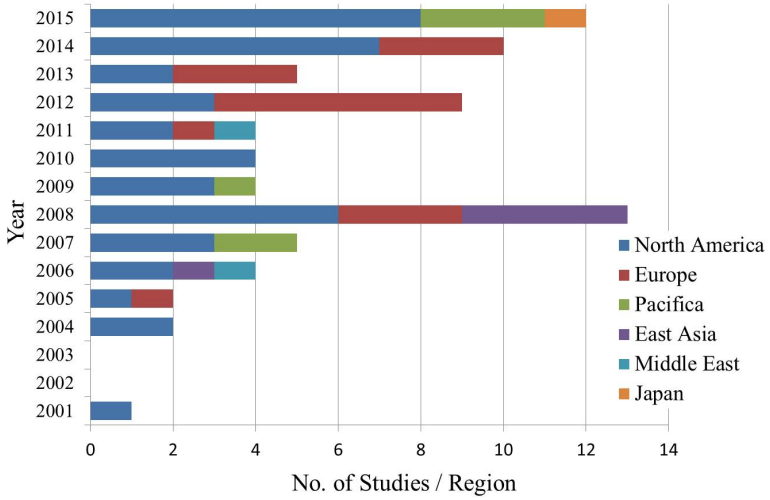


Figure 3: The development status of OVT categorized by year; Clinical trials for OVT by year.

OVT regulations in PMDA and those of the US / EU.

From the perspective described above, we first categorized the regulation in clinical data and non-clinical data for OVT development in the US, EU and Japan. In addition, we collected information on trends of clinical development of OVT to clarify the development status of this therapy in the US, EU and Japan.

In Japan, OVT is categorized as gene therapy. It is well known that there is little public funding in this area, and the regulations to facilitate the development of these therapies have only been recently issued in Japan[12]. New approval process specific for certain regenerative medical products was issued in Nov 2014. Therefore, there are few original researches conducted in Japan, which has led to the late initiation and the small number of clinical researches or OVT methods under development. With this background, this area does not seem attractive to the researcher. Indeed, few companies in Japan include OVT development as part of their business plan. However, in Japan, a conditional approval system was introduced[12] in 2015, and through this system, regenerative products can be approved with only clinical data, considering the balance between risk and benefit. The concept of this system is that promising products should be made available sooner rather than later, considering both the patients' QOL and the opportunity for additional clinical data; in particular, safety data will be collected

Table 4. Comparison of the viruses used for OVT categorized by region.

Region/ country	Number of Studies	Type of virus								
		Vaccina virus	Adenovirus	HSV	Reovirus	Measles virus	Coxsackie virus	Newcastle Disease Virus	Seneca valley virus	Parvovirus
World	65	-	-	-	-	-	-	-	-	-
North America	43	15	6	5	9	8	1	0	1	0
Europe	16	5	9	2	0	0	0	0	0	1
Pacifica	4	1	0	2	0	0	3	0	0	0
East Asia	4	5	0	0	0	0	0	0	0	0
Middle East	2	0	0	1	0	0	0	2	0	0
Japan	1	0	0	1	0	0	0	0	0	0

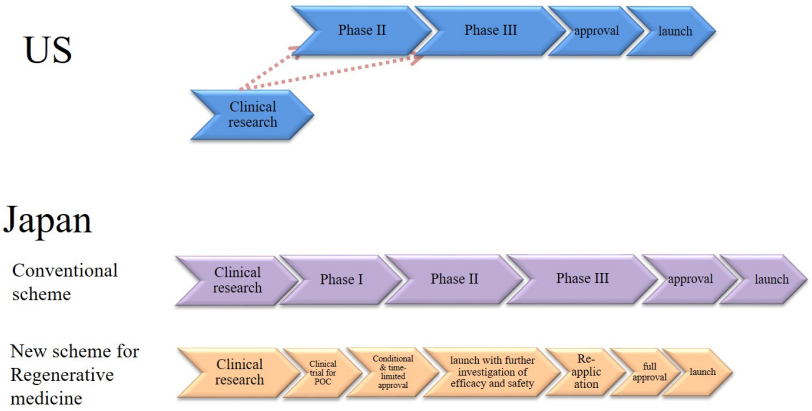


Figure 4: Ideal clinical development scheme for OVT in Japan in comparison with that of US.

through post-marketing surveillance. The same process can be applied to OVT for early access to this therapy.

