# JP's Future Perspective on Collaboration with USP

Haruhiro OKUDA, Ph.D.
Pharmaceutical and Medical Device
Regulatory Science Society of Japan (PMRJ)

# Today's Topics

- Future Perspective of JP

- Future Perspective on Collaboration
  - Mutagenic Impurities
  - Nitrosamines
  - General Tests

# Future Perspective of JP

# Strategy of JP Drafting

**[Principles for JP drafting]**

- Basic principles for preparation of JP (notified by MHLW)
- Procedures for JP drafting (notified by PMDA)
- Guideline for JP drafting（distributed by KPIA and PMAT）

**[Strategy for international relationship]**

- International Pharmaceutical Regulatory Harmonization Strategy ~Regulatory Science Initiative~ (published by MHLW)
- PMDA’s strategy for international affairs (published by PMDA)

# Basic Principles for Preparation of JP

- Summary of principles for discussion toward next revision
- Drafted by Standing Committee, JP, and deliberated by the JP Committee, the Pharmaceutical Affairs and Food Sanitation Council, MHLW
- Latest version is for JP18. Principles for JP19 is under discussion.
- Core description is called '**5 pillars**'

1) Including all drugs which are important from the viewpoint of health care and medical treatment;
2) Making qualitative improvement by introducing the latest science and technology;
3) Promoting internationalization corresponding to globalization of pharmaceuticals;
4) Making prompt partial revision as necessary and facilitating smooth administrative operation; and
5) Ensuring transparency regarding the revision, and disseminating the JP to the public.

# Pharmacopoeia Used in Global

**[International Pharmaceutical Regulatory Harmonization Strategy ~Regulatory Science Initiative~] (published by MHLW in June, 2015)**

*III-3. Strategic initiatives with specified priorities in each product area – To implement measures more effectively –*

- *Leading role in international harmonization as a member of the tripartite entity of Japan, the United States, and Europe*

  *Taking the lead in discussions, etc. on the international regulatory harmonization framework as a short-term initiative.*

  - *Global harmonization of the Japanese Pharmacopoeia will be promoted, together with incorporation of the latest quality control measures.*
- *Strong partnership in the Asia region centered on ASEAN, China, Korea, etc.*

  *Within 10 years, cooperation on reviewing, etc. will be promoted in the Asian region.*

  - *Establishment of the Japanese Pharmacopoeia as the reference pharmacopoeia for each Asian country will be promoted.*

https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/150827-01-01.pdf

# Expansion of PDG

**[PDG November 2020 and March 2021 Videoconference Press Release]**

On Nov 6, virtual meeting, hosted by USP / On Mar 12, virtual meeting, hosted by Ph. Eur.

*A particular focus of the videoconference was preparation for the upcoming ICH Assembly meeting, where an update on the PDG's pilot phase proposal for the maintenance of the ICH Q4B annexes would be given with the aim of getting the ICH's approval to start the process.*

*On 12 March 2021, the PDG held its regular interim videoconference focusing again on strategy and policy topics. The PDG discussed several concrete ideas about how to use opportunities to enhance the global reach and impact of international harmonisation of quality standards. Continuing thought is being given to interactions with regulators, industry and other pharmacopoeias.*

*The PDG remains fully committed to expanding recognition of harmonised pharmacopoeial standards with a view to achieving global convergence and will continue its reflection on opportunities in 2021.*

https://www.pmda.go.jp/files/000240394.pdf

# Cooperation with Other Pharmacopoeias

**[12th International Meeting of World Pharmacopoeias]**

On Feb 22-24, virtual meeting, hosted by WHO

*A major outcome of the collaboration is the global pharmacopoeial alert system initiated by the Brazilian, British, Chinese, European, Indian, International, Japanese, Mexican, United States and Vietnamese pharmacopoeias and other global pharmacopoeial partners. This has resulted in a dashboard listing of COVID-19 investigated medicines mapped to available monographs published in the various world pharmacopoeias. This listing is now available to allow easy identification of quality control specifications for therapeutics under consideration for COVID-19 treatment.*

https://www.who.int/news/item/01-03-2021-world-pharmacopoeias-support-public-health-during-covid-19-pandemic

