Welcome to CMC Strategy Forum Japan 2018

On behalf of the CASSS Board of Directors and the CMC Strategy Forum Global Steering Committee, we would like to extend to you a warm welcome to the second meeting of the CMC Strategy Forum Japan 2018.

We are very pleased that with the strong support from the Pharmaceuticals and Medical Devices Agency (PMDA Japan), as well as the Japan Pharmaceutical Manufacturers Association (JPMA), and with the continued organization by CASSS and the support from the United States Food and Drug Administration, that we are continuing with the CMC Strategy Forum Japan 2018. The Forum will follow the established model of the CMC Forum series with focus on topics and regulatory updates relevant for Japan and Asia and will feature an opening regulatory session that will include presentations from PMDA, FDA, EMA, as well as Asian health authorities. The technical sessions will include discussions on new trends for quality control of biopharmaceutical products; new trends in manufacturing of biologics: technologies involved in continuous manufacturing and regulatory perspectives; and CMC development of regenerative medicines regulations and mandatory quality control of products, raw materials and cell substrates.

The success of the CMC Strategy Forum Japan will depend on your active participation in discussing and raising issues pertaining to the development of biologics. We encourage you to participate wholeheartedly in the panel discussions that have been designed to stimulate exchange of ideas and information.

We would like to thank the speakers and the panel members who are giving generously of their time and resources and to you for your attendance. We would also like to acknowledge the generosity of our program partners for the continued support of the Forum series: Biogen; F. Hoffmann-La Roche Ltd.; MedImmune, a Member of the AstraZeneca Group; Novo Nordisk A/S. We are grateful for the expert management from CASSS and the audio-visual expertise of Michael Johnstone from MJ Audio-Visual Productions. Their experience and guidance in the preparation of this Forum has been invaluable.
ACKNOWLEDGEMENTS

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Chikako Torigoe, CBER, FDA, USA
The scientific organizing committee gratefully acknowledges the pharmaceutical and biotechnology industry for their generous support of the CMC Strategy Forum Japan 2018.

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Monday, 3 December 2018

06:30 – 08:45 Buffet Breakfast for all CMC registered guests of the Tokyo Marriott Hotel in the Dining Grill (Lobby Level)

07:30 – 09:30 Coffee Service in the South Ballroom Foyer

07:30 – 17:00 Registration in the Oak Room

08:30 – 09:00 CASSS Welcome and Introductory Comments in the South Ballroom
Wassim Nashabeh, Genentech, a Member of the Roche Group, USA

CMC Strategy Forum Japan 2018 Welcome and Introductory Comments in the South Ballroom
Takao Yamori, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Recent Trends in the Regulation of Biopharmaceutical Products
Plenary Session in the South Ballroom
Session Chairs: Yasuhiro Kishioka, Pharmaceuticals and Medical Devices Agency (PMDA) and Ingrid Markovic, Genentech, a Member of the Roche Group

09:00 – 09:30 PMDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals
Ayako Enokida, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

09:30 – 10:00 Recent Trends in the Regulation of Biopharmaceuticals – A Korean Perspective
Gi Hyun Kim, Ministry of Food and Drug Safety (MFDS), Republic of Korea

10:00 – 10:30 NMPA Perspective: Recent Trends in the Regulation of Biopharmaceuticals
Meng Yang, China National Medical Products Administration (NMPA), China

10:30 – 11:00 AM Break in the South Ballroom Foyer

11:00 – 11:30 US FDA Update: Recent Trends in the Regulation of Biopharmaceuticals
William Hallett, CDER, FDA, USA

11:30 – 12:00 CBER Regulatory Updates: Initiatives for Product Review and Licensure
Robin Levis, CBER, FDA, USA

12:00 – 12:30 Current Hotspots during CMC Evaluation – A European Regulatory Perspective
Steffen Gross, Paul-Ehrlich-Institut, Germany
Monday, 3 December continued…

