Outline of Revised Pharmaceuticals and Medical Devices Act / Proposals for Change Control System

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JAPAN PHRMACEUTICAL TRADERS'ASSOCIATION
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JAPAN PHARMACEUTICAL TRADERS' ASSOCIATION

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JAPAN PHRMACEUTICAL TRADERS'ASSOCIATION (JAPTA)

1 Objectives

JAPTA will contribute to the improvement of the national healthcare by supporting adequate provision of medicines through fervent efforts of stable import and supply of safe and good quality APIs, etc.

2 Membership

JAPTA consists of traders of medicines, APIs, their related products, cosmetic materials, additives for food, etc. who agree to the objectives of the Association and are accepted as regular or associate members.

JAPAN PHRMACEUTICAL TRADERS'ASSOCIATION (JAPTA)

3 Operation of Quality Assay Labs

JAPTA operates quality assay laboratories in Tokyo and Osaka, which meet GMP standards.

4 Dissemination of Japanese Pharmaceutical Regulation and Contribution to International Harmonization

JAPTA also hold seminars and conferences for member companies and their customers on Japanese pharmaceutical regulations. Especially, we also present our services to foreign API manufacturers in their countries so that smooth business can be achieved by providing Japanese pharmaceutical regulatory information.

発表内容には演者の個人的見解を含むものであり、正式には関連する通知により確認頂きたい。

The content of the presentation includes the personal views of the performers, and should be officially confirmed by the relevant notice.

本日の内容　Table of contents

Outline of Revised Pharmaceuticals and Medical Devices Act

医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律
Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act)

PMD Act has been amended to on Dec. of 2019.
And it is implemented on Sep. 1 of 2020 to 2022.

	Implementation
Pharmaceutical Affairs Law(revised)	April, 1 of 2005
Pharmaceuticals and Medical Devices Act	Nov. 25 of 2014
Pharmaceuticals and Medical Devices Act (revised)	Sep. 1 of 2020 (1) August 1 of 2021(2) August 1 of 2022(3)

Outline of Revised Pharmaceuticals and Medical Devices Act

Main purpose

・承認審査制度の合理化
Rationalization of approval examination system
・医薬品、医療機器に関する安全対策の強化
Strengthen Safety Measures regarding Drugs, Medical Devices
[施行] 2020年9月1日
[Implementation] Sep. 1 of 2020

・国際的に整合性のとれた品質管理手法の採用
Adoption of internationally consistent quality control method
・法令遵守体制等の整備
Development of legal compliance system, etc.
[施行] 2021年8月1日
[Implementation] August 1 of 2021

・薬剤師・薬局のあり方の見直し等
Review of pharmacists and pharmacies, etc.
[施行] 2022年8月1日
[Implementation] August 1 of 2022

Adoption of internationally consistent quality control method

第十三条の三の二　Article 13-3-2
（医薬品等外国製造業者の保管のみを行う製造所に係る登録）
New Registration system for a foreign manufacturer that only storing operation

[New system]
保管のみを行う外国製造所について登録を行うことにより、外国製造業者認定を取得する必要はない。
It is not necessary to get an Accreditation by registering a foreign manufacturer that only storing operation.

[Current system]
保管のみを行う外国製造所であっても外国製造業者認定を取得する必要がある。
It is necessary to get an Accreditation for a foreign manufacturer that only storing operation.

Adoption of internationally consistent quality control method

第十三条の三の二　Article 13-3-2
（医薬品等外国製造業者の保管のみを行う製造所に係る登録）
New Registration system for a foreign manufacturer that only storing operation

次は除く。
In this case, the manufacturer that only storing operation dose not include following case.

- 表示や包装、検査を行う製造所
  A manufacturer that performs labeling, packaging, testing.
- 市場出荷判定直前の製品の保管を行う製造所
  A manufacturer that stores a product just before the market releasing decision.
- 特に適切な管理が求められる製品の保管を行う製造所
  A manufacturer that stores products that require special management, such as biological products and radiopharmaceuticals.