# Basic Principles for Preparation of JP19

**[Key discussion points for revision]**

- Emphasis of objectives to publish pharmacopoeia
- Contribution to robust supply chain and stable supply
- Reinforcement of reference standards distribution
- Expansion of PDG activity, alignment among other pharmacopoeias
- Making up-to-date long existing General Tests and Official Monographs
- Consideration for additional usage, such as education

- *JP continues to proceed with exclusion of harmful reagents, 3R, and introduction of new sciences/technology.*

# Supply Chain

- JP aimed to establish monographs without Reference Standards (RS) as much as possible (Currently JP has also adopted monographs having RS on a case by case basis).
  - Identification by comparing with referential spectrum
  - Impurities control based on relative retention time

- The embargo of APIs and drug products by India in 2020 highly impacted domestic / global supply chain.
  - Second API source from another country has been considered.

- The decrease of international flights increased the uncertainty of import / export of APIs, drug products, and reference standards.

→ *How to proceed with release testing when reference standards are not available? E-standards?*

# Future Perspective on Collaboration

# Collaboration History with USP

- Liaisons/Scientist Exchange Program
  - Since 2010, 6 Liaisons were dispatched for 1 or 1.5 years
    - Planning and engaging in collaborative project, smoothing communication, and promoting mutual understandings
  - A Scientist from NIHS stayed for 3 months
    - Research related to USP-JP bilateral harmonization project
- MHLW/PMDA Delegates continue to participate in USP Convention meeting;
  - USP Convention consists of nearly 500 member organizations such as health practitioners, manufacturers, academic institutions, governmental bodies, and is held every 5 years. In the Convention meeting, strategic plan for next 5-year cycle is discussed.
  - In 2020, the Convention meeting was held on virtual in May.
- USP-PMDA/MHLW Joint Workshop
  - the First joint Workshop; virtual meeting in 1.5 days

# Candidates for Future Collaboration

**[Agenda of this joint WS]**

Session 1: Introduction of each Pharmacopeia

Session 2: New Technologies and Modalities

(1) Continuous manufacturing

(2) qNMR

(3) Performance Testing

Session 3: Standards for Biologics

Session 4: Impurities

Panel Discussion

Key Notes

# Impurities (Mutagenic Impurities)

**[Current situation in Japan to enforce ICH-M7]**

- Risk assessment is required in NDA and ANDA (in the case brand products are controlled under ICH-M7), as well as partial change application.
- When new mutagenic impurities are found in a certain API or drug product and there is safety concern, related brand products and generic products are directed to conduct risk assessment on the impurities. In the case the impurities are found in other brand products or generic products and cannot ignore safety concern, those products will be recalled.
  - Example of recall: Epinastine Hydrochloride Dry Syrup 1%
    https://www.info.pmda.go.jp/rgo/MainServlet?recallno=2-9990 (Japanese only)
- Some impurities are found in risk assessment directed by foreign regulatory agency, but others are found at Japanese review process.

→*Transparency of regulation and international communication are expected.*

# Impurities (Mutagenic Impurities)

## [Class II Recall of a brand product]

1. 一般的名称及び販売名

一般的名称：
販売名　　：アレジオンドライシロップ１％

4. 回収理由

当該製品ロットは承認規格に適合しているものの、ICH－M7ガイドラインにてクラス2に分類される可能性のある分解物が製剤中で許容限度値を超えていることが判明したため、当該製品ロットを自主回収することにいたしました。

5. 危惧される具体的な健康被害

本剤をICH M7ガイドラインで定める10年超から一生涯服用にした場合において、健康被害が生じる可能性は完全には否定できないものの、直ちに重篤な健康被害が発生する恐れはないと考えられます。本剤を服用し、更にその後アレジオン錠へ切り替えて服用し続けた場合、ICH-M7ガイドラインで定める10年超から一生涯服用に該当する可能性がありますが、アレジオン錠につきましては、許容限度値内であることを確認しているため、直ちに重篤な健康被害が発生する恐れはないと考えられます。
なお、現在までに本件における健康被害に関する報告は受けておりません。

6. 回収開始年月日

令和3年3月15日

# Impurities (Mutagenic Impurities)

## [Class II Recall of a generic product]

1. 一般的名称及び販売名

一般的名称：
販売名　　：エピナスチン塩酸塩ＤＳ小児用１％「サワイ」

4. 回収理由

当該製品ロットは承認規格に適合しているものの、ICH-M7ガイドラインにてクラス２に分類される可能性のある不純物が製剤中で許容限度値を超えていることが判明したため、当該製品ロットを自主回収することにいたしました。

