API Management in Taiwan

藥求安全　食在安心

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Food and Drug Administration,
Ministry of Health and Welfare

http://www.fda.gov.tw/

大綱

- Introduction
- Definition
- The Implementation of API GMP
- The Strategies for Source Management
- Conclusion

The role of TFDA in Pharmaceutical product management

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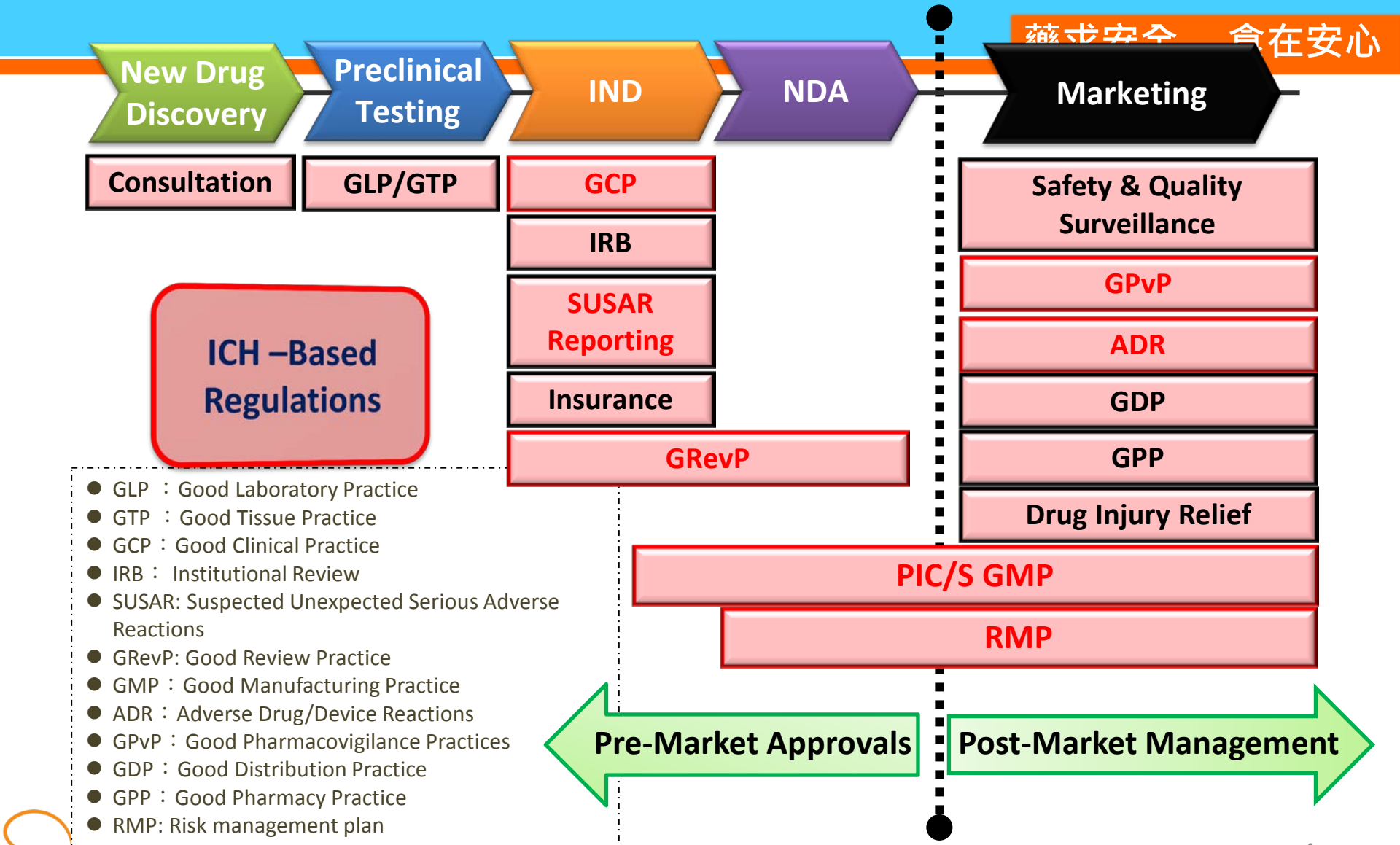
Protect:
Assure Quality, Safety, Efficacy of Medicinal Products

Promote:
Help to Speed the Development of Innovative Medicine and drug accessibility

- **Protect the Public**
  - Pre-marketing review is Scientific evidence based and Good Review Practice (GRevP) followed
  - GCP inspection、PIC/S GMP standard
  - post-marketing surveillance

- **Promote the Science and Innovation**
  - Patients' need centered
  - Good Review Practice (GRevP) followed: streamlining, transparency, communication, internationally regulatory convergence

Medicinal Product Life Cycle Management



- GLP ：Good Laboratory Practice
- GTP ：Good Tissue Practice
- GCP：Good Clinical Practice
- IRB： Institutional Review
- SUSAR: Suspected Unexpected Serious Adverse Reactions
- GRevP: Good Review Practice
- GMP：Good Manufacturing Practice
- ADR：Adverse Drug/Device Reactions
- GPvP：Good Pharmacovigilance Practices
- GDP：Good Distribution Practice
- GPP：Good Pharmacy Practice
- RMP: Risk management plan

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Definition of Drug Substance

FDA (21CFR314.3(b))

Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient.

EU (ICHQ7&Q1A)

Active Pharmaceutical Ingredient (API) (or Drug Substance) Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

(Taiwan) Substances (Active pharmaceutical ingredients):

An active substance or ingredient manufactured through physical and chemical processes or bio-tech procedures and with pharmacological effects that are often used for the manufacturing of drugs, bio-pharmaceuticals or bio-tech products

Japan (Pharmaceutical Affairs Law)

The term "drugs" refers to the following substances.
1. listed in the JP. 2. including dental materials, medical supplies, and sanitary materials, which are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals. 3. intended to affect the structure or functions of the body ofhumans or animals.

HAS (MEDICINES ACT)

"medicinal product" means any substance or which is manufactured, sold, supplied, imported or exported for use of the following ways:
use as an ingredient in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose (treating or preventing disease, diagnosing disease etc).

Drug Master File for API

Definition: ASMF/DMF system is a mechanism for providing confidential information directly to Regulatory Authority by the ASMF/DMF Holder

– Taiwan (Previously)

- Issued in 1st Oct. 2009
- Is the same as that used in the ICH guidelines
- Abbreviated dossier scheme for DMF/ASMF that has been approved by 10 advanced countries was introduced in 21th June 2011

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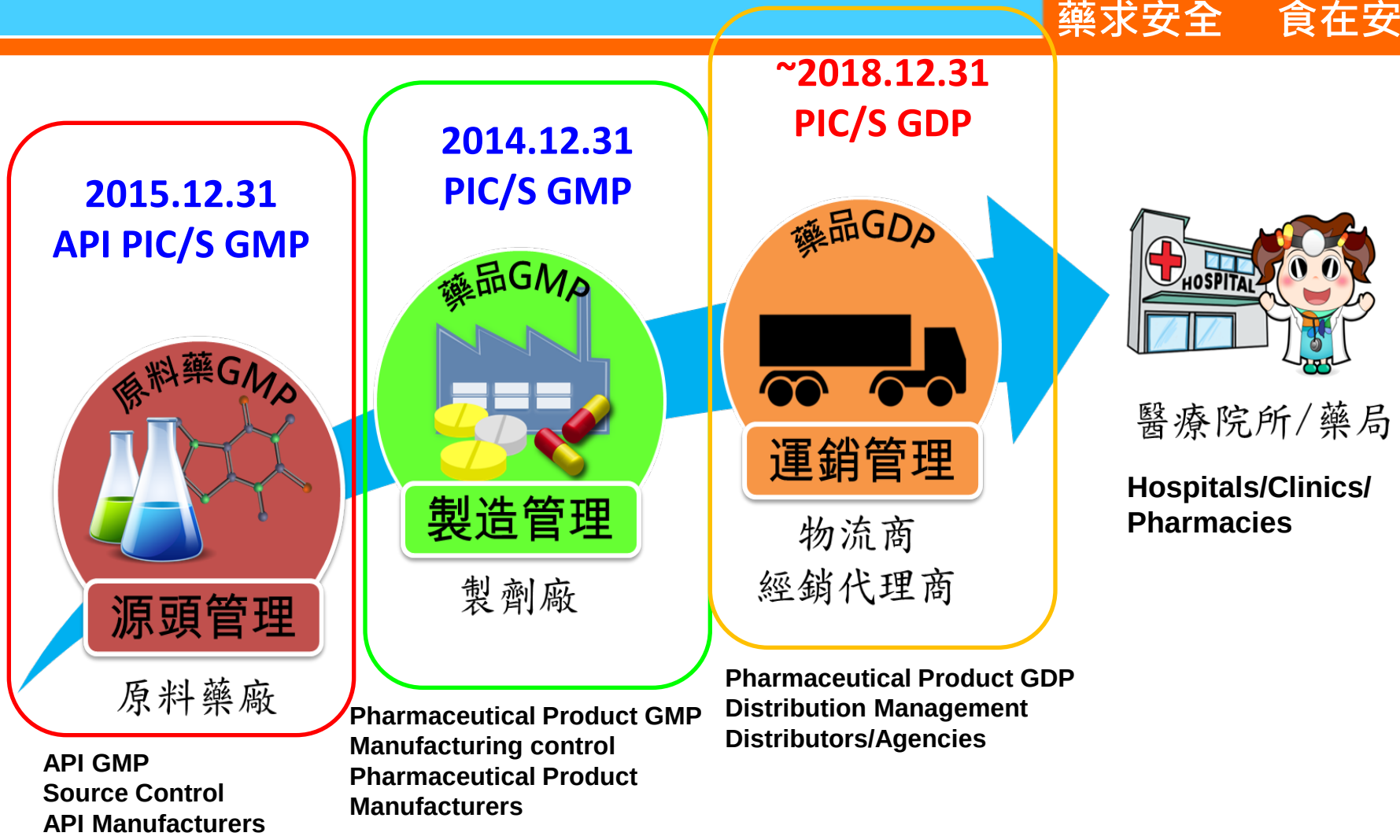
From GMP to GDP



Milestones of API in compliance with GMP

time	Important event
2012.08.08	initiation meeting for the implementation of API in compliance with GMP
2012.09.27	GMP consultative meeting: full compliance in 2017-1-1
2013.01.17	co-signing of 14 stakeholders for API in compliance with GMP
2013.01.23	Declaration that the full compliance is shifted ahead to 2015-12-31
2013.05.25	Announcement of GMP part II (API)
2013.09.25	**Announcement of the timeline for API in compliance of GMP : by the end of 2015.** (公告2015年底前原料藥全面符合GMP)
2014.09.17	Courtesy reminding the stakeholders for necessary preparation
2015.05.12	**Reminding the stakeholders to apply for inspection or sign for** Affidavit of non production
2015.07.31	**Announcement of GMP compliance of API and registering the sources: by the end of 2015**(公告2015年底前製劑使用之原料藥全面符合GMP並應完成上傳登錄)
2015.08.25	Courtesy reminding the stakeholders for improvement of deficiency
2015.08.26	Notifying the stakeholder associations for the recognition principle for GMP document
2015.10.	**Courtesy reminding the downstream (product) manufacturers for non-compliance of upstream (API) license holders** (無法取得GMP之代理商，提醒其下游製劑廠速找貨源)
2015.10.16	**Re-announcement of the policy and conduct a survey on API sources of product license holders.** (函製劑許可證持有者，需原料藥上傳登錄，調查其原料藥取得與否現況)
2015.11.5	**Courtesy reminding the stakeholders for alternative API sources if necessary** (函國內未申請GMP查核業者提醒下游製劑廠，速找其他貨源)

Actions TFDA made to promote GMP compliance of API (TFDA推動製劑使用GMP原料之努力)

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The strategies for implementing medicinal products using API in compliance with GMP

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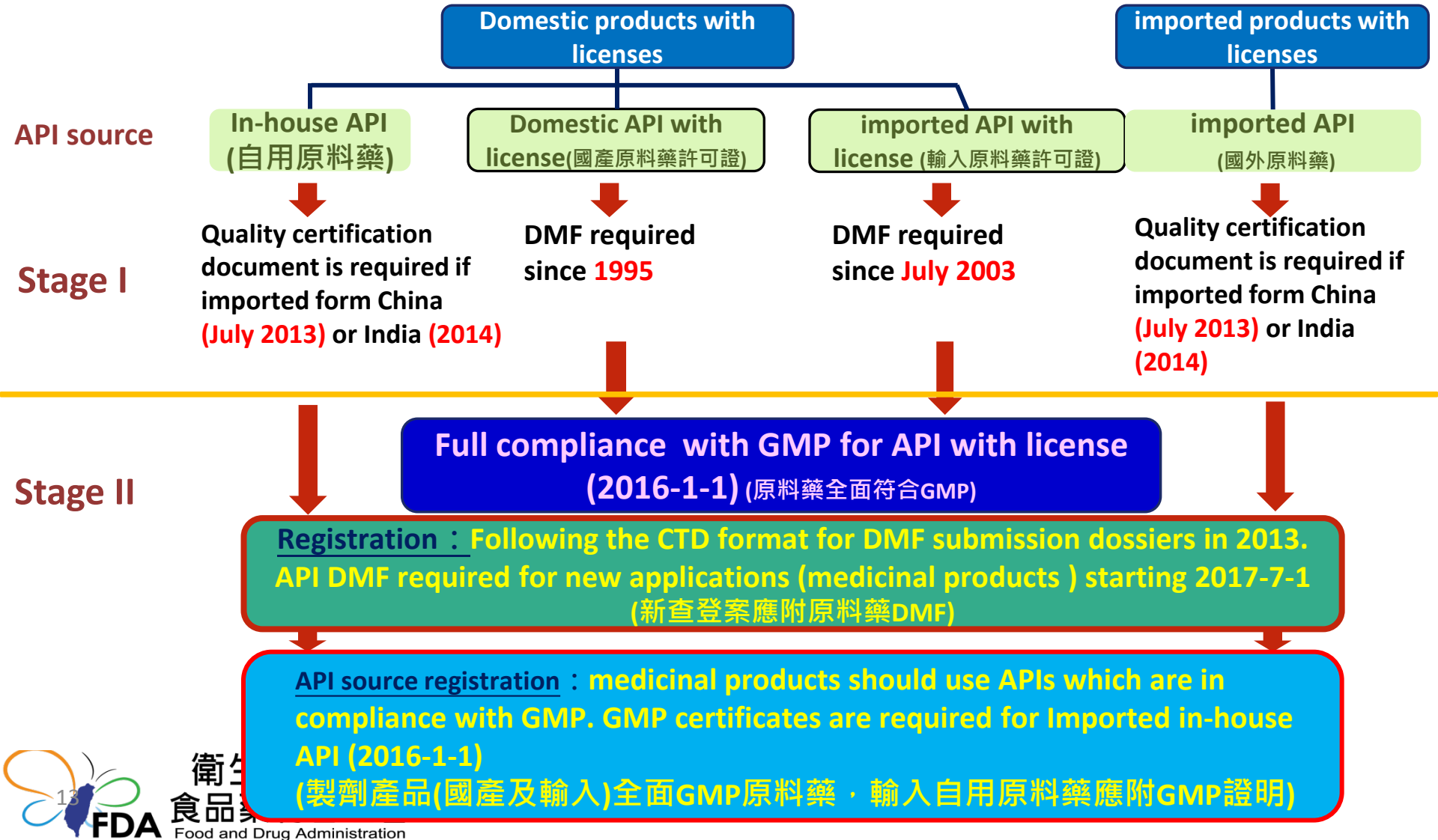

Related measures for promoting products using API in compliance with GMP (製劑符合GMP之配套)

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MOHW announced that all medicinal products should use APIs which are in compliance with GMP and register the API sources (2015-7-31)

Acceptable documents (to show GMP-compliance):

1、GMP certificates of API

2、For other non-prescription drugs or materials in medical devices: (非處方藥或國際間列為醫材者之原料)

(1) Free sale certificates from the 10 medically advanced countries (接受10大心進國採用證明)

(2) Excipient-applicable documents (showing no pharmacologically activity). (檢附資料證明其為賦形劑)

(3) Chinese medicine extract or powder with Chinese medicine license (生藥粉末或中藥浸膏，同意用中藥許可證)

(4) The food ingredients qualify the pharmacopeia standards(除前三項外，國際間列屬食品，除10大先進國之CPP,應符合藥品規格)

The electronic upload of the sources of active ingredients of drug products

- The completion rate is up to 99%.
- Not completion will be cancelled the drug license (article 48 of Pharmaceutical Affairs Act)

Post-marketing management

- Regulations for Registration of Medicinal Products
  - Amended Date:2016.04.06
  - Mainly for API
  - The provisions of article 53, article 39 related appendix 2, and article 40 related appendix 4 amended on April 6th, 2016 in this Regulation shall come into force as of July 1st, 2017.

http://law.moj.gov.tw/Eng/LawClass/LawContent.aspx?PCODE=L0030057

Regulations for Registration of Medicinal Products

- Article 17
  - 10.The sources of active ingredients of drug products (manufacturers' names, manufacturers' addresses and the country of origin) should be specified. Source data can be declared electronically after the approval of the registration.
- Article 32
  - Active ingredients of drug products shall comply with GMP Guidelines.

Regulations for Registration of Medicinal Products

- Article 49
  - For active pharmaceutical ingredients with approved licenses or active ingredients of drug products, data changes in technical documents shall be submitted in accordance with Appendix 12.
- Article 53
  - When applying for an addition or change of the source of active ingredients of the drug, the following documents shall be submitted:
    1. The application form for post-approval changes;
    2. Original copy of the drug license;
    3. GMP compliance certificate of the newly added or changed active ingredients;
    4. The approval of the technical documents of the active ingredients issued by the central health competent authority;

    (continue)

Regulations for Registration of Medicinal Products

- Article 53
  - 5. Description of the differences of specification between the new and old source of active ingredient with evidential proof;
    6. Comparison and evaluation data of the finished preparations according to the characteristics of the dosage forms;
    7. According to the preceding paragraph, a dissolution test shall be conducted； if the comparison results of dissolution curves are dissimilar (f2<50), a drug BE test report shall be submitted.

Regulations for Registration of Medicinal Products

- Article 73
  - The following documents are required for license extension:
    - 5. The supporting documents of the GMP compliance certificate of the active ingredients.

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Win-Win-Win Situation

FDA

Public: protection

Ensure drug quality, safety efficacy, and accessibility

Product promotion

Harmonization with international regulations

Health authority: regulation

Manufacturer: promotion

Become the stepping stone of Taiwan manufacturers

Thank You for Your Attention

Chiang Kai-shek Memorial Hall

Taipei 101

Yehliu Geopark

Sun Moon Lake

North-East coast of Taiwan

Pingxi Flying Lanterns

Penghu

Night Markets

Temples

For more information, please go to: http://www.fda.gov.tw

Appendix 12

- **Documents for the Application of Registration of API Technical Document Changes**

Major changes

Documents to be submitted:

1. Application form for post-approval changes, explaining the difference between the old and new contents.
2. Scientific basis of changes.
3. Change in the manufacturer of the active substance, the GMP-compliance certificate shall be proved.
4. Changes in the manufacturer, manufacturing process, control of starting materials, reagents, intermediates and active ingredients, batch analysis data of three consecutive batches (at least one industrial scale batch) manufactured according to the currently approved and proposed process shall be submitted.

   For active substances known to be stable*: three months data on at least one batch of at least pilot scale batch size. For active substances known to be unstable: six months data on at least three batches of at least pilot scale batch size.
5. Change in immediate packaging of the active ingredient, accelerated testing conditions of six months in duration on at least 2 batches of at least pilot scale shall be submitted.
6. If the comparative data between the currently approved and proposed can not provide, the full dossier (presented in the CTD format) of the technical documents of active ingredients shall be submitted.
7. For imported active ingredient, the notification letter of post approval changes issued by the original manufacturer shall be submitted.

*If after 2 years' long-term test (25℃/60% RH or 30℃/65% RH) and six months' acceleration test (40℃/75% RH), the test results are equivalent to that at the time of release,it can be regarded as an active substance known to be stable.

Changed items	
1. Manufacturer	Change in the manufacturer of a starting material/ intermediate used in the manufacturing process of the active substance or change in the manufacturer of the active substance.
2. Manufacturing process	1. Change in the synthetic route of active ingredients.
	2. Changes of reagents and solvents used in the manufacturing process.
	3. Changes of reaction conditions in the manufacturing process which may have a significant impact on the quality.
	4. Widening of the approved in-process test limits.
	5. Deletion of an in-process test.
3. Control of starting materials, reagents, intermediates and API	1. Deletion of an approvaled test limit item in the specifications.
	2. Widening of the approved specifications limits.
4. Container closure system	1. Change in immediate packaging of the active substance, and the proposed packaging material is different with the approved material.
	2. Changes of the immediate packaging materials of sterile and liquid active ingredients.

Minor changes
Documents to be submitted: 1. The application form for post-approval changes, explaining the difference between the old and new contents. 2. Scientific basis of changes. 3. Change in the manufacturer of the active substance, the GMP-compliance certificate shall be proved. 4. Batch analysis data of one batche manufactured according to the currently approved and proposed process. 5. Accelerated testing conditions of three months in duration on at least one batch . 6. Change in the specification parameters and/or limits of the immediate packaging of the active substance, stability test results are not required. 7. For imported APIactive ingredient, the notification letter of the post approval changes of issued by the original manufacturer shall be submitted.

Changed items	
1. Manufacturer	Changes of the manufacturer (e.g. changes of the manufacturer's addresses, same factory but different manufacturing area or relocation of factory; manufacturing process does not involve changes of synthetic pathways and specifications, and in process control and analytical methods remain the same as approved) and quality control testing sites.
2. Manufacturing process	1. Up to 10-fold increase compared to the originally approved batch size.
	2. Addition or replacement of an in-process test as a result of a quality issue.
3. Control of starting materials, reagents, intermediates and drug substance	Addition or replacement of a specification parameter with its corresponding test method.
4. Container closure system	1. Addition or replacement of a specification parameter as a result of a safety or quality issue.
	2. Deletion or change of a specification parameter.
5. Stability	Change of storage conditions of active ingredients.