保管のみを行う製造所に対してもGMP適合性調査が必要となる。
The manufacturer that only storing operation must accept GMP Compliance Inspection.
登録は5年毎に更新する。
Registration needs to be renewed every 5 years.

Adoption of internationally consistent quality control method

第十四条の二　Article 14-2
（基準確認証の交付等）
New application system of periodic GMP Compliance Inspection

[New system]

同一の製造工程の区分の医薬品につき、製造業者が定期GMP適合性調査の申請を行うことができる。同一の製造工程の区分の医薬品は、全ての品目を含める。（3年毎に更新）

For all products that are same manufacturing process category, the manufacturer can apply an application of periodic GMP Compliance Inspection. (Every 3 years.)

[Current system]

特定の医薬品につき、製造販売業者が定期GMP適合性調査の申請を行う。（5年毎に更新）

For specific product, only MAH can apply an application of periodic GMP Compliance Inspection for specific product.　(Every 5 years.)

Adoption of internationally consistent quality control method

第十四条の二　Article 14-2
New application system of periodic GMP Compliance Inspection

[Selection of Application system]

定期GMP適合性調査の申請に当たり、従来のシステムか新規のシステムを選択する。

When applying periodic GMP Compliance Inspection, it can be selected either New system or Current system.

[Selection conditions]

どちらのシステムを選択するかは、同一製造工程区分の品目数や有効期間の違いを考慮する必要がある。

It is necessary to carefully consider which one to select, the number of products in the same manufacturing process category and the difference in validity period.

If MAH approves, the application from the manufacturing site will be possible.

[Issuance of Certificate]

調査の結果GMP適合が確認されれば、基準確認証が交付される。基準確認証が交付された場合、品目毎の定期GMP適合性調査の申請は必要ない。

The certificate will be issued to the manufacturer that meets the inspection.

If the certificate exists, there is no need to apply each product for periodic GMP Compliance Inspection.

Adoption of internationally consistent quality control method

第十四条の二　Article 14-2
New application system of periodic GMP Compliance Inspection

[Inspection fee]

For the products except Biological Products, Radioactive pharmaceuticals etc., Inspection fee is as follows;

Basic charge: 593,800JPY [around 5600*US$]

Price per one product: 13,700 JPY [around 128*US$]

Price per one MAH: 10,000 JPY [around 128*US$]

Travel and Stay expensive

Daily allowance: 200,000JPY [around 1900*US$] x required number of days

* 1US$:107JPY

** It is possible to pay in local currency. (In this case, please care must be taken so that the payment amount does not fall below the billed amount.)

Adoption of internationally consistent quality control method

第十四条の二　Article 14-2
New application system of periodic GMP Compliance Inspection

For example,

Number of the products to apply: 5

Number of the MAHs to use: 10

Inspection Days: 4 days (total 6 days as 2 days to move)

[Total Inspection fee]

Basic charge: 593,800JPY

Price per one products: 13,700 JPY x 5 =68,500 JPY

Price per one MAHs: 10,000 JPY x 10 =100,000 JPY

Daily allowance: 200,000JPY x 6 =1,200,000 JPY

Total fee: 1,962,300 JPY (18,340US$)

+ Travel and Stay expensive (+Interpreter fee)

* 1US$:107JPY

Adoption of internationally consistent quality control method

第十四条の二　Article 14-2
New application system of periodic GMP Compliance Inspection

［今後、確認が必要なこと］
・外国製造業者は直接申請が可能か。
Can foreign manufacturers apply directly?
・基準確認証により品質システムが確認されている場合、新規品目の適合性調査において品質システムは調査対象外となるのか。
If the quality system is confirmed by the certificate, is the quality system excluded from the conformity survey of new product?
・基準確認証発行後に利用を希望する製販はどの様に扱うのか。
After the certificate is issued, how will MAH that newly wish to use it be handled?

