Quality Risk Management of the Changes of Sponsors and Production Sites of Drug Clinical Trial – Taking FDA's Management as Reference

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Abstract

Objective To explore the risk management of the changes of sponsors and/or production sites during drug clinical trials based on the theories of quality management, risk management, and change management. **Methods** The method of failure modes and effect analysis (FMEA) was used to identify risks through literature research, expert consultation, comparative research, and comprehensive analysis. Besides, risk priority number (RPN) was used to evaluate the risks. **Results and Conclusion** A FMEA of the changes of sponsors and/or production sites in clinical trials was constructed and RPN values of every failure mode and causes were obtained. Based on the RPN values, the core risk control points for different combination modes of sponsors and/or production sites after their changes were identified. It is recommended that China should strengthen the construction of the sponsor responsibility system. In addition, the changes of sponsors and/or production sites during the clinical trial period should be allowed in an orderly manner under the premise of ensuring the quality of clinical trials and subject protection.

Keywords: sponsor; production site; quality management; risk management; change management; drug clinical trials

To meet the medical needs of the public, China's government has strongly encouraged drug innovations. At the same time, to make sure drug efficacy and safety, China health authority (HA) needs more scientific evidence to approve drug marketing as FDA in the USA and other national drug administrations. During clinical trials, the core work of China HA is to ensure the safety of subjects.

With the reform of drug review and approval [1-3] and the implementation of the drug marketing license holder (MAH), China's regulatory framework has been gradually optimized, which also has improved the rapid transformation of China's pharmaceutical industry. This transformation brings about more active innovations as well as new challenges. For instance, how to implement the main responsibilities of clinical trial sponsors (especially of overseas sponsors), how to manage the oversea sponsors and clinical drug production sites, and how to control risks during the

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change of sponsors and production sites of clinical trial samples are challenges faced by National Medical Products Administration (NMPA) considering the limits of oversea inspections.

Therefore, based on a comparative analysis of clinical trials and their change management modes in the United States and China, combined with the specific situation in China, this paper studies the key risk management elements for the change of oversea sponsors and production sites during clinical trials in China. Through comprehensive risk identification, qualitative and quantitative risk assessment methods, the core risks before and after the changes of sponsors and production sites are investigated, and some relevant regulatory recommendations are proposed.

1 The administration of clinical trials in the United States

1.1 General introduction of clinical trials administration in the United States

To ensure the subjects safety, the sponsor, as the responsible subject, should conduct clinical trials after obtaining the clinical trial approval and other permits from FDA [4]. During clinical trials, the change should get the related permission too. The administration of FDA focuses on the following two points: (1) Ensuring the safety and rights of subjects; (2) The quality of pre-clinical and clinical activities to ensure the evaluation of the drug's safety and efficacy [5].

When sponsors submit the first clinical trial application with related documents package, FDA will give a unique number of the invested new drug (IND) for this drug. Based on the update of its documents package, FDA implements full process management.

Within 30 days after receiving the submitted IND application, FDA will give the "objection" or "no objection" opinions based on the evaluation of the safety characters of the drug and the rationality of the clinical trial design, or as implied recognition. The progress of clinical trials should be reported timely as FDA required. When there are significant or potential significant risks to the subject, FDA can request the termination and suspension of the clinical trial.

In addition, FDA will check the "Good Clinical Practice (GCP)" compliance of sponsors, investigators and others through the official inspections. If there are major findings during the inspection, FDA will refuse to allow the clinical trial to be done at the related site or refuse to accept the new drug application (NDA) from this sponsor. FDA also has the right to revoke the qualifications of investigators with strict violation issues. For the sponsors and the study sites that are located overseas, FDA will conduct the inspection according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards.

Changes are inevitable during the drug developments. To encourage innovation and improve the efficiency of the change administration, there are two approaches by FDA for the change management of major or minor changes based on the impaction on the safety of the subject. For major changes, the sponsor should submit a supplementary application, and FDA will review and approve it. FDA can give an approval or no-approval response within 30 days based on the evaluation results, or as implied recognition. For minor changes, sponsors may decide by themselves and implement them at any time, but they should inform FDA in the annual report [6, 7].

