

Data Quality

-from Inspectors' Point of View-

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Disclaimer

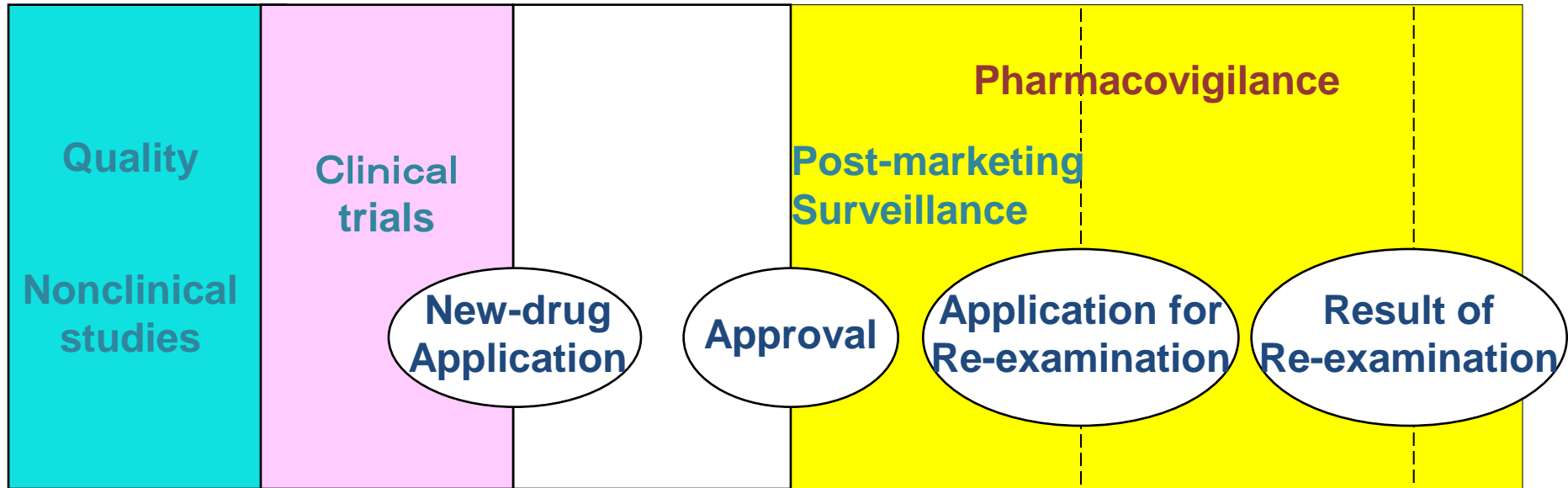


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1. Product Lifecycle and Conformity Inspection
2. Conformity Inspection Conducted by PMDA
3. Data Flow and Quality
4. View Point of Inspection
5. From Recent Topics
6. Summary

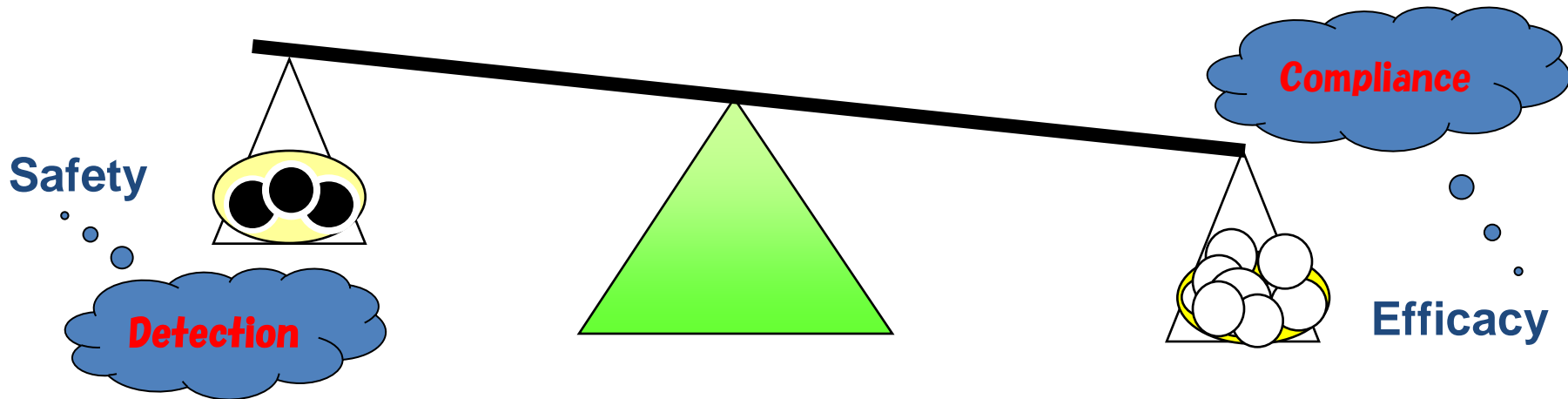
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Product Lifecycle



Evaluation and Data Reliability

It is stipulated in Pharmaceutical Affairs Act that examination of Efficacy and Safety of the relevant product item shall be conducted on the basis of the data and materials attached to the application.

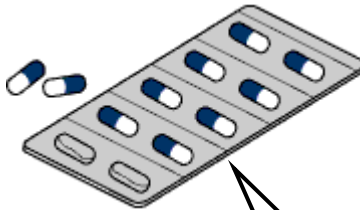


Evaluation with Unreliable Data?