5. 危惧される具体的な健康被害

ICH-M7に基づくリスク評価をした結果、対象不純物を含む製品を服用した場合に健康被害が生じる可能性は完全には否定できないものの、直ちに重篤な健康被害が発生する恐れはないと考えられます。なお、現在までに本件における健康被害に関する報告は受けておりません。

6. 回収開始年月日

令和3年3月15日

# Impurities (Mutagenic Impurities)

- Challenges to implement ICH-M7 into Pharmacopoeias;
  - Difference of target impurities and testing conditions between APIs/products
  - Process-dependent impurities (ex. reagents, intermediates) in the same APIs from different manufacturing processes
  - Preparation & distribution of Reference Standard
  - QSAR recommendation
  - Regulation for excipients
  - Regulation for products under clinical development
  - Impact against patients by discontinuing medication of impurity-containing drugs
- Considering JP's contents, some options for implementation can be considered. The difference of approach among pharmacopoeias may cause different regulation or testing duplication.
  *→Early discussion may be helpful for pharmacopoeias and stakeholders.*

# Impurities (Mutagenic Impurities)

**Option 1:**

- High-level direction at General Notices
- Some similar description in General Notices with Elemental Impurities;

> *34. In principle, the JP Drug Products are controlled appropriately according to the direction under the Elemental Impurities of the General Tests. When elemental impurities in the drug products are appropriately controlled in accordance with the direction, it is not necessary to perform the tests on elemental impurities such as heavy metals and arsenic in the monographs including but not limited to those of drug products, drug substances and excipients.*

- Without General Tests, description in General Notices only would be meaningless for stakeholders.

# Impurities (Mutagenic Impurities)

**Option 2:**

- Description at Official Monographs, ‘Manufacture’
- Some similar description in ‘Manufacture’ in Official Monograph with ‘Eribulin Mesylate’;

- Large discussion and description will be needed.
- When new synthetic root is applied to API synthesis, the update of Official Monograph is expected.

# Impurities (Mutagenic Impurities)

## Option 2 (example):

### Manufacture

Eribulin Mesylate has 19 chiral carbons, and its purity tests can not estimate all isomers derived from them. Therefore, based on s ound science and the understanding of the product and the manufacturing process, control and manage the isomers and related substances during manufacturing process, and ensure the three-dimensional structure of eribulin mesilate. In the quality control strategy of Eribulin Mesylate, control the related substances including the principal isomers in the drug substance or starting materials and intermediates in upstream process. The acceptance value are not more than 0.22% and not more than 0.68% for the related substances B and C, which are the isomers at position C34 and controlled in the drug substance, and are not more than the threshold requiring identification (0.10%) for the related substances including other isomers. When Eribulin Mesylate is manufactured through the compounds 1 and 2, control as follows.

In the compound 1, control so that the isomers at positions C3 and C11, C12 *cis*-olefin, and other related substances are not more than the threshold requiring identification (0.10%). In the compound 2, control so that the isomers at positions C17 and C29 are not more than 0.30%, and the isomer at position C20 is not more than 0.50%, the isomer at position C25 is not more than 0.40%, and the isomers at positions C23, C27, C34 and C18/C19 *endo*-olefin and the other related substances are not more than the threshold requiring identification (0.10%).

Furthermore, ensure that the isomers at positions C17, C20, C25 and C29 are not more than the threshold requiring identification (0.10%) in the processes after the compounds 1 and 2, and the other related substances are not more than the threshold requiring qualification (0.15%).

When manufactured without reaction using the compounds 1 and 2, perform the control based on the control mentioned above.

# Impurities (Mutagenic Impurities)

**Option 3:**

- High-level direction at General Notices and each specified impurity at Official Monographs
- Some similar description in General Notices with General Notices #36 in JP18 as follows;

> *36. Concerning harmful substances reported as intentionally contaminated to drugs, the control requirement for the presence or absence of contamination is described in the heading "Potential adulteration" in the monograph, as necessary. These substances are controlled by tests on materials, manufacturing processes, intermediates, or final products. The necessity and frequency of the tests are specified separately on individual drugs depending on the control strategy established as part of quality risk management.*

# Impurities (Mutagenic Impurities)

**Option 4:**

- General Information Chapters similar to ICH-M7 Guideline itself

- General Information Chapters are not legal-binding.