Changes should trigger the IND documents update. Sponsors needs to add or revise them under the unique IND number. In NDA stage, sponsors will summarize and submit final package to support the drug's approval by FDA. After approval, MAH also needs to produce and market the drug following the approved NDA package to ensure the compliance. FDA can conduct the compliance inspections after NDA approval based on the package, including oversea inspections. The full traceability of application package is the cornerstone of ensuring the full lifecycle supervision.

1.2 The role and responsibility of clinical trials in the United States

Through various attraction policies, the drug innovations from multi-national pharmaceutical

industry are actively carried out in the United States. However, there are risks inherent in drug research and development, clinical trials require multiple parties to cooperate and clear role and responsibility (R&R). FDA widely uses legal means to adjust civil relations during clinical trials, that is, civil subjects exercise legitimate rights and benefits, and violations face punishment.

The clinical trials are jointly completed by sponsors and their entrusted vendors as third-party service providers CRO (contract research organization)/CMO (contract production sites organization and others), investigators (and their affiliated research institution), and the subjects. The three parties of sponsors, vendors and investigators have the most basic legal relationship based on the "Contracts/Authorization Letter for the Clinical Trials" "Informed Consent", and others. FDA will pay more attention to the sponsors' R&R, and they are required to submit a 1 571 application form in IND submission. The sponsors (including CROs, etc.) have to clarify the R&R with investigators, which supports the foundation for subsequent "social supervision". It should be noted that FDA also administrates the investigators initiated clinical trials (IITs). The investigators may be familiar with the R&R as the sponsors in IITs.

In the United States, the lawyer community has actively participated in the "supervision" activities of drug research and development. The lawyer association actively participates in the collection of evidence of illegal operations by clinical trial participants such as sponsors and researchers and strives for relevant benefits for the subjects by obtaining partial winning compensation fees. The above social regulatory actions will continue after the drug is marketed [8]. For example, U.S. courts attach importance to consumer feedback, and if the product fails to meet the relevant evaluation after the product is marketed, it will be judged as defective. Under certain state laws in the U.S., high punitive damages will be awarded for intentionally concealing the cautionary content of product instructions, including safety information obtained during clinical practice.

To this end, a sponsor must have sufficient capabilities, including the ability to meet GCP, GMP, GVP, and other requirements, and comply with research, production, and marketing activities. The sponsor and researcher, as well as third-party service providers (including entrusted production sites, etc.), determine the research agreement in detail. If the service provider correctly implements the agreement, it will receive corresponding service remuneration to avoid litigation or compensation. The sponsor bears some risks such as research and development failures as well as service provider errors. When there is a change in the sponsors, in order to ensure their own interests, the changed sponsors will also conduct a rigorous and comprehensive evaluation (due diligence) of the preliminary work to avoid losses. The marketing license holder also needs to have sufficient capacity to take compliance actions to assume responsibility for the full life cycle management. Under this management mode of social co governance, a certain degree of industry self-discipline has been formed. At the same time, this social co governance system has also promoted a prosperous pharmaceutical industry.

Based on this management mode, FDA allows flexible cooperation modes between sponsors and production sites, including the use of overseas clinical drug production sites by U.S. sponsors, or the use of production sites within the United States by overseas sponsors. At the same time, changes in the sponsor during a clinical trial usually do not have a significant impact on the safety of the subject, which are minor changes. Changes to production sites require specific analysis and evaluation based on relevant technical requirements, but their changes will not be limited by whether the production site is located within or outside the United States.

2 The administration of clinical trials in China

In order to encourage drug innovation, NMPA continuously promotes the reform of drug review and approval and the establishment of the MAH system. Therefore, China's pharmaceutical industry

is gradually undergoing transformation. The development of the industry has promoted some demands for market-oriented division of labor and cooperation, including the cross-border situation of sponsors and production sites. In order to meet the needs of industry development, NMPA attempts to adjust the existing regulatory mode while ensuring the quality of clinical trials.

2.1 General introduction of clinical trials administration in China

According to the "Measures for the Administration of Drug Registration" [9], China's drug regulatory agencies manage clinical trials of drug for the purpose of drug registration on the market. The Center of Drug Evaluation (CDE) of the NMPA shall decide whether the clinical trial of the drug can be implemented within 60 working days after the acceptance of the clinical trial application (CTA).