In addition to the paucity of human resources devoted to research, the manufacturing and supply systems of viruses are limited. We found out that clinical trial notification (CTN) in this area is a complicated and time-consuming process, especially in Japan (Figure 1). Therefore, Japan should align its regulations process with that of the US to initiate clinical development in a timely manner with the least delay and to stimulate the further development of OVT. In this system, the data can be obtained from both clinical trials and clinical researches. Although the safety signal may not be detected, these changes to Japan's regulatory code are necessary if we want cancer patients in Japan to receive cutting-edge therapy at the global standard.

Table 4 shows that multiple types of viruses can be oncolytic viruses for OVT. In addition, it is well known that the safety profile of OVT was preferable and tolerable, as the most of the adverse events are well known events caused by infection [13–16]. As all the anti-cancer agents have side effects that drastically decrease a patient's quality of life, numerous additional medications have to be prescribed for toxicity management[17]. If the efficacy is confirmed in future clinical trials, new OVT methods will become in high demand. If safety concerns are detected in clinical trials, post-marketing surveillance should be conducted to collect additional clinical data after the launch of OVT. It is reported that in Japan there is a specific post-marketing system that makes the review time particularly short, thereby securing the safety of Japanese patients in a timely fashion[18].

It is important to mention the Cartagena Protocol on Biosafety when it comes to therapeutic viruses. The Cartagena Protocol on Biosafety is the first international agreement to regulate the trans-boundary movements of genetically engineered organisms including the viruses used for OVT[19]. Japan and the EU has ratified this Protocol and there are regulatory requirements in these countries to prevent viral shedding during clinical trials using OVT as well as gene therapy in Japan[20, 21]. This means that special attention must be paid to these matters in the clinical development and clinical research of OVT, and sometimes these considerations can encumber the related research and development. However, the US, Argentina and Canada have not ratified this Protocol. Therefore, there are no requirements or hurdles in the clinical development of OVT in these countries, with the result that OVT development is thriving there. Certainly, it is necessary to establish regulations to prevent virus shedding. However, these kinds of regulations should be applied at the late stage of clinical development, especially in OVT. Otherwise, the clinical development of OVT will be needlessly delayed. Further discussion is needed as to the timing of this type of regulation in clinical development. At the very least, considering the importance of developing OVT, the regulations should not be applied at the early stage of the clinical development (i.e., Phase I).

The specificity of oncolytic viruses to the cancer cells leads to the idea that they have the potential to treat cancers that are not responsive to other forms of treatment like surgery,

chemotherapy, or radiation[22]. In this context, one of the benefits of OVT is that viruses can be engineered to target cancer cells specifically based on their expression of certain growth factors or receptors[22]. Therefore, researching the use of such agents against cancers that have been unresponsive to other treatments offers the greatest opportunity for high-impact discoveries.

To assess the efficacy of OVT in a clinical trial, it is imperative to have several rigorous discussions on the primary endpoint. Overall survival (OS) is known to be the gold standard for a hard end point in clinical studies in the area of oncology[23]. PMDA, FDA and EMA have strongly demanded that OS be included in the clinical data package at New Drug Application (NDA) for marketing approval of all anti-cancer drugs [24–26]. However, these discussions should be conducted after the regulations on OVT such as guidelines are properly set in Japan. In conclusion, we hope that PMDA and the Japanese government will develop better guidelines based on our findings in this paper.

5. Conclusions

OVT is one of the novel approaches for treating cancer and this therapy has preferable safety profile. If a response to an agent can be clinically confirmed, OVT can become one of the main therapies for cancer.

Clinical development of OVT has been generally encouraged; however, there are geographical trends in its development status, with most of the development occurring outside of Japan. We argue that this trend results from the differences in regulations surrounding OVT. In Japan, unlike the US, data from clinical development are required to obtain regulatory approval from PMDA; in other words, data from clinical research are not sufficient. However, in the US, either data from clinical trials for regulatory approval or clinical research can be utilized for new drug application. In addition, Japan ratified the Cartagena Protocol, thereby agreeing to special attention or countermeasures in developing OVT, which the US need not abide by, as it did not ratify the Protocol.

All in all, in order to stimulate the development of OVT at the global level as well as in Japan, the harmonization of regulations on OVT around the world should be pursued. The authors believe that the perspectives obtained from this article focusing on regulatory differences among countries and regions will encourage revisions to the Japanese regulatory code that will in turn stimulate further clinical development of OVT in Japan.

6. Conflict of Interest

Atsushi Aruga has no conflicts of interest to disclose. Takuma Matsuda is an employee of Gilead Sciences K.K., but being part of the company has not influenced the results and discussion in this paper.

7. Article Information

The article was received June the 1st, 2016, in revised form August the 3rd, 2016 and available on-line September the 15, 2016.

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