Introduction to the CTA & NDA process in China

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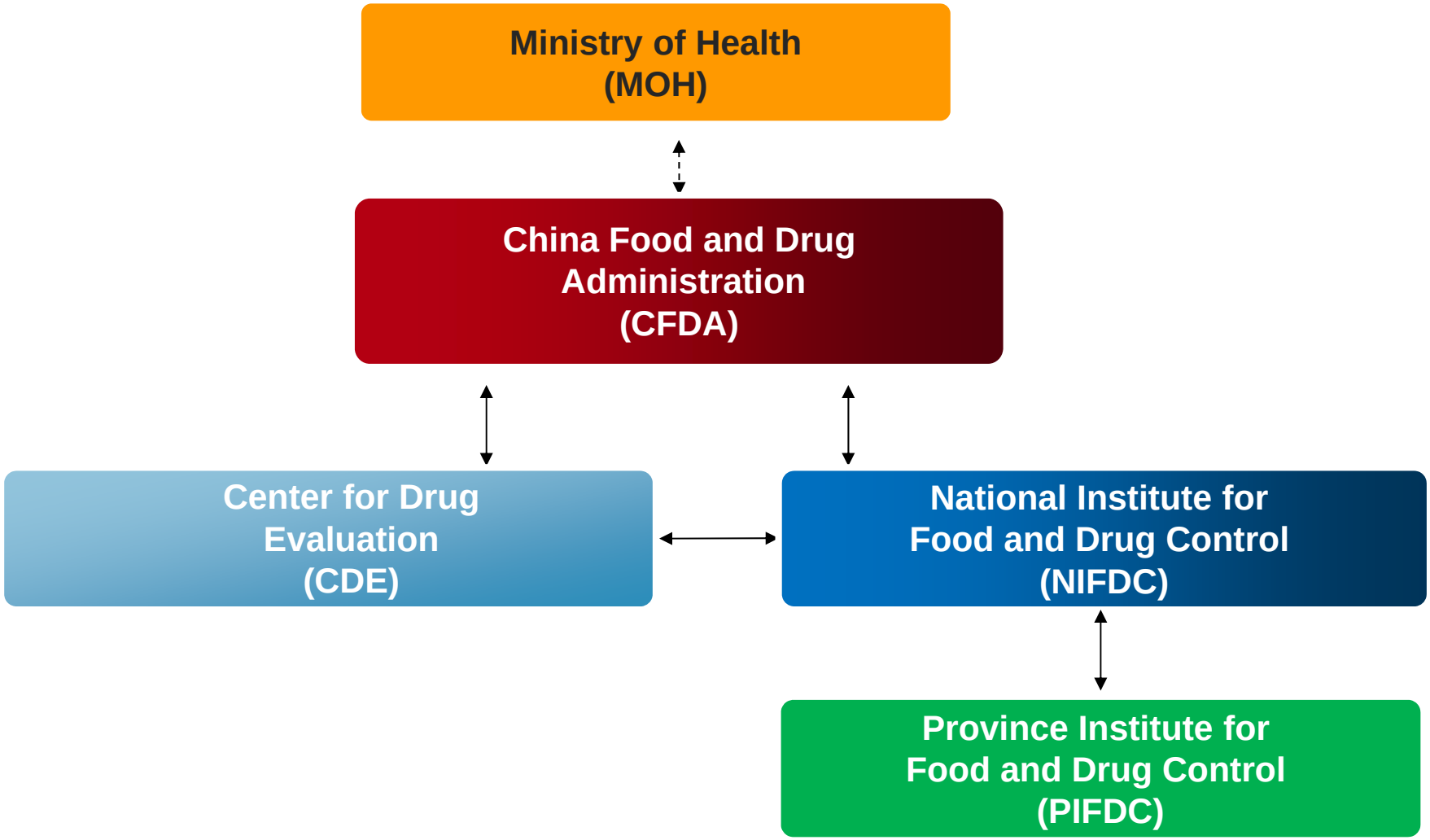
Overall Regulatory Environment*