Adoption of internationally consistent quality control method

第十四条の七の二　Article 14-7-2
（医薬品、医薬部外品及び化粧品の承認された事項に係る変更計画の確認）
Confirmation of Post Approval Change Management Protocol

MAHは、承認を受けた医薬品の承認された事項の一部の変更に係る計画について、次に該当する時は確認を受けることができる。

MAH can receive confirmation of plans for partial changes to the approved matters of approved pharmaceutical products in the following cases.

製造方法の変更

Change of manufacturing method.

定められた基準に適合しない変更でないこと

The change meets with the established standards.

効能又は効果に影響を与えないもの等

The changes do not affect efficacy or efficacy etc.

[fee]　Application: 20,600JPY (193US$)
Confirmation: 323,000～1,386,800JPY (3,019～12,961US$)

医薬品の品質に係る承認事項の変更に係る取扱い等について（薬生薬審発0309第１号、薬生監麻発0309第１号、平成30年３月９日）により試行していた事前相談制度が法制化された。

The pre consultation system for PACMP that had been implemented on a trial basis from April, 2018 by notification has been legislated.

Adoption of internationally consistent quality control method

第十四条の七の二　Article 14-7-2
Confirmation of Post Approval Change Management Protocol

ICH Q12 Life Cycle Management

PACMPの要素　　Elements of a PACMP

・提案する変更及びその妥当性を含む詳細な説明 A detailed description of the proposed change(s)
・提案する変更の潜在的な影響を評価するために実施する試験及び検討の一覧　A list of specific tests and studies to be performed to evaluate the potential impact of the proposed change(s)
・承認されている管理戦略への適合性 The suitability of the approved control strategy
・その他の満たすべき条件 Any other conditions to be met
・同一又は類似製品における過去の経験から得られたリスクの低減に有用な参考データ Supportive data from previous experience with the same or similar products to allow for risk mitigation
・提案する変更カテゴリー　Proposed reporting category
・PQSの下で継続的な検証が行われることの確認 Confirmation that ongoing verification will be performed under the PQS.

•Elements of PACMP are consistent with Questions and answers on post approval change management protocols (EMA, 30 March 2012) and
Comparability Protocols for Human Drugs and Biologics (*DRAFT GUIDANCE , FDA,* April 2016)

Adoption of internationally consistent quality control method

第十四条の七の二　Article 14-7-2
Confirmation of Post Approval Change Management Protocol

変更計画の確認で望まれること
PACMPに要求される項目はICH Q12等のガイドラインで統一されている。
各項目に対して要求される技術資料の内容は、グローバルに整合性が図られることが期待される。
It is expected that the contents of the technical data required for each item will be globally consistent.

Contents of required Technical data for PACMP

Elements of a PACMP

Japan

USA

EU

It is desirable to be globally consistent.

Adoption of internationally consistent quality control method

第十四条の七の二　Article 14-7-2
Confirmation of Post Approval Change Management Protocol

後発医薬品MF確認相談

・ＭＦの新規登録に先立ち、ＭＦに関する事前の論点整理や資料の十分性等についての新相談システム

Prior to the new registration of MF, a new consultation system regarding the arrangement of issues regarding MF in advance and the adequacy of documents, etc.

・MFに登録された事項の変更に関する新相談システム

New consultation system regarding changes in matters registered in MF

　　軽微変更の妥当性について、データの審査に基づいての確認を行う。

In new system, the validity of minor changes is reviewed based on the data review.

　　従来の簡易相談では、データに基づく審査は行われていない。

In the conventional simple consultation, the examination based on the data is not performed.

[Current system]　Simple Consultation　No data-based review　Fee: 22,600JPY(211US$)

[New system]　New Consultation　Arrangement of issues/ Data-based review　Fee: 320,000JPY(2,991US$)

Change Control system in the approval system

Change Control system

Comparison for Reporting Categories

Basic relationship

J-DMF	US-DMF	ASMF	CEP
変更登録 (Partial change)	Major change	Type II variation	Major revisions (MAJ)
軽微変更届 (Minor change)	Moderate change (CBE in 30 days/ or CBE)	Type IB variation	Minor revisions
		Type IA_{IN} variation	Immediate notifications (IN)
	Minor change (Annual report)	Type IA variation	Notification with annual reporting (AN)
			Renewal

Change Control system in the approval system

Change Control system

Comparison for Reporting Categories

変更管理システムで望まれること-1

軽微変更届出はMinor changeと対訳されているが、 US-DMFのMinor changeやASMFのType IA variationと混同して理解される恐れがある。

US-DMFのMinor change等と区別する必要がある。

It is translated as Minor change, but it may be confused with Minor change of US-DMF and Type IA variation of ASMF. It is necessary to distinguish it from US-DMF Minor change etc.

[Example]
J-DMF

Minor change → Minor change(INR)

INR: Immediate Notification required after the time of releasing

Change Control system in the approval system

Change Control system

Comparison for Reporting Categories

変更管理システムで望まれること-2

変更管理システムについてグローバルな整合性を図る上で、**US-DMF**や**ASMF**の**Moderate change**と同様なシステムを導入することが望まれる。

In order to achieve global consistency of change control systems, it is desirable to introduce a system similar to Moderate change of US-DMF and ASMF.

J-DMF

Partial change
Minor change (INR)

Partial change
Moderate change
Minor change

医療用医薬品の安定確保に関する関係者会議

医薬品の安定確保を図るための取組
(3) 実際に供給不安に陥った際の対応
⑥ 増産・出荷調整等
⑦ 迅速な承認審査
製造方法の一部変更を要する場合には、厚労省・PMDAにおいて迅速に承認審査等を実施
⇒ （品質規格基準について国際的整合化の観点からの見直しの検討）
⑧ 安定確保スキーム

*後発医薬品MF確認相談の活用により同等の効果の可能性

Change Control system in the approval system

Change Control system

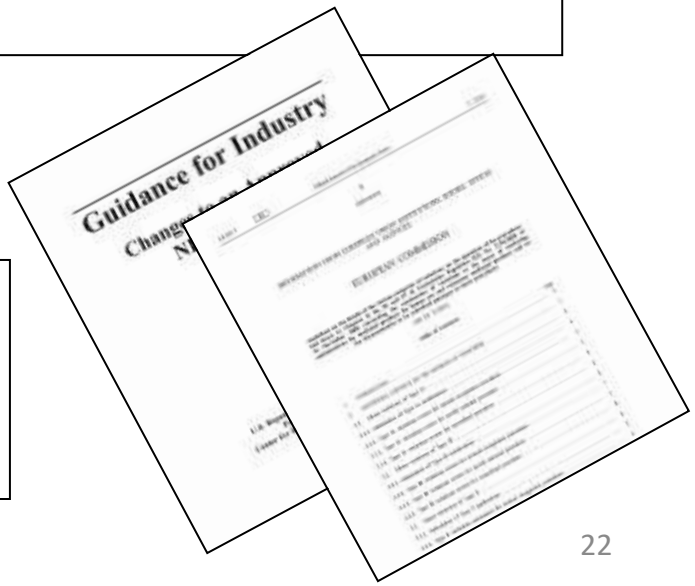
Comparison for Reporting Categories

変更管理システムで望まれること-3

US-DMFや ASMFでは各種変更に対しての変更カテゴリーや、変更に当たって必要となる資料を示したGuidelineを発行している。

変更管理に必要な対応が明確となるGuidelineの制定が望まれる。

It is desirable to establish a guideline that clarifies the measures required for change control.



US-DMF: Guidance for Industry-Changes to an Approved NDA or ANDA (April, 2004)

ASMF: Variations Guideline (2013/C223/01)

Another proposal for MF system

Pre-examination system

MFシステムで望まれること-1

MFの審査は引用する製剤の承認申請により審査が開始される。

現在のシステムに加えて、Certification of Suitability to the EP monograph(CEP) のような事前審査が行われるシステムの併用も望ましいのではないか。

It would be desirable to use a system that undergoes pre-examination, such as the Certification of Suitability to the EP monograph (CEP).