12:30 – 13:45  
**Buffet Lunch** in the North Ballroom

13:45 – 15:00  
**Panel Discussion – Questions and Answers**  
Ayako Enokida, *Pharmaceuticals and Medical Devices Agency (PMDA), Japan*  
Steffen Gross, *Paul-Ehrlich-Institut, Germany*  
William Hallett, *CDER, FDA, USA*  
Gi Hyun Kim, *Ministry of Food and Drug Safety (MFDS), Republic of Korea*  
Robin Levis, *CBER, FDA, USA*  
Meng Yang, *China National Medical Products Administration (NMPA), China*

15:00 – 15:30  
**PM Break** in the South Ballroom Foyer

| New Trends for Quality Control of Biopharmaceutical Products  
| Workshop Session in the South Ballroom  

15:30 – 15:55  
**Evaluation of Protein Aggregates/Subvisible Particles in Therapeutic Protein Injections**  
Hiroko Shibata, *National Institute of Health Sciences, Japan*

15:55 – 16:20  
**Novel Virus Clearance and Virus Detection Technologies and Applications**  
Qi Chen, *Genentech, a Member of the Roche Group, USA*

16:20 – 16:45  
**Multi-attribute Method by Mass Spectrometry: Current and Future State**  
Jette Wypych, *Amgen Inc., USA*

16:45 – 18:00  
**Panel Discussion - Questions and Answers**  
Qi Chen, *Genentech, a Member of the Roche Group, USA*  
Niklas Ekman, *Finnish Medicines Agency, Finland*  
William Hallett, *CDER, FDA, USA*  
Yasuhiro Kishioka, *Pharmaceuticals and Medical Devices Agency (PMDA), Japan*  
Chunming Rao, *China National Medical Products Administration (NMPA), China*  
Hiroko Shibata, *National Institute of Health Sciences, Japan*  
Jette Wypych, *Amgen Inc., USA*

18:00 – 19:30  
**Networking Reception** in the North Ballroom

19:30  
**Adjourn Day One**
Tuesday, 4 December 2018

06:30 – 08:45  **Buffet Breakfast** for all CMC registered guests of the Tokyo Marriott Hotel in the Dining Grill (Lobby Level)

07:30 – 09:30  **Coffee Service** in the South Ballroom Foyer

08:00 – 17:00  **Registration** in the South Ballroom Foyer

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<td>08:45 – 08:50</td>
<td>Introduction</td>
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| 08:50 – 09:15 | **The Landscape of Continuous Manufacturing in Japan**  
Kyoko Sakurai, *Pharmaceuticals and Medical Devices Agency (PMDA), Japan* |
| 09:15 – 09:40 | **Continuous Biomanufacturing: Relevant Experiences with Development,**  
*Hybrid Implementation and Emerging Opportunities**  
Erik Fouts, *BioMarin Pharmaceutical Inc., USA* |
| 09:40 – 10:05 | **Back Pack Medicine: A Real Possibility?**  
Michael Abernathy, *Amgen Inc., USA* |
| 10:05 – 10:30 | **Chugai Next Generation Factory Concept: Application of Continuous DS**  
*Manufacturing Processes*  
Yasufumi Ueda, *Chugai Pharmaceutical Ltd., Japan* |
| 10:30 – 11:00 | **AM Break** in the South Ballroom Foyer                              |
| 11:00 – 12:15 | **Panel Discussion - Questions and Answers**  
Michael Abernathy, *Amgen Inc., USA*  
Erik Fouts, *BioMarin Pharmaceutical Inc., USA*  
Steffen Gross, *Paul-Ehrlich-Institut, Germany*  
Ingrid Markovic, *Genentech, a Member of the Roche Group, USA*  
Kyoko Sakurai, *Pharmaceuticals and Medical Devices Agency (PMDA), Japan*  
Yasufumi Ueda, *Chugai Pharmaceutical Ltd., Japan* |
| 12:15 – 13:30 | **Buffet Lunch** in the North Ballroom                                |
Tuesday, 4 December continued…