- Evolving – Challenges and Opportunities
- Ever-changing and unpredictable policy & rules
- Conservative CFDA (previous SFDA) climate
- Lengthy IND/CTA process
- Local sample testing & clinical trial required
- Biologics – stringent guidelines and longer review**

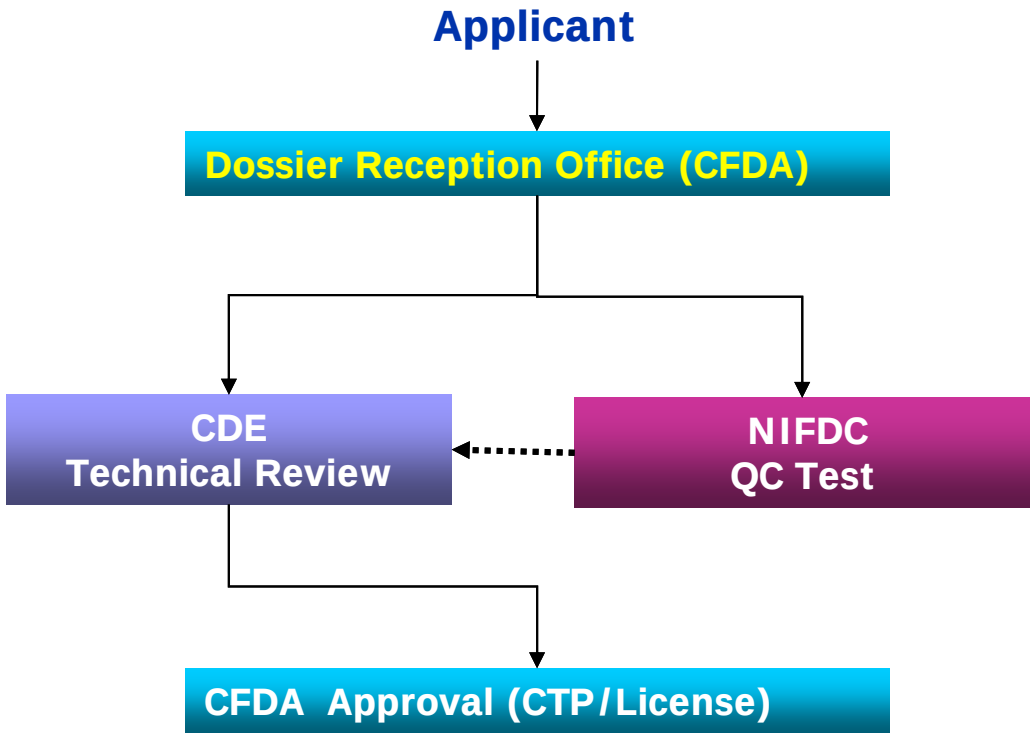
*) From: Victoria Elegant – Critical Success Factors for Clinical Trials in Emerging Markets (2013) (http://www.globalengage.co.uk/gctos/9Elegant.pdf)

**) 2014: Timelines for chemical drugs have increased and have become similar to biologics

Key Regulatory Players in China



General Registration Flow Chart



Approval Timeline for Chemical drug (based on RDPAC survey)

- **IDL-CTA: 36±4 m**
- **IDL-NDA: 29±4 m**
- **IMCT-CTA: 13±2 m**
- **IMCT-NDA: 36±4 m**

CTA = Clinical Trial Application, IDL = Import Drug License, IMCT = International Multi-country Clinical Trial, NDA = New Drug Application, RDPAC = R&D-based Pharmaceutical Association Committee