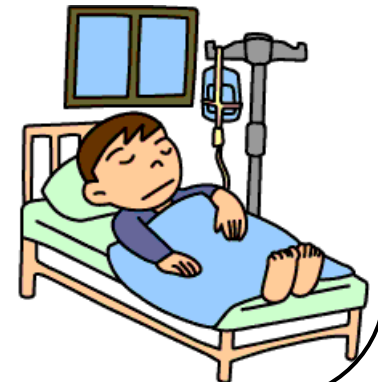
Inaccurate
Data . . .



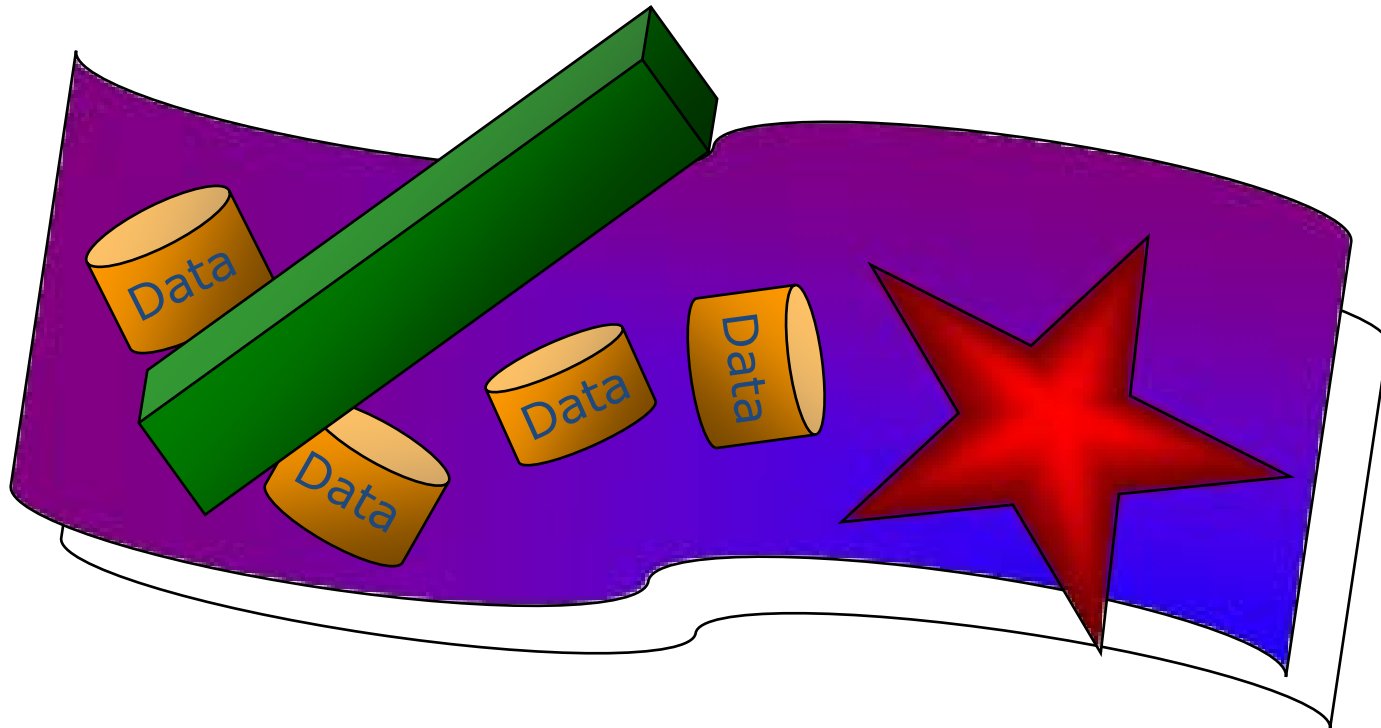
Approved?



Without Appropriate
Safety
Information . . .



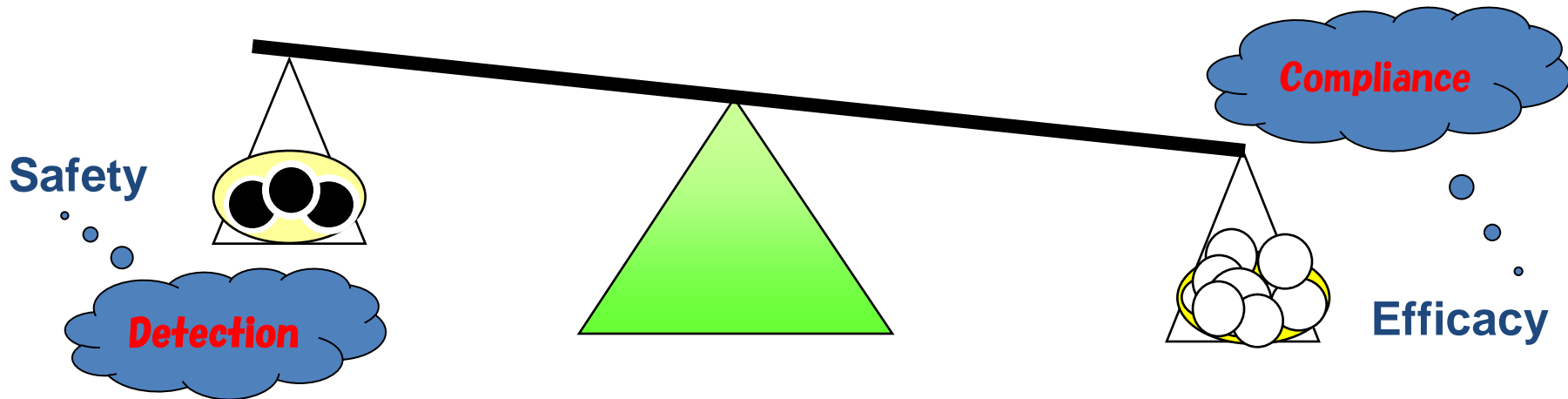
Efficacy and Safety Cannot be Evaluated Appropriately!