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| 13:30 – 13:55 | Perspectives from the CASSS CGTP 2018 Conference: Manufacturing, Quality and Regulatory Considerations  
Andrew Weiskopf, Biogen, USA |
| 13:55 – 14:20 | CMC Consideration and Technical Requirements of Cell Therapy Products at the Clinical Stage  
Wei Wei, China National Medical Products Administration (NMPA), China |
| 14:20 – 14:45 | CMC Consideration for the Development of Regenerative Medical Products  
Kazunobu Oyama, Pharmaceuticals and Medical Devices Agency (PMDA), Japan |
| 14:45 – 15:15 | TBD  
Kiwamu Imagawa, JCR Pharmaceuticals Co., Ltd., Japan |
| 15:15 – 15:40 | Regulatory Developments in the EU Relevant for Cell-based and Regenerative Medicines  
Christiane Niederlaender, MHRA-Medicines and Healthcare Products Regulatory Agency, United Kingdom |
| 15:45 – 16:15 | PM Break in the South Ballroom Foyer |
| 16:15 – 17:30 | Panel Discussion – Questions and Answers  
Kiwamu Imagawa, JCR Pharmaceuticals Co., Ltd., Japan  
Shigemi Kitagawa, Novartis K.K., Japan  
Ingrid Markovic, Genentech, a Member of the Roche Group, USA  
Christiane Niederlaender, MHRA-Medicines and Healthcare Products Regulatory Agency, United Kingdom  
Kazunobu Oyama, Pharmaceuticals and Medical Devices Agency (PMDA), Japan  
Wei Wei, China National Medical Products Administration (NMPA), China  
Andrew Weiskopf, Biogen, USA |
| 17:30 – 17:45 | Closing Remarks  
Wassim Nashabeh, Genentech, a Member of the Roche Group, USA |
| 17:45       | Adjournment |
Welcome and Introductory Comments

Wassim Nashabeh

*Genentech, a Member of the Roche Group, USA*

**AND**

Takao Yamori

*Pharmaceuticals and Medical Devices Agency (PMDA), Japan*

NOTES:
Recent Trends in the Regulation of Biopharmaceutical Products

Session Chairs: Yasuhiro Kishioka, Pharmaceuticals and Medical Devices Agency (PMDA) and Ingrid Markovic, Genentech, a Member of the Roche Group

Biopharmaceutical industry has experienced considerable transformation in the recent years due to advancement of new therapeutic modalities such as cell & gene therapies, tissue engineering, antibody drug conjugates or bispecific antibodies, which have explored new therapeutic targets or identified more sophisticated ways to address existing ones. Such therapies are often customized to the patient with the intent to match the patient specific genetic make-up achieving the desired therapeutic effect while minimaxing the undesired outcomes. As these complex therapies have evolved, so have the processes to manufacture them in a consistent manner with accompanying analytics assuring that products meet the desired quality criteria. In that regard, the manufacturing environment seems to be moving away from the labor and resource-intensive batch manufacturing towards processes where given unit operations can be integrated, or in some cases, fully continuous process can be realized. Alongside with modern manufacturing, the analytics are becoming more sophisticated moving toward a multi-attribute continuous monitoring where multiple Critical Product Quality Attributes can be monitored and adjusted as needed in real-time. The innovative technological approaches are enabled by modern facility designs with smaller footprint, modular units and reliance on single-use systems with smaller batch size ensuring an agile and flexible manufacturing environment. In this regard, the regulatory landscape has become even more challenging in ensuring the quality of these products and the safety of the patients that use them. The strong incentive to increase the competition by boosting the biosimilars market, to accomplish an accelerated development and approval timelines (e.g., Breakthrough/PRIME/Sakigake designation), both the regulators and industry, may have to continually adapt to address these challenges in order to assure continuous supply of safe and effective medicines to the patients.