ICH Q11
DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES

ICH M7
ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

*後発医薬品MF確認相談の活用により同等の効果の可能性

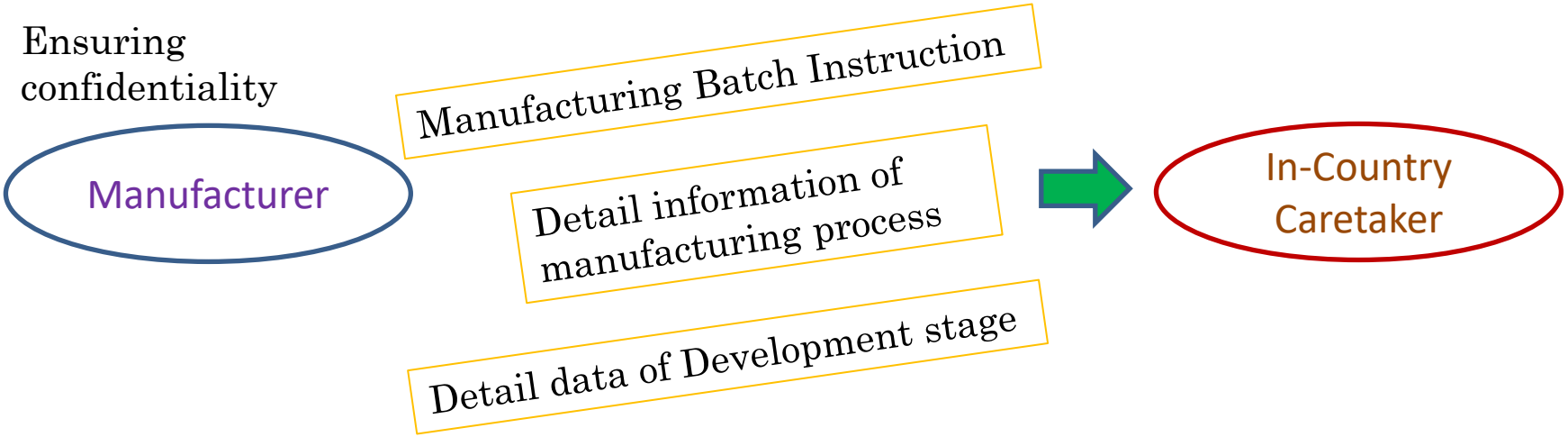
Another proposal for MF system

In-Country Care Taker

MFシステムで望まれること-2

外国製造業者がMFを登録する場合、薬機法施行規則第280条の3, 第2項により原薬等国内管理人を選任する必要がある。日本語に堪能なスタッフを抱える等の対応を図る製造業者については、現在のシステムに加えて、直接申請が可能なシステムの併用も望ましいのではないか。

For foreign manufacturers who have staff who are fluent in Japanese, it would be desirable to use a system that allows direct application in addition to the current system.



Another proposal for Notifications

通知/ガイドライン Notification(s)/Guideline(s)

通知/ガイドラインの発出で望まれること

外国製造業者の理解を促進し、通知/ガイドラインに従った適切な対応を求めるためには、これらの発出と同時に英訳版の公表が望まれる。

In order to promote the understanding of foreign manufacturers and request appropriate responses in accordance with notifications / guidelines, it is desirable to publish an English translation at the same time as these promulgation.

これらの対応が困難な場合も、キーとなる用語について通知/ガイドラインの発出時に英訳の公表が望まれる。

Even if it is difficult to deal with these issues, it is desirable to publish an English translation of key words when notification / guidelines are issued.

[例]　基準確認証

ＱＭＳ適合性調査における「基準適合証」については、
“Certification of conformity”とされている。

Outline of Revised Pharmaceuticals and Medical Devices Act / Proposals for Change Control System

ご清聴ありがとうございました

Thank you for your Attention

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