Just as FDA's clinical trial management, the applicant approved for clinical trials is the sponsor in China, who should take responsibilities in the clinical trial. Currently, the requirements for clinical trials and the international ICH are gradually converging, and sponsors need to strictly implement the "Good Clinical Practice for Drug Trials (No. 57, 2020)" (hereinafter referred to as "GCP") [10] and ICH requirements and establish a full clinical trial quality management system. Meanwhile they have to provide qualified clinical trial drug in accordance with the Appendix for Clinical Trial Drug (Trial Implementation) of the "Good Manufacturing Practice for Medical Products (Revised in 2010)" (Order No. 79 of the Ministry of Health) (hereinafter referred to as the "Clinical GMP") [11] to ensure the safety of subjects. During the clinical trials, if safety issues or other risks are found, the sponsor shall promptly adjust the clinical trial protocol, suspend or terminate the clinical trial, and report it to the CDE in accordance with the GCP and the "Good Manufacturing Practice for Pharmacovigilance (Announcement No. 65 of the NMPA, 2021)" (hereinafter referred to as GVP) [12]. CDE also has the right to suspend, terminate, or restart clinical trial research based on the latest research situation.

It is like FDA's hierarchical management of changes, in China, sponsors need to evaluate changes that occur during clinical trials. If the evaluation results do not affect the safety of the subjects, they can directly implement them and report them in the safety update report during research and development. After evaluation, if there is possibility of the safety of the subjects, a supplementary application should be submitted and approved by the regulatory department before implementation. In the event of a change in the sponsors, the changed sponsors shall bear the relevant responsibilities and obligations for the clinical trial.

2.2 The chances and challenges of clinical trials administration in China

Currently, there are only two combinations modes of sponsors and production sites for clinical trials in China.

Combination mode 1: Domestic sponsors and their clinical trial drug are produced in domestic production sites.

Combination mode 2: Overseas sponsors and their clinical trial drug are produced in overseas production sites.

For changes that occur between combination mode 1 and combination mode 2, (new) sponsors can apply for registration through supplementary applications. Changes between combination modes 1 and 2 require (new) sponsors to submit a new CTA, as shown in Fig. 1. In addition, the current regulations do not have clear rules on the channels through which to apply for individual changes to the sponsor. However, when other information in the original CTA approval document changes, changes in the sponsor's information can be merged. It should be noted that this change is only a change in the content of administrative documents, and at this time, the regulatory authorities will not judge the ability or qualifications of (new) sponsors.

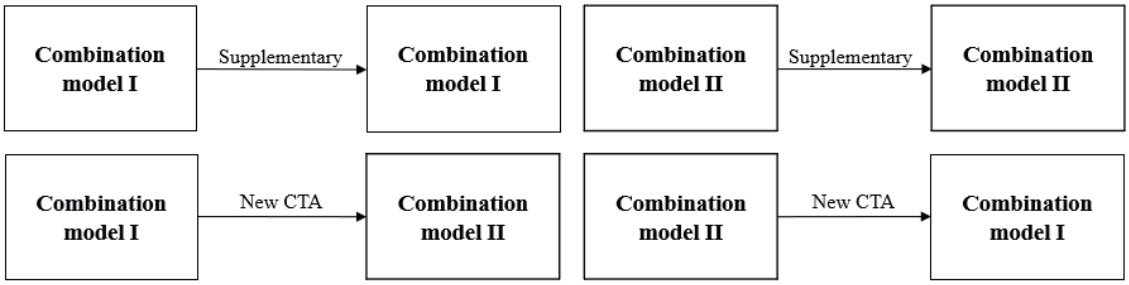

Fig. 1 The allowed changes of sponsors and their production sites

Currently, Chinese pharmaceutical innovational enterprises begin to license in overseas technology, or license out their new drug technology, or cooperate with overseas enterprises to conduct drug research and development, resulting in some new combination models, as the cross-board modes below.

Combination mode 3: A domestic sponsor hopes to use clinical drug produced outside of China for the clinical trials implemented in Chinese subjects.

Combination mode 4: An overseas sponsor hopes to conduct clinical trials using clinical drug produced in China.