More Effective and Safer Drug(s) Cannot be Conveyed promptly to the People who are waiting its(their) arrival.

Evaluation and Data Reliability

It is stipulated in Pharmaceutical Affairs Act that examination of Efficacy and Safety of the relevant product item shall be conducted on the basis of the data and materials **with ensured reliability** attached to the application.



The Pharmaceutical Affairs Act

(Approval to Marketing of Drugs, etc.)

➤ Article 14 (3)

A person who intends to obtain an approval under paragraph (1) shall attach data related to the results of the clinical study or any other materials to the application, as provided for by Ordinance of the Ministry of Health, Labour and Welfare. In such cases, when the drug or medical device pertaining to the application is any of those drugs or medical device specified by Ordinance of the Ministry of Health, Labour and Welfare, the data or materials shall be those collected and prepared in accordance with the standards specified by the Minister of Health, Labour and Welfare.

(For re-examination : Article 14-4)

Ordinance for Enforcement of the Pharmaceutical Affairs Act ①

(Data Reliability Standards for Applications)

➤ Article 43

The materials prescribed in the last sentence of paragraph (3) of Article 14 of the Act (including a case with application mutatis mutandis in paragraph (9) of Article 14) must be collected and prepared pursuant to the following items in addition to those specified in the Ordinance of Implementation Standards for Non-Clinical Studies on Safety of Drugs (Ordinance of Ministry of Welfare No.21 of 1997), the Ordinance of Implementation Standards for Clinical Studies on Drugs (Ordinance of Ministry of Welfare No.28 of 1997), the Ordinance of Implementation Standards for Nonclinical Studies Related to Safety of Medical Devices (Ordinance of Ministry of Health, Labour and Welfare No. 37 of 2005), and the Ordinance of Implementation Standards for Clinical Studies of Medical Devices (Ordinance of Ministry of Health, Labour and Welfare No. 36 of 2005). (to be continued)

Ordinance for Enforcement of the Pharmaceutical Affairs Act ②

(Data Reliability Standards for Applications)

➤ Article 43

- (i) The materials concerned must be prepared precisely in accordance with results provided in investigations or examinations carried out for the purpose of making this **(Accuracy)**
- (ii) Upon investigations or examinations listed in the preceding item, if obtained results of the investigations or results of the examination etc. cast doubt on quality, effectiveness or safety of drugs or medical devices concerned pertaining to the application, results of investigation and results of the examination concerned must be examined and evaluated, and the outcome must be described in the materials concerned **(Completeness, Integrity)**
- The materials that form the basis for the materials concerned must be retained until the date when a decision is made on the approval pursuant to the provision of Article 14 of the Act **(Retention)**

(For re-examination : Article 61)¹²

Standards for Data Reliability

- GLP : Good Laboratory Practice (Ministerial Ordinance)
- GCP : Good Clinical Practice (Ministerial Ordinance)
- GPMSP : Good Post-marketing Surveillance Practice (Ministerial Ordinance)
- GPSP : Good Post-marketing Study Practice (Ministerial Ordinance)
- Data Reliability Standards for Applications (Ordinance for Enforcement of the Pharmaceutical Affairs Act)

The Pharmaceutical Affairs Act

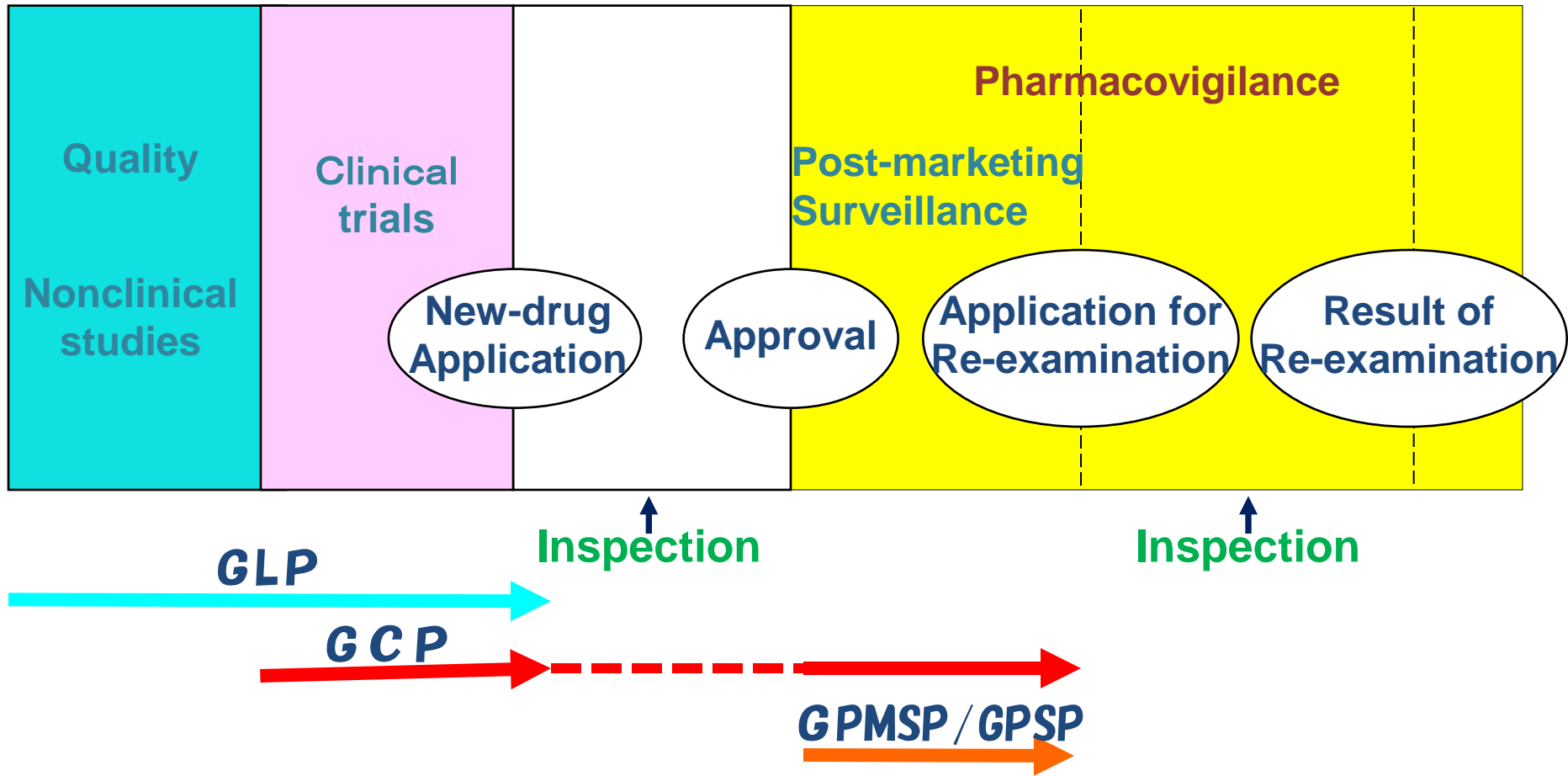
(Approval to Marketing of Drugs, etc.)

➤ Article 14 (5)

In the review pursuant to the provision of paragraph (2), item (iii), examinations of the quality, efficacy and safety of the relevant product item (including examinations of the equivalence of ingredients, quantities, structure, dosage and administration, direction of use, indications, effects, performance, etc., to those of product items which have already been approved for manufacturing and sales) shall be conducted on the basis of the contents of the application for the item concerned as well as the data and materials provided for in the first sentence of paragraph (3). In such cases, when the product item concerned is any of those drugs or medical device specified by Ordinance of the Ministry of Health, Labour and Welfare as provided for in the second sentence of said paragraph, prior written or on-site examinations shall be conducted on whether the data and/or materials on the relevant product item comply with the provision of the second sentence of said paragraph.

(For re-examination : Article 14-5)¹⁴

Product Lifecycle



GLP : Good Laboratory Practice, GCP : Good Clinical Practice, GPMSP : Good Post-marketing Surveillance Practice, GPSP : Good Post-marketing Study Practice

Data reliability standards for applications

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The Pharmaceutical Affairs Act

➤ (Reviews, etc. Performed by the PMDA)

Article 14-2 (1)

The Minister of Health, Labour and Welfare may have the PMDA perform the review for approval pursuant to the provision of paragraph (1) or (9) of the preceding paragraph as well as the examinations or inspections pursuant to the provision of paragraph (5) of said Article or the examinations or inspections pursuant to the provision of paragraph (6) of said Article (including the cases where applied mutatis mutandis pursuant to paragraph (9) of said Article), with respect to those drugs (excluding those intended exclusively for use in animals; hereinafter the same shall apply in this Article), quasi-drugs (excluding those intended exclusively for use in animals; hereinafter the same shall apply in this Article), cosmetics or medical devices (excluding those intended exclusively for use in animals; hereinafter the same shall apply in this Article) which are specified by Cabinet Order.

(For re-examination : Article 14-5)

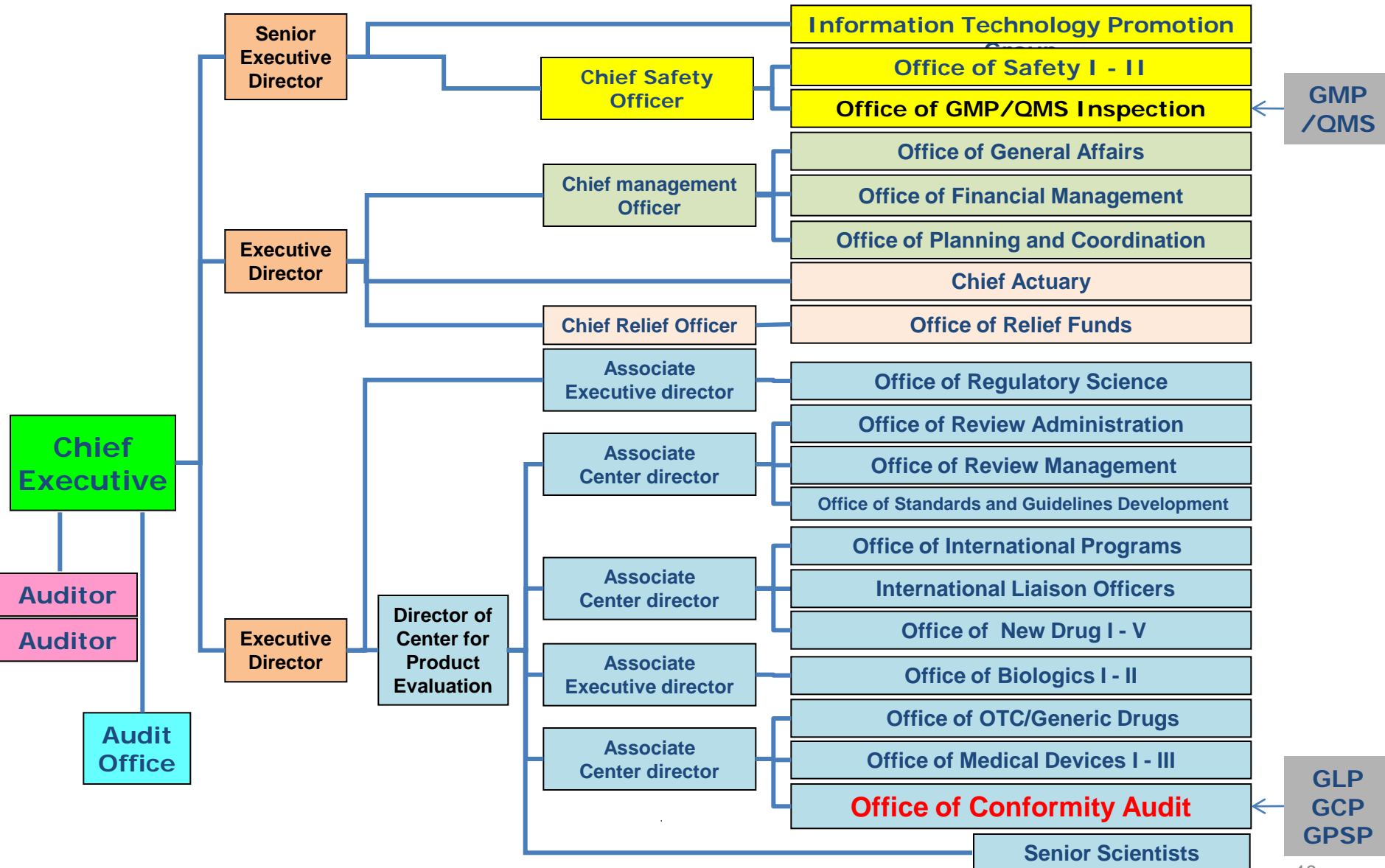
Our philosophy

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

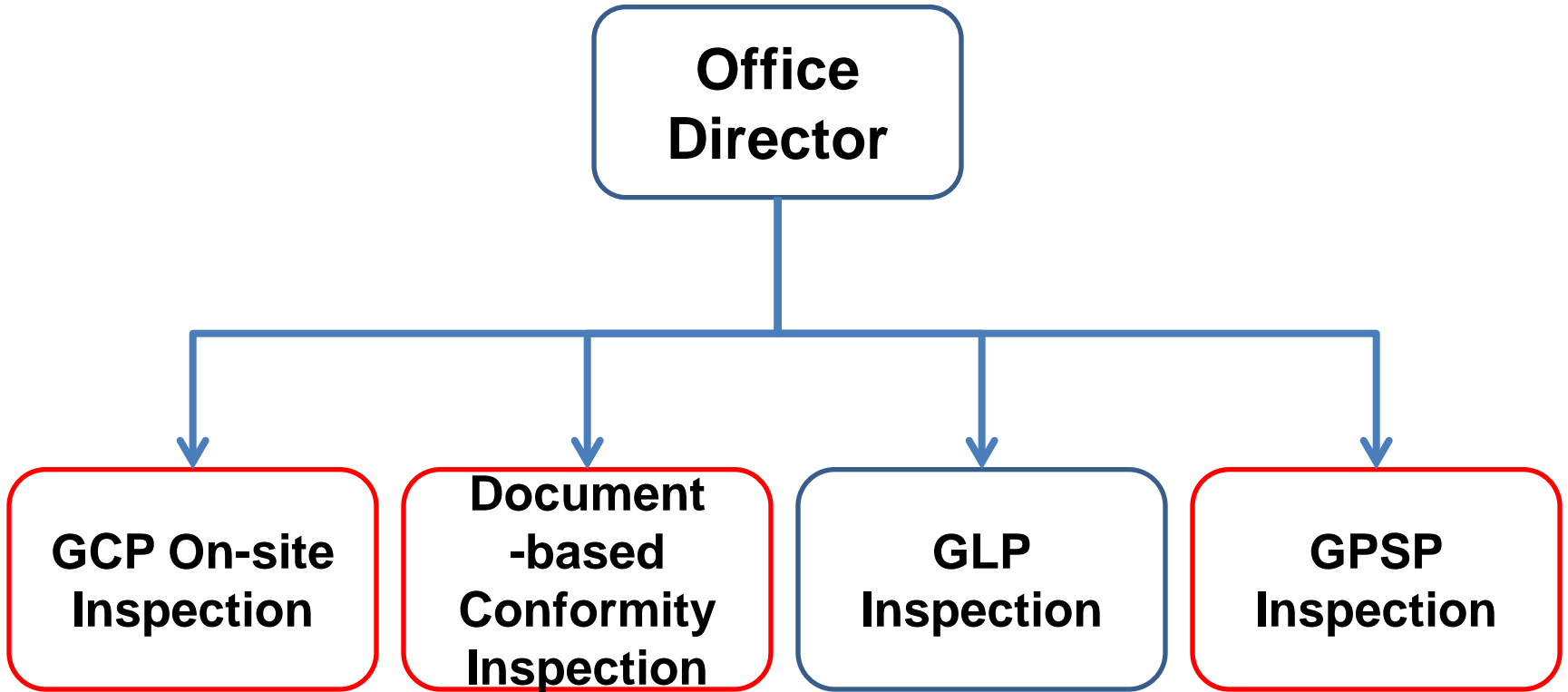
- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.

Organization Chart of PMDA



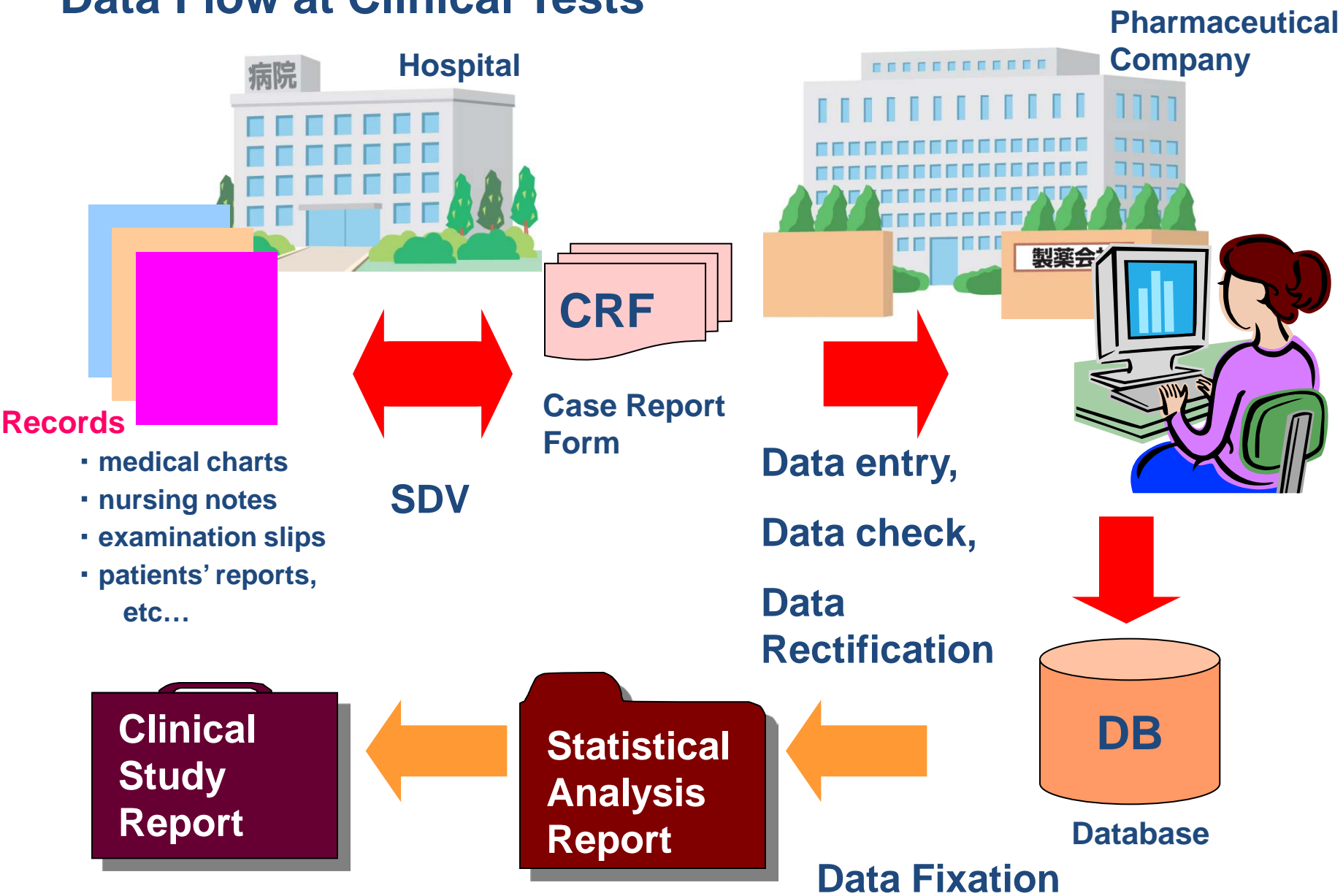
(As of November 2011)

Office of Conformity Audit, PMDA

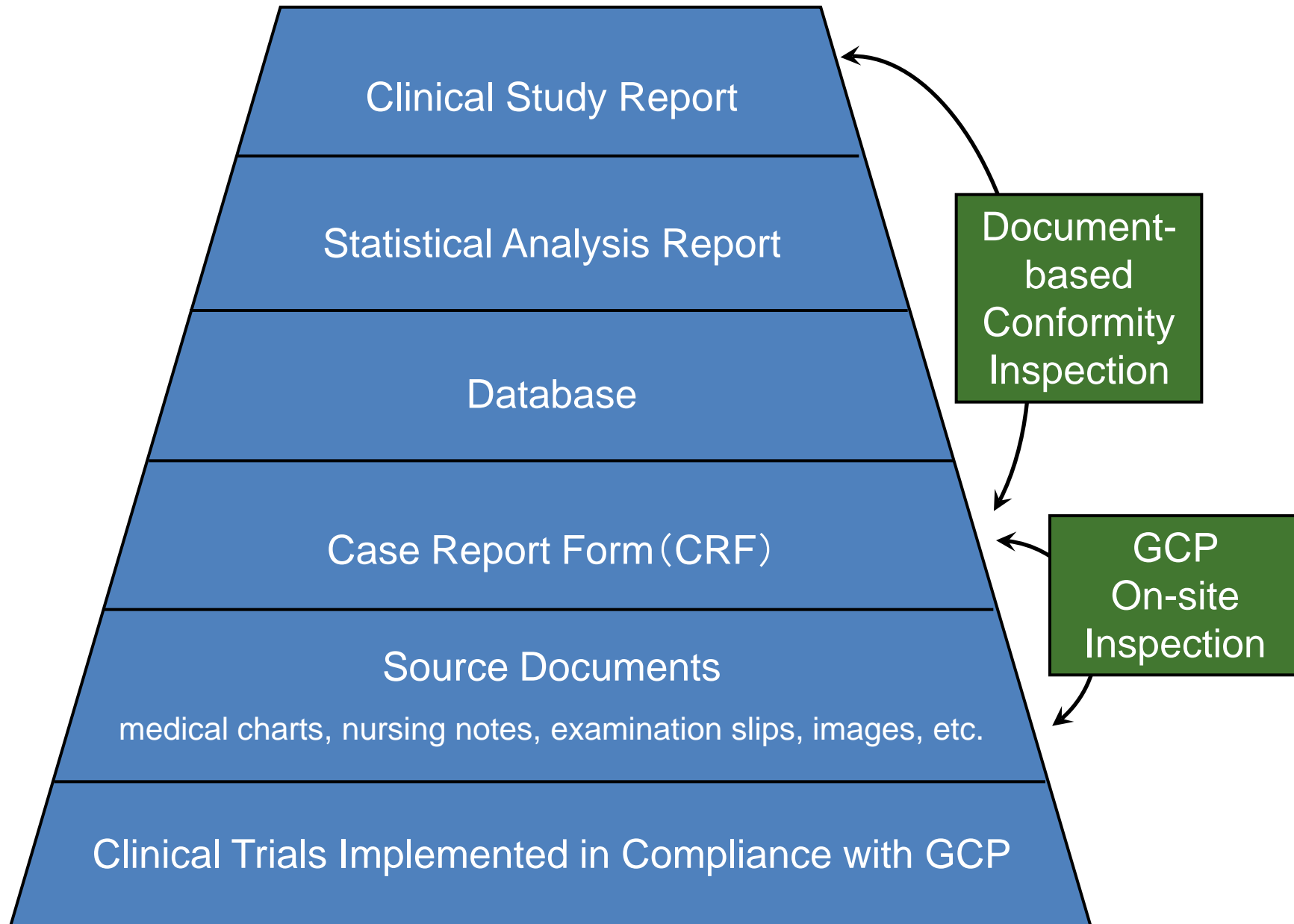


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Data Flow at Clinical Tests



Preparation of Clinical Study Report



Reliability of Documents for the conduct of Clinical Trials

- All information on a clinical trial should be recorded, handled and stored so as to ensure the precise reporting, interpretation and examination thereof.
- Documents for the conduct of clinical trials, whether printed materials or electronic records, should be prepared on the basis of ALCOA-principle.

Attributable – Legible – Contemporaneous – Original – Accurate

Analysis Sets and Quality of Clinical Trial①

- **Full Analysis Set (FAS)**

The set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle. It is derived from the set of all randomised subjects by minimal and justified elimination of subjects.

- **Per Protocol Set (PPS)**

The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations.

Analysis Sets and Quality of Clinical Trial②

- In general, clear-cut discrepancy between FAS and PPS is observed when clinical trials were not conducted in compliance with protocol or protocol had flaws.
- If the discrepancy is found, it is necessary to clarify the background and examine its potential for bias. The difference between analysis results obtained from each analysis set should also be considered.

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Major factors influencing the Quality of Clinical Trials

- Protocol
 - ✓ Often, quality of the protocol impacts quality of clinical trials.
 - ✓ Important thing is to examine closely what kind of data to collect in the course of preparing protocols.
- Implementation system

Major factors influencing the Quality of Clinical Trials

- Protocol
- Implementation system

Key points are...

- ✓ To capture the problems on conducting clinical trials (e.g., interpretation of inclusion criteria, exclusion criteria, etc.) as soon as possible.
- ✓ To feed back the solution to all related sites.

Findings and our point of view

➤ Deviation from the Protocol

- The eligibility of subject was not examined appropriately.

⇒ Was the criteria well-defined?

⇒ Was the criteria reasonable from ethical and/or scientific point of view?

Findings and our point of view

➤ Deviation from the Protocol

- Noncompliance with the rules on evaluating product efficacy and/or safety

⇒ Was the method and/or index for evaluation well-defined, and reasonable from the scientific point of view?

⇒ Did PI (or responsible person) ask about or confirm the interpretation to the sponsor when he/she was not sure about it?

⇒ Did sponsor provide the answer for the question to all related sites as necessary?

⇒ Did sponsor revise the protocol as necessary?

...

Findings and our point of view

- Inappropriately obtained informed consent
 - Informed consent was obtained by using the not fully explained information document.
 - ⇒ Check if the IRB reviewed the document appropriately.

Findings and our point of view

- Inappropriately obtained informed consent
 - Although the written information document was revised, nor were the subjects informed in a timely manner or was the communication of this information documented.
- ⇒ Check if the subject decided to continue participation with his/her own will.

Examples of Inquiry

~Document-based Conformity Inspection~

- Background of Inconsistency
between CRF and CSR, between SAR and CSR,
within CSR
- Handling of ineligible subjects
- Handling of subjects in efficacy analysis set
- Handling of electronic data
- Adequateness of timing of PI signature
- The reason why the blind was broken not in
accordance with the stipulated procedure

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Spread of Electronic Documentation

Of course,

We ACCEPT Electronic Documents!

- EDC(Electronic Data Capture)
- eCRF (Electronic Case Report Form)
- eCTD(Electronic Common Technical Document)
- Document management system
- Electronic medical chart . . . etc.

We are checking . . .

- ✓ if the process can be described with sufficient grounds
- ✓ if it is possible to clarify where responsibility lies

Quality by Design (QbD) in Clinical Trials

- QbD approach is proceeding steadily in the manufacturing field.
- Recently, the concept has been introduced into the field of clinical trials to ensure the quality.

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- Implementation of clinical trials is essential to improve the medical environment by introducing new drug(s). Data must be reliable for appropriate evaluation.
- The actual status of the drug utilization must be reflected to data collected for appropriate re-examination of approved drugs .

We are checking . . .

- ✓ If the quality is assured or not.

How to assure the quality is not our major concern.

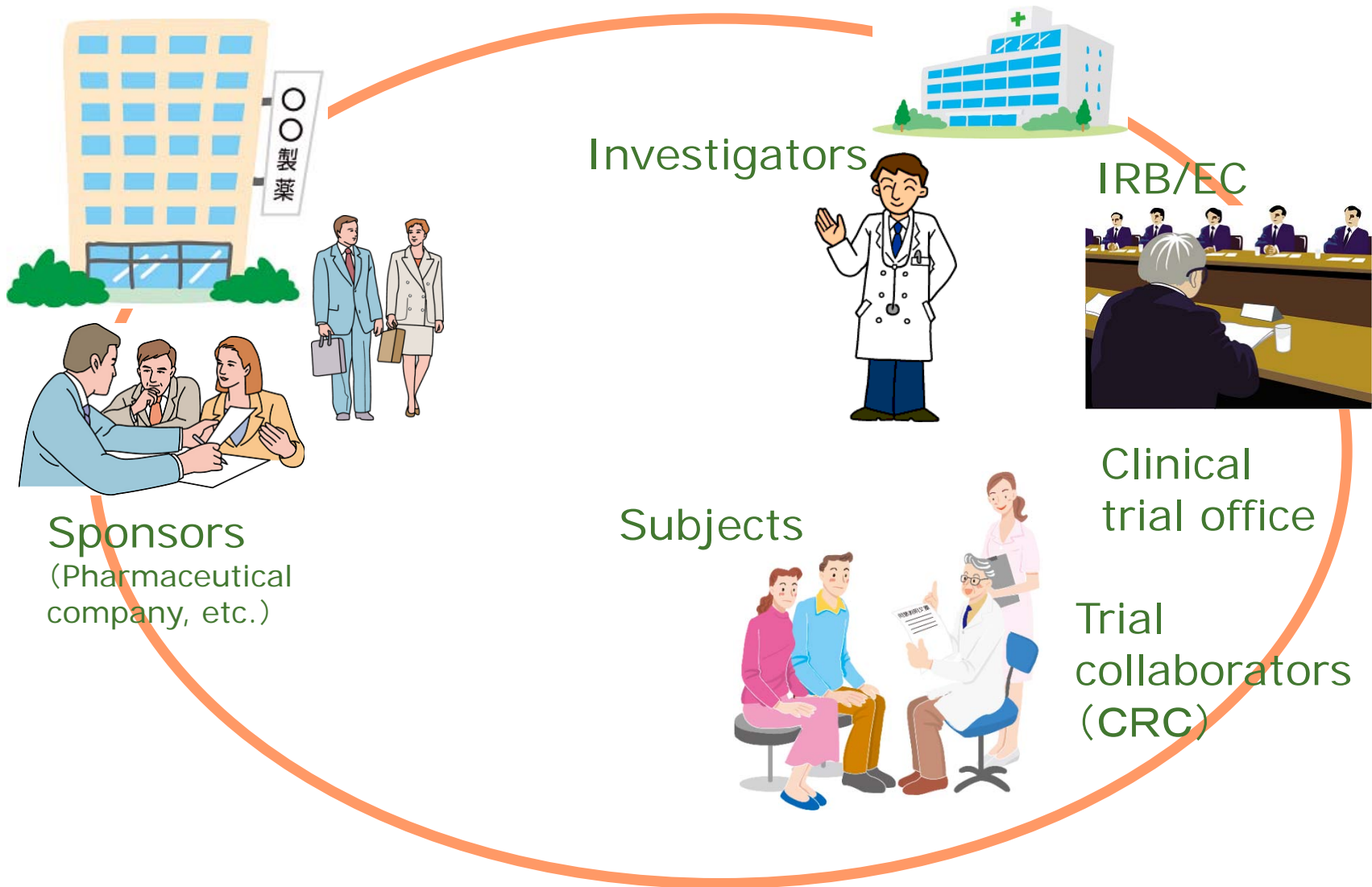
- ✓ If the results and explanations are same with those from data without error.

To consider errors' impact on the results is important.

- ✓ If the data is handled appropriately or not.

Intentionally-handled data will be our major concern.

Smooth implementation of Clinical trials



Cooperation is indispensable.

We try to help improve public health by watching the pre-approval and post-marketing stages also from inspectors' point of view.



Thank you for your attention!

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