# Impurities (Nitrosamines)

- Firstly, *N*-dimethyl nitrosamine was found in sartans in 2018.
- Since then, nitrosamines are found in many APIs/drug products, although root causes of contamination are not completely investigated.

  →*End product testing is one of the key components in control strategy.*
- Guidances for control of nitrosamines and testing methods are published in the US, EU, and other countries.
  - US FDA: Guidance for Industry 'Control of Nitrosamine Impurities in Human Drugs', testing methods for each product (https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications)
  - EMA: Guidance (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities#guidance-for-marketing-authorisation-holders-section)
  - EDQM: Ph. Eur. <2.5.42. *N*-NITROSAMINES IN ACTIVE SUBSTANCES>

- Harmonization of testing method and specification are expected.

# Impurities (Nitrosamines)

**[Experience in Japan to assess nitrosamines]**

- LC-MS/MS and GC-MS methods are established by NIHS to measure nitrosamines.
- NIHS conducted a forced degradation study to assess nitrosamines formation from Ranitidine.

*Biol. Pharm. Bull.* **42**, 547–551 (2019)

**Analysis of an Impurity, *N*-Nitrosodimethylamine, in Valsartan Drug Substances and Associated Products Using GC-MS**

Tomoaki Tsutsumi, Hiroshi Akiyama,* Yosuke Demizu, Nahoko Uchiyama, Sayaka Masada, Genichiro Tsuji, Ryoko Arai, Yasuhiro Abe, Takashi Hakamatsuka, Ken-ichi Izutsu, Yukihiro Goda, and Haruhiro Okuda

*National Institute of Health Sciences; 3–25–26 Tonomachi, Kawasaki-ku, Kawasaki 210–9501, Japan.*

Received January 6, 2019; accepted January 22, 2019; advance publication released online February 7, 2019

SCIENTIFIC REPORTS
nature research

**Rapid and efficient high-performance liquid chromatography analysis of *N*-nitrosodimethylamine impurity in valsartan drug substance and its products**

Sayaka Masada, Genichiro Tsuji, Ryoko Arai, Nahoko Uchiyama, Yosuke Demizu, Tomoaki Tsutsumi, Yasuhiro Abe, Hiroshi Akiyama, Takashi Hakamatsuka, Ken-ichi Izutsu, Yukihiro Goda & Haruhiro Okuda

*Chem. Pharm. Bull.* **68**, 1008–1012 (2020)

**Temperature-Dependent Formation of *N*-Nitrosodimethylamine during the Storage of Ranitidine Reagent Powders and Tablets**

Yasuhiro Abe,# Eiichi Yamamoto,# Hiroyuki Yoshida, Akiko Usui, Naomi Tomita, Hitomi Kanno, Sayaka Masada, Hidetomo Yokoo, Genichiro Tsuji, Nahoko Uchiyama, Takashi Hakamatsuka, Yosuke Demizu, Ken-ichi Izutsu,* Yukihiro Goda, and Haruhiro Okuda

*National Institute of Health Sciences; 3–25–26 Tonomachi, Kawasaki-ku, Kawasaki 210–9501, Japan.*

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**Temperature-dependent formation of *N*-nitrosodimethylamine (NDMA) during the storage of ranitidine reagent powders and tablets**

Yasuhiro Abe, Eiichi Yamamoto, Hiroyuki Yoshida, Sayaka Masada, Hidetomo Yokoo, Genichiro Tsuji, Nahoko Uchiyama, Takashi Hakamatsuka, Yosuke Demizu, Ken-ichi Izutsu, Yukihiro Goda, Haruhiro Okuda

National Institute of Health Sciences, Japan

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**PURPOSE**

In 2019-2020, ranitidine products were voluntarily recalled worldwide due to contamination by *N*-nitrosodimethylamine (NDMA), which is classified as a probable human carcinogen.

The intrinsically unstable nature and tertiary amine structure of ranitidine raised some questions regarding the cause of NDMA contamination. Early FDA reports on elevated NDMA levels following GC-based analysis also suggested that the identified NDMA was a degradation product of ranitidine [1].

It is of particular interest whether NDMA is formed during the storage of the active pharmaceutical ingredients (APIs) or solid formulations.

**OBJECTIVE**

The main objective of this study is to examine the effects of storage at high-temperatures of ranitidine tablets and reagent powders on the potential for NDMA formation.