However, China has not allowed clinical trials of these two cross-border combinations, nor the existing combination model to be changed to combination models 3 and 4, as shown in Fig. 2.

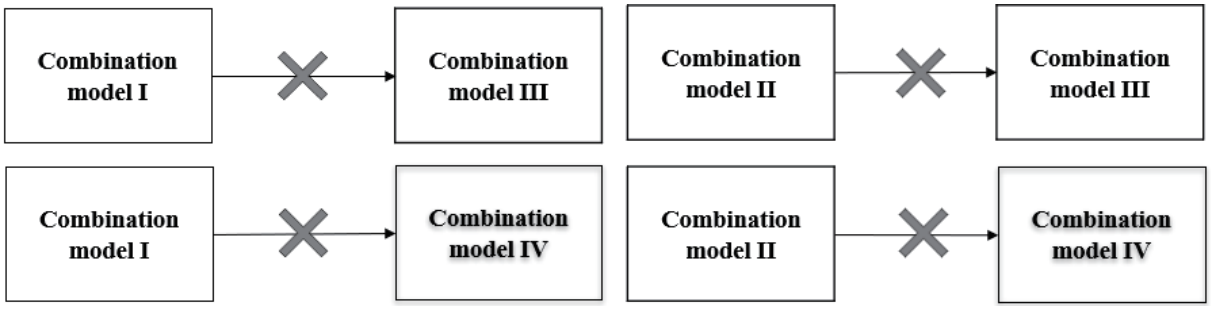

Fig. 2 The not allowed changes of sponsors and their production sites

Currently, China's pharmaceutical industry is in the development stage, and there are significant differences in the capabilities of sponsors. Some sponsors' capabilities of quality management and risk prevention and control for cross-border commissioned production need to be further improved. At the same time, although China has made significant progress in the reform of drug review and approval, the regulatory guidance system still needs to be improved. The social publicity system for sponsors is under construction. Due to restrictions on resources, conditions, and sudden health conditions, there are also practical challenges for China's drug regulatory agencies to implement relevant regulatory activities for overseas sponsors and production sites. Therefore, there are some challenges in implementing the supervision of the main responsibilities of sponsors. It is necessary to conduct in-depth research, fully identify the core risks of clinical trial changes, focus on high and secondary risks, and recommend relevant risk control measures based on the specific situation in China.

3 Risks identification and analysis of clinical trials in China

In this study, failure modes, effects, and criticality analysis (FMECA) [13] is used to form a FMEA (failure modes and effect analysis) report during the risk identification process. In the risk analysis and evaluation process, the risk priority number (RPN) method is used for criticality analysis (CA).

3.1 Risks identification

The FMEA method requires a detailed analysis of the object, identifying all possible failure modes, and determining the possible causes and effects of each failure mode. The failure causes, failure modes, and failure effects in FMEA correspond to the risk factors, risk accidents, and losses caused by risks among the three elements. This study uses clinical trials as the object, combines literature research method and expert consultation method, and constructs its FMEA report through expert brainstorming to identify the risks of clinical trials.

3.1.1 Assumption of risks identification

Clinical trials are taken as a "production" activity using "clinical trial drug" in accordance with "clinical protocols (including their supporting informed consent forms, researchers' manuals, etc.)". As this study ultimately focuses on the risks associated with changes in the sponsor and production site, risk identification looks for all possible failure modes in the dimensions of "people" "machine" "material" "method", and "environment". Due to the complexity of the clinical trial process of innovative drug and the characteristics of constantly adjusting to new situations, the following assumptions have been made to focus on risk management of subsequent changes.

It is assumed that the sponsor of a clinical trial has only entrusted the clinical drug production site to simplify the commission of CRO. At the same time, because the impact of China's ethics committee and researchers can offset each other before and after the change, in the analysis of "people", we should focus on the risk identification of "sponsor" and "production site" to facilitate the regulatory department to control the risk. In the analysis of "law", the focus is on the implementation of GCP, clinical research drug GMP, and GVP, simplifying other requirements such as ethical and human genetic resource management.

It is assumed that the performance of the equipment and instruments required for clinical trials is stable and reliable. At present, China's pharmaceutical industry has developed to a relatively mature stage, and equipment and instruments in both clinical institutions and production sites can be routinely managed, simplifying the consideration of "machine".

It is assumed that the quality of clinical trial drug is controllable, we should focus on the quality management of clinical trial drug in the "material".

This study focuses on how to obtain qualified "clinical trial drug" (materials) for the sponsor and production site in clinical trials, and clinical trials are conducted in accordance with the "clinical trial protocol", GCP, GMP for clinical trial drug, and GVP for clinical trial. In addition, this study will also assess aspects such as the "environment".

3.1.2 Failure modes and effect analysis (FMEA)

In the final FMEA, the initial agreed level is "clinical trial", and the second agreed level is "sponsor" and "production site". Based on literature research, the FMEA is analyzed at the levels of "person" "material" "method", and "environment". Then, the first draft of the FMEA report is formed. After that, the expert meeting consultation method is used to revise and supplement the initial FMEA report. The experts attending the meeting include representatives from the sponsors, regulators, production sites, and researchers. They are all senior experts in the field of drug research and development. After discussion at the expert meeting, the final FMEA report contains a total of 33 failure modes and 118 failure causes, as listed in Table 1.

Table 1 The summary of failure modes and causes

Level	Failure mode	Failure cause
FMEA report for sponsors in clinical trials	21	94
FMEA report for production sites in clinical trials	12	24
Total	33	118

3.2 Risks analysis and evaluation

3.2.1 Risks analysis process

The research is conducted using the expert brainstorming method in the following three steps.

Step 1: Under the combined modes of four different sponsors and production sites, the scoring criteria of severity (S), occurrence (O), and detectability (D) for 33 failure modes in the FEMA report of each combined mode should be determined, and then, they are scored based on the criteria. The scoring criteria are shown in Table 2.

Table 2 The standards of S/O/D scoring

Score	Severity (S)	Occurrence (O)	Detection (D)
5	The highest risks to subjects	The most frequent happened and almost inevitable	Extremely difficult to be found
4	Higher risks to subjects	More frequent happened	Difficult to be found
3	Middle level risks to subjects	Happened in a while	Be found through certain methods
2	Small risks to subjects	The most infrequent happened	Easier to be found
1	No risks to subjects	More infrequent happened	Very easy to be found

This study is to propose management recommendations for regulation, so risk assessment is to assess the impact of changes on the safety of subjects during clinical research from a regulatory perspective. In the study, various failure modes are scored based on expert knowledge and experience through discussion and resolution. The participating experts are composed of multiple representatives of domestic and foreign sponsors, production site representatives, regulatory review experts, regulatory inspection experts, etc., all of whom are middle and senior management personnel. Enterprise representatives are all industry executives with sufficient knowledge and experience to evaluate the situation of sponsors and production sites. It should be noted that this expert meeting consultation does not include researchers and ethics committee experts.

Step 2: Based on the scoring results, the scores of severity (S), occurrence (O), and detectability (D) should be multiplied using the following formula ($RPN = S \times O \times D$) to obtain the final *RPN* value. Namely, Risk index = Severity × Possibility × Detectability. The higher the risk index value, the higher the potential risk.

Step 3: The difference between the RPNs corresponding to each failure mode before and after the change of different combination modes should be calculated. If the *RPN* difference after the change is a positive number, it means that the risk increases after the change. The failure modes of the increasing risks are defined as the focus of risk control, and some targeted risk control measures are recommended.

When calculating the difference, it is necessary to subtract the value before the change from the value after the change. When a relatively low risk portfolio mode changes to a relatively high-risk portfolio mode, the high *RPN* value is subtracted from the low RPN value, and the difference represents the degree of risk change.

3.2.2 RPN value

Based on expert scoring and calculation results, *RPN* values of the four combination modes and *RPN* differences before and after the change of different combination modes are obtained, as shown in Table 3. The risks increased are marked in gray.

Table 3 Thermodynamic chart of RPN values

No.	Level		Failure mode (abbreviated)	I	II	From I to II	From II to I	III	IV	From I to III	From I to IV	From II to III	From II to IV
1	Sponsor	P	No related organization in the company	10	30	20	−20	10	30	0	20	−20	0
2	Sponsor	P	No professional colleagues	30	30	0	0	30	30	0	0	0	0
3	Sponsor	L	No qualified protocol provided to investigators	60	40	−20	20	60	40	0	−20	20	0
4	Sponsor	L	No qualified Informed Consent form provided	16	16	0	0	16	16	0	0	0	0
5	Sponsor	L	No qualified investigator brochure provided	30	20	−10	10	30	20	0	−10	10	0
6	Sponsor	M	No qualified clinical samples/drugs provided	30	30	0	0	30	30	0	0	0	0
7	Sponsor	L	No qualified monitor had been done for Manu. sites QMS	8	16	8	−8	16	16	8	8	0	0
8	Sponsor	L	No qualified documents provided to Manu. sites	10	10	0	0	10	10	0	0	0	0
9	Sponsor	L	No qualified management had been done for CAPA	6	18	12	−12	12	12	6	6	−6	−6
10	Sponsor	L	No qualified management for drug release	10	20	10	−10	15	20	5	10	−5	0
11	Sponsor	L	No qualified management for drug shipping	12	12	0	0	16	12	4	0	4	0
12	Sponsor	L	No qualified management for drug withdrawal	5	5	0	0	5	5	0	0	0	0
13	Sponsor	L	No qualified monitor QMS had been done in clinical sites	30	30	0	0	30	30	0	0	0	0
14	Sponsor	L	No qualified management to investigators	27	18	−9	9	27	18	0	−9	9	0
15	Sponsor	L	No qualified monitor	24	24	0	0	24	24	0	0	0	0
16	Sponsor	L	No qualified actions to ensure subjects compensation	2	2	0	0	2	2	0	0	0	0
17	Sponsor	L	No qualified management to documents in clinical sites	4	8	4	−4	4	8	0	4	−4	0
18	Sponsor	L	No qualified pharmacovigilance system had been done	10	15	5	−5	10	15	0	5	−5	0
19	Sponsor	L	No enough pharmacovigilance actions had been done	20	10	−10	10	20	10	0	−10	10	0
20	Sponsor	L	No pharmacovigilance actions aligned within sites	20	20	0	0	20	20	0	0	0	0
21	Sponsor	E	Short of compliance from sponsors	12	12	0	0	12	12	0	0	0	0
22	Prod. site	P	No related organization and people in the site	10	20	10	−10	20	10	10	0	0	−10
23	Prod. site	M	No qualified start materials had been used	8	10	2	−2	10	8	2	0	0	−2
24	Prod. site	L	No qualified standards had been used	5	5	0	0	5	5	0	0	0	0
25	Prod. site	L	No qualified QMS had been set up	10	30	20	−20	30	10	20	0	0	−20
26	Prod. site	L	No qualified production action had been done	10	30	20	−20	30	10	20	0	0	−20
27	Prod. site	L	No qualified equipment had been used	5	5	0	0	10	5	5	0	5	0
28	Prod. site	L	No actions had been done to avoid cross contamination	10	20	10	-10	20	10	10	0	0	−10
29	Prod. site	L	No qualified management had been done for CAPA	12	16	4	-4	16	12	4	0	0	−4
30	Prod. site	L	No enough support for monitor, inspection and others	5	10	5	-5	10	5	5	0	0	−5
31	Prod. site	L	No enough support for audit	8	8	0	0	8	8	0	0	0	0
32	Prod. site	L	No enough actions to ensure the data checking	20	20	0	0	20	20	0	0	0	0
33	Prod. site	E	Short of compliance from production sites	20	30	10	-10	30	20	10	0	0	−10
Numbers of high risks						Total 14	Total 4			Total 13	Total 6	Total 6	0

Note: Prod. site = Production site; CAPA = Corrective action preventive action; QMS = Quality management system; P = People; M = Materials; L = Law and regulatory; E = Environment; I = Combination model I; II = Combination model II; III = Combination model III; IV = Combination model IV.

3.2.3 Risks analysis results

(1) Risks analysis for the allowed combination modes. When combination mode 1 is changed to combination mode 2, that is, domestic sponsors (and their clinical trial drug is produced in domestic production sites) are changed to overseas sponsors (and their clinical trial drug is produced in overseas production sites), there are a total of 14 key risk control points: 6 in terms of sponsors and 8 in terms of production sites. The expert scoring results are shown below.