Recommendation of RDPAC benchmark in 2014

Type	Category	RDPAC survey results in 2013		CDE officially released 1st round waiting Time * (as of Apr 2014)	Time gap between RDPAC survey results and CDE data (trend of prolonged waiting time)	Recommended Timeline in 2014
		Overall timeline	1st round waiting time (as of Dec 31st 2013)			
Chemical Product	IDL CTA	31.8	17	21	4	36 ± 4
	IDL NDA	25.3	12	16	4	29 ± 4
	IMCT	9	4	7.6	3.6	13 ± 2
	IMCT- NDA	In IDL-CTA queue, recommend to follow IDL-CTA				36 ± 4
Therapeutic biological product	IDL/IMCT CTA(with 1 round formal query)	28.4	10	15	5	33± 4
	IDL/IMCT CTA(No formal query)	15.5	10	15	5	21 ±2
	IDL NDA**	--				33 ± 4
	IMCT- NDA	In IDL-CTA queue, recommend to follow IDL-CTA				33 ± 4

Calculation method:

Timeline = RDPAC overall timeline + Time gap btw RDAPC survey results and CDE data ± 4 or 2 ***

* Published by the CDE in the China 6th DIA Annual Meeting or monitoring via CDE website.

** There're only 2 cases for Bio IDL NDA(18.0m without query and 30.0m with formal query), not representative. So it's suggest to refer to recommended timeline of Thera. Bio. IDL-CTA

*** As for the deviation region, if the timeline is above 2 years, it's should be 4 years plus or minus; if the timeline is about 1 year, it should be 2 years plus or minus.

Minimal study cases requirements for clinical trials in China

Item	Phase	Sample Size
Import Chemical Drug	PK	8-12
	Phase III	≥100 pairs
Biological Product	Phase I	20 (testing group)
	Phase II	100 (testing group)
	Phase III	300 (testing group)

- For biological products only very few companies go through Phase I to III entirely.
- The estimation of local number of study cases is based on regulation, experiences, specific indications and can be discussed.

Pre-approval requirements for Clinical Trial Applicants (I)

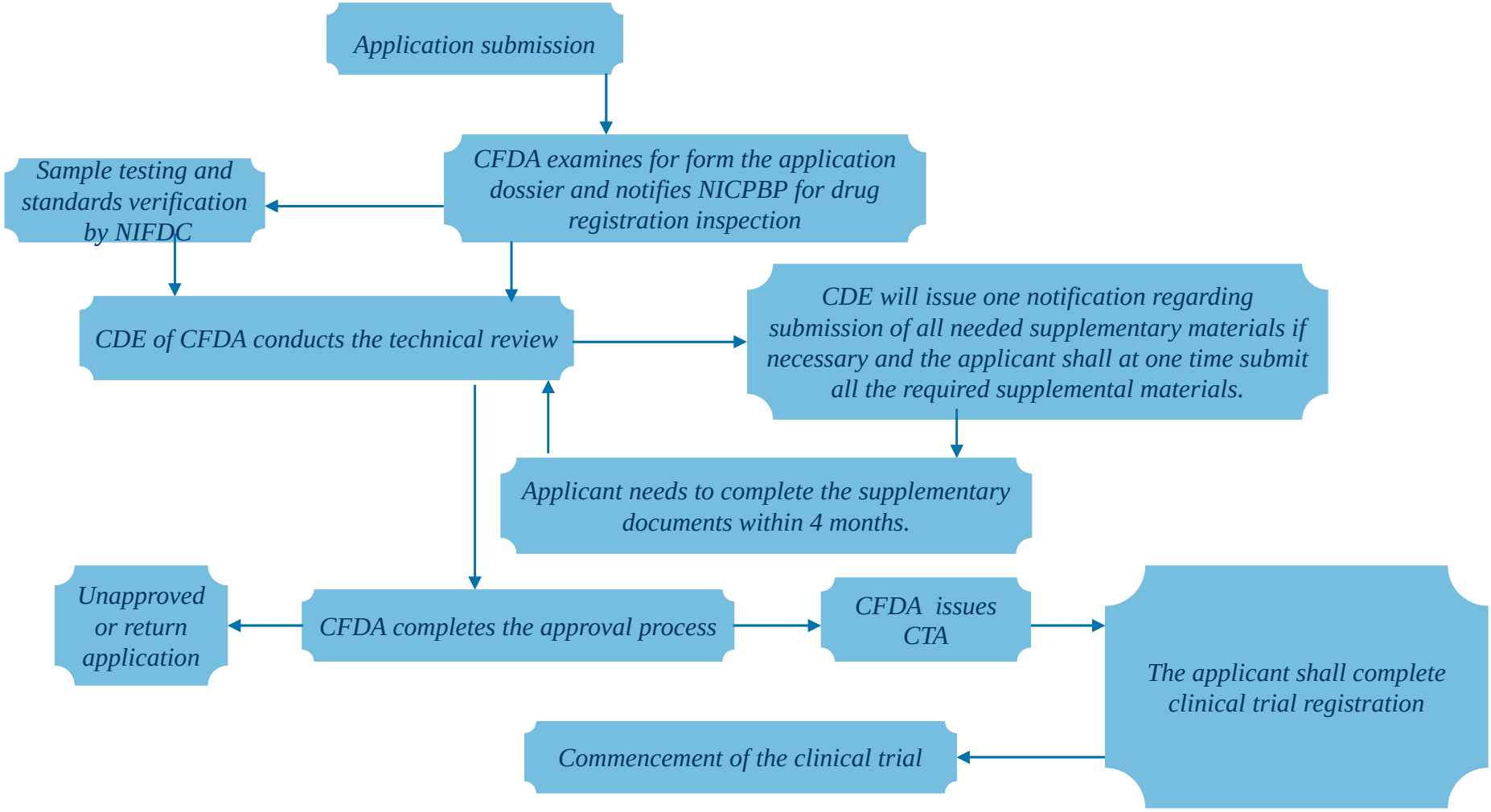
- Safety evaluation in pre-clinical studies should comply with GLP.
- Clinical trials (including bioequivalence studies) should be conducted in compliance with GCP.
- Drugs used for clinical trials should be manufactured in facilities in compliance with GMP.
- A drug can be used for a clinical trial only after being tested and qualified.
- Vaccines, blood products and other biological products specified by the CFDA should be tested by drug testing institutes designated by the CFDA.

Pre-approval requirements for Clinical Trial Applicants (II)

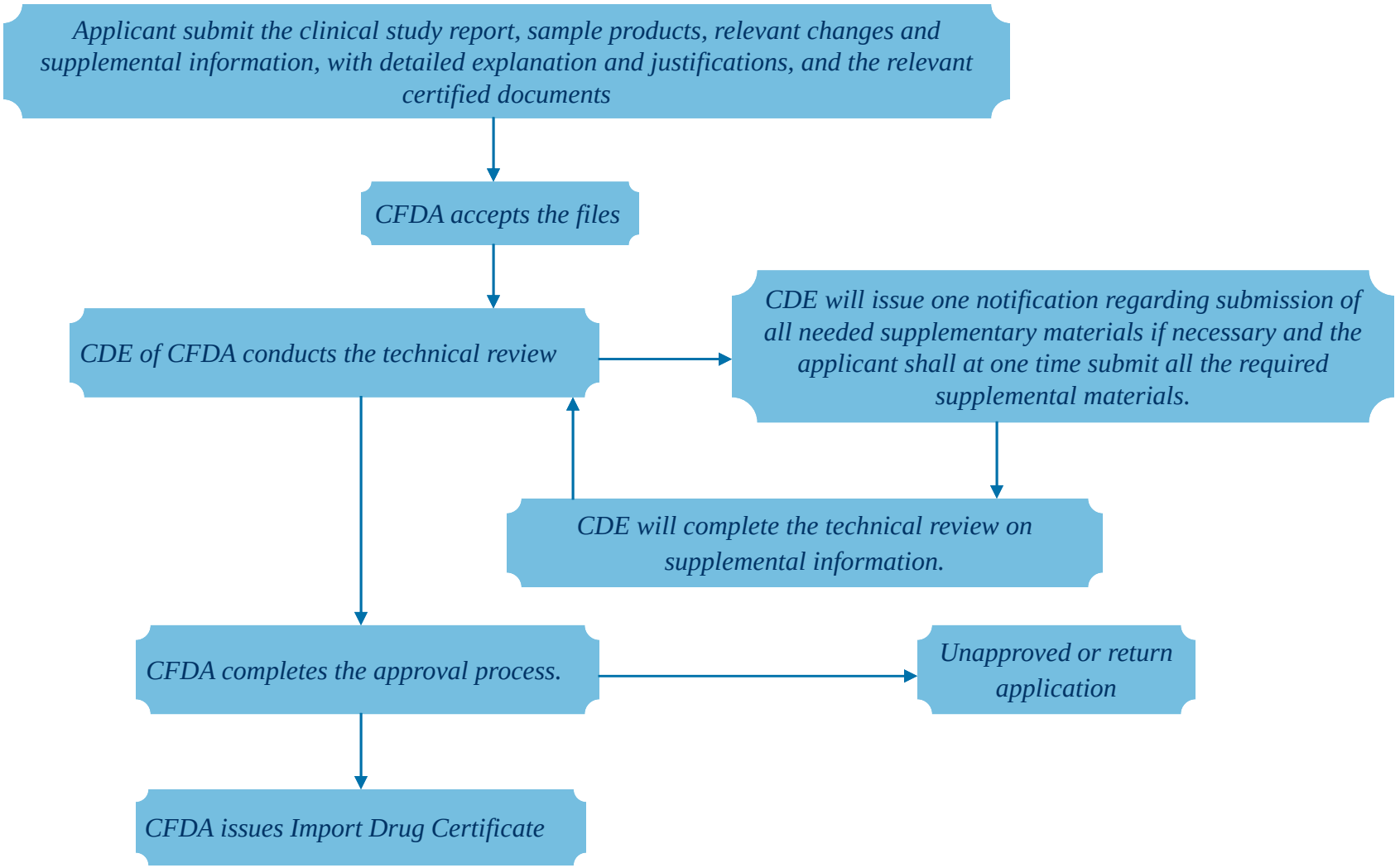
All clinical trials (including bioequivalence studies) need prior CFDA approval.

- The approved clinical trial should be conducted in a certified research institution that operates in compliance with Chinese GCP.
- For overseas applicants intending to conduct an international multicenter clinical trial in China, the drug should already be approved or in phase II or III clinical trial overseas.
  While approving the conduct of an IMCT, the CFDA may require the applicant to first conduct a phase I trial in China.
- Any preventive vaccine trial not having first been registered overseas is prohibited in China.

Registration Procedure for CTA



Registration Procedure for NDA



Further Reading

- Dong Lu, Wenglong Huang
  Overview of the drug evaluation system in China
  Scientific Research and Essays, Vol 5(6), 514-518 (2010)
- Xiaoqiong Zheng
  Regulation of medicines in China
  WHO Drug Information, Vol. 26(1), 3-14 (2012)
- CDE - Principles and Procedures for Drug Review and Evaluation
  http://www.cde.org.cn/linshi/regulatEn/Principles%20and%20Procedures%20for%20Drug%20Review%20and%20Evaluation.pdf
- CFDA - Provisions for Drug Registration (SFDA order no. 28)
  http://eng.sfda.gov.cn/WS03/CL0768/61645.html
- CFDA – Regulatory Guide
  http://eng.sfda.gov.cn/WS03/CL0769/
- CFDA - Approval for clinical trials of imported (incl. from Hong Kong, Macao and Taiwan) chemicals
  http://eng.sfda.gov.cn/WS03/CL0769/98158.html
- CFDA – Good Clinical Practice (SFDA order no. 3)
  http://www.sfda.gov.cn/WS01/CL0053/24473.html

Thank you!

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