**METHODS**

The amount of NDMA in ranitidine tablets and reagent powders were measured using headspace (HS)-GC/MS or LC-MS/MS. The detailed methods were described in our recent publication [2].

HS-GC/MS: HS-GC/MS analysis was performed on a 7890B/5977B equipped with 7697A HS auto-sampler (Agilent). The HS oven temperature was operated isothermally within the range of 80–110°C for 10 min.

LC-MS/MS: LC separations were performed on a Nexera LC-40 UHPLC system (Shimadzu) with a Shimpack ARATA C18 column (3.0 × 75 mm, 2.2-μm particle size, 12-nm pore size). MS detection was performed on a Shimadzu LCMS8060 tandem mass spectrometer with an electrospray ionization source in the positive ion mode.

Ion chromatography ($HNO_3^-$): Ranitidine tablets and powders dissolved in purified water were dechlorinated using a MetaSep Ag SPE column. The amount of nitrite in the ranitidine samples was analyzed using a Dionex Integrion HPIC System equipped with an IonPac AS19-4 μm anion exchange column and UV detector (214 nm).

**RESULTS**

**1. Rapid forced-degradation study by HS-GC/MS**

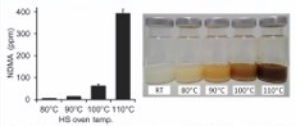



Fig. 1 Effect of HS oven temperature on HS-GC/MS analysis of NDMA in ranitidine tablets.

- Short-term heating (10 min) of ranitidine tablet at 80–110°C induced temperature-dependent formation of NDMA.

**2. NDMA formation in ranitidine samples under accelerated and stress conditions**

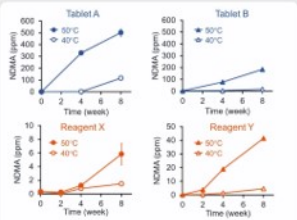



Fig. 2 The amount of NDMA in ranitidine stored at 40°C/75% RH or 50°C/75% RH were measured by LC-MS/MS

- The amount of NDMA formed exceeded the acceptable daily intake limit of 0.32 ppm in ranitidine, as defined by the ICH-M7 criteria, during the accelerated storage conditions.

**3. Factors affecting the formation of NDMA**

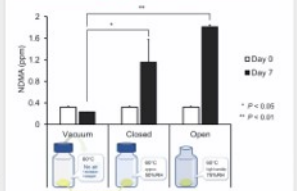



Fig. 3 The amount of NDMA in ranitidine reagent powder X stored under various environmental conditions at 60°C were measured by LC-MS/MS.

- Absence of air in the vials resulted in smaller amounts of newly formed NDMA detectable during observed on storage conditions.
- The variation rates of NDMA formation observed on storage of tablet A and B (Fig. 2) can be partially explained by their different coatings and/or packaging, which determined the exposure to moisture and oxygen.

| Storage conditions | Nitrite ion (ppm) | | |
|---|---|---|---|
| | Day 0 | 8 weeks 40°C/75% RH | 8 weeks 50°C/75% RH |
| Ranitidine tablet A | 11.1 ± 1.0 | 300.3 ± 5.1 | 155.3 ± 0.7 |
| Ranitidine tablet B | 25.9 ± 0.6 | 186.3 ± 10.8 | 177.7 ± 2.0 |
| Ranitidine reagent X | 9.2 ± 1.3 | 16.0 ± 1.4 | 42.2 ± 1.4 |
| Ranitidine reagent Y | 25.4 ± 0.9 | 58.5* | 117.9* |

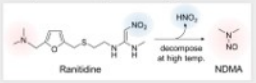
Each result represents the mean ± SD (n=3). * n=1

Table 1. The amount of nitrite in ranitidine after storage for 8 weeks were measured by Ion chromatography.

- Storage of each ranitidine tablets/reagents for 8 weeks at high-temperatures increased nitrite levels, which is considered to be one of the factors influencing NDMA formation.

**CONCLUSIONS**

- Temperature-dependent formation of NDMA occurs during the storage of ranitidine powders and tablets. This clearly supports the risk of NDMA formation in ranitidine formulations is attributable to storage under ambient conditions.
- The formation of NDMA in ranitidine formulations was triggered by exposure to both atmosphere conditions (e.g., moisture, oxygen) and to high-temperature conditions.
- The formation of NDMA as a degradation product, rather than as a result of contamination during the API manufacturing process, indicates additional approaches are required to control the product quality.
- Further investigation of NDMA formation pathways and how these are influenced by various factors (e.g., temperature, atmosphere, excipients, nitrite ratio) is necessary to mitigate the safety risk of these products throughout their lifecycle.




**REFERENCE**

[1] U.S. Food and Drug Administration. "10/2/19: FDA provides update on testing of ranitidine for NDMA impurities" https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine

[2] Abe Y. *et al.* "Temperature-dependent formation of NDMA during the storage of ranitidine reagent powders and tablets" *Chem. Pharm. Bull.* [Online ahead of print, 2020 Aug 8.]

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# Continuous Manufacturing and QbD

- To establish the robust supply chain, alignment on how to regulate continuous manufacturing is expected.
- Batch-release testing such as HPLC will become less important, however in-process control testing will become more important.
- Pharmacopoeias may be able to contribute especially in the following points;
  - Summary of technical recommendation for in-line assays using Near-Infrared spectroscopy (NIR), Infrared spectroscopy (IR), and Raman spectroscopy
  - General Information Chapter on establishing and maintenance of calibration model
  - Development of General Tests to measure Physico-chemical attributes (ex. Cohesive property, Liquidity, Surface characteristics of particle) of APIs/excipients
- In continuous manufacturing, enhanced approach (QbD) is usually adopted and some of the CQAs are controlled in process.
  *→How can we include CQAs that are controlled in process into monographs?*

# Continuous Manufacturing and QbD

[JP's approach for QbD]

- General Information 'Basic Concepts for Quality Assurance of Drug Substances and Drug Products'
- Example: **Sitagliptin Phosphate Tablets**

**Manufacture**

The management strategy of Sitagliptin Phosphate Tablets is based on systematic development methods, which put emphasis on prior setting targets, understanding of products and processes, and process control, and which is based on quality risk management and proven science. In addition when it can be scientifically possible to explain that a disintegration test ensure quality with distinguishability equal or better than a dissolution test, the following disintegration is alternative for the estimation of dissolution.

Disintegration <6.09> Perform the test for 5 minutes: it meets the requirement.

# Alignment of General Tests

- Starting from information exchange on developing/planning General Tests, we could establish the new prospective collaboration project when USP and JP can find the topics which both pharmacopoeias are interested in. Consequently, the picked-up testing methods may become harmonized General Tests in the case both pharmacopoeias can align almost all the aspects.

- By setting comparable General Tests related to outlines of apparatus, calibration methods, testing procedures, etc., duplication of testing for each region might be decreased.

# Alignment of General Tests

**[qNMR]**

- qNMR can be applied to assays by using common internal qNMR reference compound (such as 1,4-BTMSB-$d_4$ for nuclear magnetic resonance spectroscopy) without Reference Standards or reagents specific to the target material. The resources to establish and maintain Reference Standards or reagents can be decreased.

- qNMR has been introduced into in-house Reference Standards or reagents for impurity assay, and alignment of technical recommendation are expected in near future.

# Alignment of General Tests

**[Performance Testing]**

- Functionality of dosage forms are important to ensure consistency of pharmacokinetics, efficacy and safety in human.
  →*The testing method to assess functionality is essential.*

- Expectation to new testing methods for appearing dosage forms
  - Shampoo
  - Oral film
  - Abuse-resistant

- Revision & addition of evaluation methods of functionality along with the progress of analytical technology

# Alignment of General Tests

**[Biologics]**

- Developing monitoring techniques for cell culture process
  - FT-IR/NIR/Raman spectroscopy: useful for monitoring concentration of media components (ex. Glucose, lactic acid)
  - Biocapacitance: viable cell density
  - Multi-Attribute Method (MAM)

- Expectation for Continuous Manufacturing

# Expectation for Communication

- Liaison Exchange Program:
  - Continuing Liaison dispatch from MHLW/PMDA after COVID-19
  - Expectation to welcome USP's Liaison at MHLW/PMDA

- Joint Workshop:
  - Opportunity to meet stakeholders and hear their opinions/expectations
  - Opportunity to inform our collaboration with USP to stakeholders
  - Opportunity to re-think about collaborative topics

***→We'd like to hold such Joint Workshop continuingly, hopefully F2F!***

*Thank you for your attention.*