When change from a domestic sponsor to an overseas sponsor, due to the fact that the organizational structure of the overseas sponsor does not necessarily have functional departments that can fully understand China's regulatory requirements, it is easy to increase risks in terms of audit and confirmation of the quality system of the production site, production change/ deviation management of the production site, release of clinical drug, management of clinical trial data, and pharmacovigilance system in accordance with China's requirements.

When the production site for clinical medication is changed from a domestic production site to an overseas production site, the organizational structure of the overseas production site may not necessarily have functional departments that can fully understand China's regulatory requirements. The production site is in the process of adopting compliant materials, establishing a quality system, implementing production activities, effectively preventing pollution, changes and deviation management, cooperation with Chinese regulatory authorities for overseas inspections, and non-compliance due to lack of supervision.

When combination mode 2 is changed to combination mode 1, it means the overseas sponsor (and the drug used for clinical trials is produced in the overseas production site) is changed to the domestic sponsor (and the drug used for clinical trials is produced in the domestic production site), there are four key risk control points, all of which are for the sponsor, but not for the production site. The expert scoring results are shown below.

When change from an overseas sponsor to a domestic sponsor, due to the growing research capacity of the domestic sponsor, there are risks in designing clinical trial plans, conducting pharmacovigilance activities, and updating the investigator's manual in a timely manner. There are also shortcomings in the management of researchers.

When the production site for clinical drug is changed from an overseas production site to a domestic production site, there are no key risk control points. It is suggested that the production capacity of domestic production sites in China can be in line with international standards, and the ease of operation of their management by Chinese regulatory agencies can better reduce clinical risks.

(2) Risks analysis for the non-allowed combination modes. Due to the absence of Combination mode 3 and Combination mode 4 in China, experts have extrapolated their scores based on their experience assumedly.

When combination mode 1 is changed to combination mode 3, in which the domestic sponsor (and the drug used for clinical trials is produced from a domestic production site) is changed to a domestic sponsor (and the drug used for clinical trials is produced from an overseas production site), there are 13 key risk management and control points for this change. The main problems are concentrated in the production site, which has 9 points. There are 4 problems connected to sponsors. The expert scoring results are as below.

Due to the growing ability of domestic sponsors to control overseas production sites, there are risks in the quality system management, change and deviation management, and drug release and shipment of overseas production sites.

After changing to an overseas production site, almost all clinical GMP related failure modes indicate risks, including personnel structure, material and production management, quality system construction, and compliance.

When combination mode 1 is changed to combination mode 4, in which the domestic sponsor

(and the drug used for clinical trials is produced in the domestic production site) is changed to an overseas sponsor (and the drug used for clinical trials is produced in the domestic production site). There are 6 key risk management and control points for this change, all of which occur on the sponsor side. The expert scoring results are shown below.

When changing from a domestic sponsor to an overseas sponsor, the degree to which the overseas sponsor understands China's regulations will determine the clinical risks. Because the organizational structure of the overseas sponsor does not necessarily have functional departments that can fully understand China's regulatory requirements, its audit and confirmation of the production site quality system, production change/deviation management of the production site, the release of clinical medication, the management of clinical trial data, and the pharmacovigilance system are prone to increase risks.

When the production site for clinical drug is changed from an overseas production site to a domestic production site, there are no key risk control points.

When combination mode 2 is changed to combination mode 3, it means the overseas sponsor (and the drug used for clinical trials is produced in an overseas production site) is changed to a domestic sponsor (and the drug used for clinical trials is produced in an overseas production site). There are a total of 6 key risk control points for this change, including 5 for the sponsor and only 1 for the production site. The expert scoring results are as below.

Due to the growing ability of domestic sponsors to control overseas production sites, there are risks in the quality system management, change and deviation management, and drug release and shipment of overseas production sites.

In terms of production sites, the most important concern is whether domestic sponsors can effectively manage overseas production sites, especially whether they can produce as required.

When combination mode 2 is changed to combination mode 4, it means the overseas sponsor (and the drug used for clinical trials is produced in an overseas production site) is changed to an overseas sponsor (and the drug used for clinical trials is produced in a domestic production site), no risk factors occur in this situation.

4 Results

4.1 Learnings from FDA's administration methods for clinical trials

FDA of America pays more attention to the role and responsibilities of the sponsors. FDA requires sponsor should submit FDA-1571 application forms at IND submission stage, which makes the responsibilities allocation between sponsors and investigators. At the same time, the construction of the legal system in the U.S. has introduced social forces to participate in the supervision of the drug research and development by widely adopting legal means to adjust civil relations (responsibility and power distribution) during clinical trials. Under this premise, the sponsor is encouraged to objectively judge their capabilities, effectively manage third-party service providers such as CROs and production sites, conduct research activities in compliance with researchers and have the ability to manage the entire life cycle. Based on this management mode, FDA allows flexible cooperation between sponsors and production sites, including the use of overseas clinical drug production sites by U.S. sponsors, or the use of production sites within America by overseas sponsors. At the same time, changes in the sponsor during a clinical trial usually do not have a significant impact on the safety of the subjects because they are "minor" changes. Changes to production sites require specific analysis and evaluation based on relevant technical requirements, but their changes will not be limited by whether the production site is located within or outside the U.S.

Currently, pharmaceutical industry in China is still in the development stage, and the results of Failure Mode, Effects, and Hazard Analysis (FEMAC) research have proven that there are significant differences in the ability of sponsors to control changes

during clinical trials. In particular, in terms of quality management of clinical drug and drug safety alert management, some sponsors need to further improve their risk prevention and control capabilities for cross-border commissioned production. Meanwhile, although China has made great progress in the reform of drug review and approval, the implementation of the main responsibilities of sponsors, such as the assessment and evaluation of sponsors and the social publicity system, is still under construction. Due to various restrictions, it relies solely on China's drug regulatory agencies to implement intensive regulatory activities on overseas sponsors. Besides, production sites also pose some practical challenges. It is necessary to take a cautious attitude towards cross-border sponsors and production site changes. We should strengthen the risk management and control of clinical trials, and pilot from lower risk situations and gradually liberalize the changes.

4.2 Suggestions to the risks administration of clinical trials in China

Some control suggestions of risk managements in China are put forward in the paper from four aspects: "people" "material" "law/regulatory", and "environment".

From the perspective of "people", we should focus on "sponsor", especially for their role and responsibilities (R&R) with all the partners, including "production sites" and others. In addition to having a clinical research and development team, the sponsor should have the related persons in charge of quality management and pharmacovigilance who should be familiar with the regulatory requirements in China. The oversea sponsors should assign the China responsible person who can be responsible for Chinese subjects in the related clinical trials.

From the perspective of "materials", we should strengthen the management of materials for overseas production sites by sponsors, especially to make sure the materials must fit for the requirements of China health authorities.

From the perspective of "law/regulatory", we should focus on the management of sponsors through more regulatory training, guiding and standardizing industry behavior. As pharmaceutical industry in China is in the infancy stage, there are big differences in the research and development capabilities among different sponsors. Therefore, the requirements for sponsors should be refined in detail. For example, China health authority can consider releasing the key checking points of sponsors during authoritative inspections, which can be referred to relevant documents of MAH, or other industry consensuses. Besides, sponsors can be asked to identify their R&R in CTA submission stage, such as submission a clarification of responsibility allocation between sponsors and investigators (production site, CRO or others), as FDA required.

From the perspective of ring, considering the different effect of social governance system in different countries. although overseas applicants in Europe and the U.S. can have certain industry self-discipline there are uneven levels in other developing countries. So there is no significant difference in the related scoring by experts. However, with referring to the management effect of the U.S., along with the construction of a legal society in China, we should continue to promote the social foundation of the responsibility system for sponsors. For instance, we should establish a blacklist or a violation publicity system for the sponsors. If they violate any regulations or rules, they will receive corresponding punishment. Meanwhile, we should promote the participation of social supervision forces and improve social co governance ability and industry self-discipline.

Through the implementation of the above measures, the quality of the trials and the safety of the subjects will be ensured. Besides, we can promote the development of the pharmaceutical industry by better management of the changes of the sponsors and production sites in China.

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