NOTES:
Recent Trends in the Regulation of Biopharmaceutical Products
Workshop Session One

Panel Members:
Ayako Enokida, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Steffen Gross, Paul-Ehrlich-Institut, Germany
William Hallett, CDER, FDA, USA
Gi Hyun Kim, Ministry of Food and Drug Safety (MFDS), Republic of Korea
Robin Levis, CBER, FDA, USA
Meng Yang, China National Medical Products Administration (NMPA), China

The following questions will guide the discussion:

1. What do you perceive as the most urgent regulatory challenges today?
2. How can those challenges be addressed?
3. How can regulatory harmonization/convergence be achieved?
4. Is global regulatory environment ready to adopt ICH Q12 and established conditions?
5. If not, what steps need to be taken to implement established conditions in your region?
6. Can you share examples and strategies used in your region to accelerate CMC development through Breakthrough/PRIME/Sakigake pathway (e.g., process validation, control strategy, stability, etc.)?
7. Regional review updates/Initiatives shared by each panelist for their respective region?
   o E.g. In the US, please provide an update on the FDA/CDER KASA initiative?
8. Can you share what regulatory pathways are used in your region to approve and implement innovative technologies (e.g., next generation sequencing, RTRT, etc.)?
   o Do you have examples to share?
   o Can you comment on reviewer readiness to review such applications in your region?
9. Biosimilars update

NOTES:
New Trends for Quality Control of Biopharmaceutical Products

Session Chairs: Robin Levis, CBER, FDA and Kazuhisa Uchida, Kyowa Hakko Kirin Co., Ltd.

Evolutions and new applications of existing analytical technologies, such as mass spectrometry, and developments of novel technologies, such as next generation sequencer, enable more rapid and efficient analyses as well as analyses of new characteristics of biopharmaceutical products. Ultimately, some of such new technologies and applications may potentially change paradigm of quality control of the biotherapeutics. For example, LC-MS (LC-MS/MS) technologies that can measure multiple quality attributes (e.g., deamidation, oxidation, degradation, and protein impurities) in one method with rapid turnaround, can potentially be used as process analytical technologies (PAT) for continuous manufacturing and, subsequently, may change the paradigm from traditional lot release testing of final products towards more real-time release with the in-process results.

In parallel with the evolutions of the analytical technologies, there are several attempts to compare and standardize various technologies for same purposes (e.g., aggregate analysis), to develop uniform test methods which could ultimately be added to the compendias.

In this session, such new technologies and efforts for the standardization will be introduced and the predicted future trend of quality control of the biopharmaceutical products will be discussed.

NOTES:
Presenter’s Abstracts
New Trends for Quality Control of Biopharmaceutical Products
Workshop Session Two

Panel Members:
Qi Chen, Genentech, a Member of the Roche Group, USA
Niklas Ekman, Finnish Medicines Agency, Finland
William Hallett, CDER, FDA, USA
Yasuhiro Kishioka, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Chunming Rao, China National Medical Products Administration (NMPA), China
Hiroko Shibata, National Institute of Health Sciences, Japan
Jette Wypych, Amgen Inc., USA

The following questions will guide the discussion:

1. What kind of novel analytical technologies and applications are being developed and being implemented in in-process and/or release testing?
2. What are best practices of implementations of novel technologies for continuous improvements? How we can catch up with, select and implement advanced technologies?
3. How can we generate uniform/standardized testing methods out of multiple technologies being developed?
4. How should we react (report/control) when a new attribute is identified with new technologies?
5. How will the quality control paradigm evolve in near future?

NOTES:
New Trends in Manufacturing of Biologics: Technologies Involved in Continuous Manufacturing and Regulatory Perspectives

Session Chairs: Akiko Ishii-Watabe, National Institute of Health Sciences and Wassim Nashabeh, Genentech, a Member of the Roche Group

Continuous manufacturing of pharmaceutical products has been a hot topic for recent years and finally selected as a new ICH topic, ICH-Q13, because of its potential to increase manufacturing efficiency (higher productivity and reduction of manufacturing time etc). While the continuous perfusion culture itself is not a new technology and has been used for manufacturing of commercial biopharmaceuticals since 1990s, other novel technologies further supporting the continuous manufacturing, such as single-use technologies (disposable bioreactors and tubing systems (including valves, connectors, etc.)), modular manufacturing designs and continuous downstream processing equipment, are being developed and being installed to actual manufacturing facilities.

These new technologies and equipment could benefit pharmaceutical companies by enabling i) more efficient production with smaller equipment in smaller facilities, ii) easier scale-up of the process and iii) facility for multiple product manufacturing without a risk of cross contamination, all of which will considerably reduce an investment for launch of new facilities and lines.

On the other hand, such new technologies will require a new set of rules to regulate and control quality risks associated with such new manufacturing schemes. For example, in the continuous manufacturing setting, how is a batch defined, what kind of in-process monitoring, and feedback loop should be built-in to the process to avoid “continuous” failures, what portion should be rejected upon out-of-specification, what change control assessment will be required for switch from conventional manufacturing, and so on. While, for low molecular drugs, rules and actual example of marketing approvals, are gradually developed recently (e.g., “Points to Consider Regarding Continuous Manufacturing” guideline has been released in Japan by AMED research group), similarity and differences between the low molecules and biologics must be analyzed.

In this session, an overview of new technologies being implemented to facilities, purposes and applications of the technologies (e.g., easy scale-up and capability for multi-product manufacturing to accelerate development with use of the single-use equipment, use of smaller tanks to scale down facility by implementing perfusion) and regulatory insight to the new manufacturing scheme will be introduced.
New Trends in Manufacturing of Biologics: Technologies Involved in Continuous Manufacturing and Regulatory Perspectives
Workshop Session Three

Panel Members:
Michael Abernathy, Amgen Inc., USA
Erik Fouts, BioMarin Pharmaceutical Inc., USA
Steffen Gross, Paul-Ehrlich-Institut, Germany
Ingrid Markovic, Genentech, a Member of the Roche Group, USA
Kyoko Sakurai, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Yasufumi Ueda, Chugai Pharmaceutical Ltd., Japan

The following questions will guide the discussion:

1. What are the novel technologies and equipment being installed in/evaluated for manufacturing of biologics?
   - Upstream: Perfusion, single-use etc
   - Downstream: continuous chromatography system, virus clearance evaluation
2. What are benefits of such new technologies and equipment?
3. What are best practices of implementation of the new technologies? How is a facility set up and validated? How should change control be made with maintaining product quality?
4. How is the new manufacturing scheme, in particular the continuous manufacturing, regulated? How similar and/or different from the continuous manufacturing of low molecular drugs?
5. Any progress in ICH-Q13 development?

NOTES:
NOTES:
CMC Development of Regenerative Medicines: Regulations and Mandatory Quality Control of Products, Raw Materials and Cell Substrates

Session Chairs: Niklas Ekman, Finnish Medicines Agency and Yoji Sato, National Institute of Health Sciences

The quality attributes of cell-based products, which should be tested, monitored and controlled, vary product by product. Several kinds of background factors, such as property of starting materials, origin and quality of raw materials, and/or complex manufacturing process, could cause the variations of the critical quality attributes amongst the cell-based products.

The recent progress in cell-based medicinal products developments could provide accumulated knowledge about several challenges commonly observed over multiple cell-based products. For example, required quality of raw material are not always achievable, under circumstances where high quality ingredients such as pharmaceutical grade are not available.

In this session, current regulatory requirements and/or considerations against these common issues in the cell-based medicinal product developments, especially regarding quality control and raw materials, will be discussed, with overviews of case studies and/or lessons learned from actual developments.

NOTES:
Presenter’s Abstracts
Panel Members:
Kiwamu Imagawa, JCR Pharmaceuticals Co., Ltd., Japan
Shigemi Kitagawa, Novartis K.K., Japan
Ingrid Markovic, Genentech, a Member of the Roche Group, USA
Christiane Niederlaender, MHRA-Medicines and Healthcare Products Regulatory Agency, United Kingdom
Kazunobu Oyama, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Wei Wei, China National Medical Products Administration (NMPA), China
Andrew Weiskopf, Biogen, USA

The following questions will guide the discussion:

1. Points to consider for quality control strategy of cell- and/or gene-therapy medicinal products;
2. Required quality grade for raw materials including ancillary materials;
3. Approach to risk assessment for strategic CMC development;
4. Considerations of consistency and comparability during CMC development;
5. Approach to process-verification and process-validation;
6. Differences in the regulatory requirements between the regions.

NOTES: