PHARMACEUTICALS EXPORT PROMOTION COUNCIL OF INDIA

(Set up by Ministry of Commerce & Industry, Govt. of India)

REGULATORY & MARKET PROFILE OF CHINA

Demography

SL. No	Parameter	Description
1	Region	Eastern Asia
2	Country	China
3	Capital	Beijing
4	Population	1,379,302,771 (July 2017 est.)
5	Population growth rate (%)	0.41% (2017 est.)
6	GDP (purchasing power parity)	$ 23.12 trillion (2017 est.)
7	GDP - real growth rate (%)	6.8% (2017 est.)
8	GDP - per capita (PPP)	$ 16,600(2017 est.)
9	Epidemiology	Cardiovascular diseases Cancers, Hypertension Increased Non-communicable diseases
10	Population below poverty line	3.3%
11	Age structure (%)	0-14 years: 17.5%
		15-24 Years: 12.78%
		25-54 years48.51%
		55-64 years: 10.75%
		65 years & over: 10.81%
Source: CIA World Fact Book updated to July 2017		

CHINA MARKET REPORT

Introduction:

China's Pharma market is estimated at $ 140.3 billion in 2017 having grown by 29% as per BMI report. It is the largest market in Asia Pacific Region and second largest in the world. In 2018 the market is expected to reach $ 142.26 Billion.

China's rapid ageing of the population and rising incomes will lead to a surge in demand for medicines and quality healthcare services. Forecast of pharmaceutical sales show market may reach USD372.4bn in 2027 with a Cagr of 9%.

Government is unable to cope with such strong growth in healthcare demand. Government is likely to open up the domestic market further to both private and foreign players. On March 5 2018, Premier Li stated that the Chinese government will remain committed to opening up the economy to foreign companies. As a result, it is believed, Beijing to adopt the negative list management system, which provide guidelines on sectors where foreign investors cannot invest in, or can only invest in under certain restrictions. Foreign companies earlier were to seek approval from the government before they were allowed to invest in China. However, with the changes to the negative list taking effect, foreign enterprises only need to register their activities with the authorities in the same way as their domestic peers, so long as their intended activities are not on the negative list. The adoption of the new system will benefit foreign companies, including drugmakers as it will help to cut red tape.

Pharma journals like BMI feel the regulatory issues that plague the Chinese pharmaceutical market will continue to pose a significant barrier to innovative multinational pharmaceutical firms' revenue growth. While the business environment is certainly showing signs of improvement, backed by the implementation of progressive reforms, the country's medicine market will continue to be met with challenges presenting a key market access barrier.

Latest Updates

- In August 2018, it was reported that representatives of leading Chinese pharmaceutical firms are exploring chances of cooperation with local partners in Nigeria.
- In March 2018, Merck KGaA announced its plans of building a single-use manufacturing operation in Wuxi to target the biosimilars market.
- Scandals regarding substandard pharmaceutical drugs will jeopardise China's ambition to become an international pharmaceutical leader. The current furore erupted in July 2018 after a rabies vaccine for humans manufactured by Changchun Changsheng Biotechnology, one of China's largest vaccine makers, was found to have violated safety standards.
- On July 18 2018, Takeda announced the company's ambitions for its China business - to make the country the second-most important market for the Japanese drug maker. Takeda now regards China as a core country for its business practice.

Proposed Changes

Hospital Sector

At present most of the health care is with the government. This is also expected to change. There are 14,500 private hospitals in the country, accounting for 52.6% of total hospitals. Premier Li pledged in his government work report, to set up closely liked medical alliances across the country to solve the problem of 'difficult medical treatment, expensive medical treatment', opening up new investment opportunities.

Medical coverage

On March 5, Chinese Premier Li Keqiang, announced that the government subsidy on basic medical insurance will increase by USD6.3 per capita to USD77.7 per capita, from USD71.3 per capita currently. This will enable a significant improvement in healthcare access which will result in increased demand for medicines, providing an improved outlook for healthcare providers and pharmaceutical firms. The government has also set a target to enroll more than 20mn people under the critical illness insurance scheme, an increase from over 17mn people in 2017. Additionally, on March 20 2018, Premier Li stated that the government plans to lower import tariffs on cancer drugs, potentially to 0%, from around 5% to 6% currently, to increase affordability.

Import Tariff

The proposed changes to China's import tariff policy for foreign cancer medicines will provide a boost to multinational pharmaceutical firms and the increased reimbursement of these medicines will increase patient access to innovative oncology therapeutics. On February 23 2017, the government also expanded the list of medicines covered by the basic medical insurance to include 339 additional drugs.

Regulatory

Registration and approval for drugs and medical devices will also be consolidated in a new drug administration that will be established and managed under the newly formed National Market Supervision Administration, which will absorb the China Food and Drug Administration (CFDA) and related responsibilities from the State Administration for Industry and Commerce (SAIC) and the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ). The CFDA, SAIC, and AQSIQ will cease to exist.

Announcement in late June 2017, accepting of the IHC implies, that China's drug regulation will now be in line with international standards and this will in turn boost the sale of Chinese pharmaceutical products internationally. ICH, set up by the US, EU and Japan in 1990, is an international organisation that standardises global drug registrations and manufacturing practices. Its mission is to ensure development and registration of safe, effective, and high quality medicines in a resource-efficient manner. The drug regulatory authorities, the pharmaceutical industry and research and development institutes will actively participate in the formulation of international rules and promote quicker domestic application of new drugs. Commenting on this, Yuan Lin, director general

of CFDA's department of international cooperation, stated, 'This marks a milestone in the history of China's pharmaceutical development history. It shows that CFDA's ongoing reform of drug review and approval has received recognition from the international community.'

IP Changes

China's weak IP protection has long been a bone of contention to various Western countries. Beijing has intentions to improve its IP practices in order to move up the value chain as part of the Made in China 2025 initiative. In April 2018, it seems, China's government announced a series of measures to increase the country's importation of drugs, including enhanced IP protection in the pharmaceutical industry. According to the World Bank, China's IP protection index came in at 4.5 out of a maximum of 7.0 in 2017, which marked an improvement from 4.0 in 2015, though critics feel a lot more to be done.

The Triggering Factor

China is increasingly interesting to the pharmaceutical industry, as the rise in cancer prevalence is expanding the market's potential. In China, according to the American Cancer Society, there were 4.3mn new cancer cases in 2016, and about 7,500 cancer-related deaths each day. Overall, cancer is now the leading cause of death in China. Cancer medicines have historically been expensive in China, and most of the advanced, targeted therapies are still foreign-made and not covered by the national medical insurance plan. Compared to other countries, the Chinese regime also places a high value-added tax (VAT) rate on imported anti-cancer drugs. From May 2018, VAT in the production and import of drugs will also drop by a large margin. It is estimated that the removal of the import tariff on oncology therapeutics will reduce the cost for cancer patients by USD280mn. At the press conference of the annual NPC in Beijing, P.M. Li , stated that, medicines, especially anti-cancer drugs urgently needed by the people, lower import tariffs to a relatively large extent to be considered, and Government to work hard to reach zero tariff for anti-cancer medicines.'

In a bid to make foreign oncology drugs more affordable for the Chinese population, Li Keqiang announced the government's plan to eliminate import taxes on cancer drugs. Companies like, **Novartis**, **Roche&BoehringerIngelheim**, has been working with regulators and provincial government administrators to lower the prices for their drugs, and new tariff cuts marks a further step in the process. This follows the November 2017 announcement where the government reduced import tax for a range of medicines, including various antibiotics and insulin products, from as much as 6% to 2%

According to state media, these import tariffs are due to be removed on cancer medicines from May 1 2018. Moreover, imported innovative drugs, especially oncology medicines, will be incorporated into the catalogue of medical insurance reimbursement from May 2018. Enlisting innovative targeted drugs will improve the availability and affordability of innovative treatments for patients in China. This is because the NRDL determines which medicines are reimbursed and the level of reimbursement offered by the state's health insurance scheme. This has direct implications on out-of-pocket patient spending, a key impediment to patient access to innovative pharmaceuticals. However, as the NRDL places a heavy emphasis on cost - with companies reducing

their prices by up to half to gain listing - multinational drugmakers will have to carefully consider the impact on the per-unit revenue, and will have to increase the sales volume of medicines significantly to offset the discounts.

Roche's chief executive officer, Severin Schwan, stated that, 'China is a big focus for the company, mainly on the pharmaceutical side and we are investing in China to bring our solutions, diagnostic tests and medicines increasingly to patients in the country.'

Epidemiology

With China's rapid economic development, the disease burden has changed in the country. Cardiovascular diseases and cancer have become the leading causes of death among Chinese adults. Hypertension and cigarette smoking are the leading preventable causes of death in China. To this end, the burden imposed by non-communicable diseases has been increasing in China, while the burden of communicable conditions is on the decline.

Generic Market

The financial sustainability of China's universal healthcare scheme will be a central issue underpinning the government's austere approach. Moreover, rising demand for medicines in the country will push the government to focus on cost-containment measures. Increasingly forceful pricing pressures, a focus on cost-effectiveness and generic substitution are trends that are likely to continue over the coming years. These factors would help Generic component of China's market move faster.

Generic drug market spending to increase from USD 76.27 bn in 2017 to USD125 bn by 2022, with a CAGR of 10%. In 2017, generic drugs accounted for 63.47% of total sales. Latest forecasts show that by 2018 ending market is likely to touch $ 90.6 bn with 18 % growth.

Pharma Trade:

As one of the largest pharmaceuticals market in Asia Pacific, China continues to present a highly dynamic pharmaceutical trade environment. Imports increases as China's demand for medicines, especially innovative treatments, continues to grow in line with the country's disease burden and healthcare modernisation. Exports are also expected to grow as Chinese pharmaceutical firms continue to look beyond the local market.

In 2017, pharmaceutical (Only finished dosage forms) imports were valued at USD22.3 bn. This is forecast to grow to USD36.2 bn by 2022 with a five-year (CAGR) of 10.2%.

The rise in China's pharmaceutical exports is driven by two main trends. First, given the attractiveness of China to multinational drugmakers, & firms have been investing heavily into the country.

In comparison, China's pharmaceutical export value was USD4.3bn in 2017(Only finished dosage forms), which is forecast to rise to USD 7.81bn by 2022 with a five-year CAGR of 12.5%.

Pricing Regime

Prices of drugs on the Essential Drugs List are set by the government, while most other drug prices are set after negotiations between the government and the manufacturers.

In place of price controls, the Chinese authorities have introduced a tendering system that has been the source of significant pressure. While a 'double envelope' approach is adopted - whereby authorities consider both the quality of a product and its price during the decision making process - reports suggest that firms have been asked to provide discounts in order to participate.

The introduction of national-level tendering in May 2016 placed pressure on prices. Products affected were AstraZeneca's Iressa (getfitnib) and Zhejiang Beta Pharma's Conmana (icotinib) and Viread (tenofovir), which saw price cuts of 53%, 54% and 67% respectively.

Moreover, in July 2017 it was announced that 36 new drugs will be added to the national insurance programme including novel pharmaceuticals. To lower their prices, manufacturers went through rounds of negotiations with China's Ministry of Human Resources and Social Security. For example, GlaxoSmithKline's (GSK) breast cancer drug Tykerb (lapatinib) was added to the list after a price cut of 42%, Bayer's liver and kidney cancer drug Nexavar (sorafenib) was reduced by 51.5% and Roche slashed the price by an average of 59% to get three monoclonal antibodies - MabThera (rituximab), Herceptin (trastuzumab) and Avastin (bevacizumab) - onto the list. While price negotiations are set to shape the immediate business environment, the longer-term trajectory will see health technology assessment (HTA) become more prominent in the country. China has been steadily building up its expertise with a total of five HTA institutes - four universities and one organisation - falling under the National Health and Family Planning Commission. It has also formed partnerships with leading organisations such as the relationship between the China National Health Development Research Centre and UK's National Institute for Health and Clinical Excellence (NICE) among others. Data limitations are an impediment but it is expected that to be gradually alleviated as more studies are conducted. The National Drug Reimbursement List, for example, notes that the cost and benefits of products will be compared using pharmacoeconomic principles. The National Development and Reform Commission's 'Guideline for reform of drug and medical service pricing' further chimes with this view, highlighting that pricing for pharmaceuticals should gradually adopt pharmacoeconomic evaluation.

Statistics:

India's Pharma Exports to China

Category	2015-16	2016-17	2017-18	GR%	contbn%
Bulk Drugs and Drug Intermediates	114.59	103.85	153.98	48.27	76.99
Drug Formulations and Biologicals	12.57	17.35	26.26	51.39	13.13
Ayush	0.52	0.59	0.58	-0.46	0.29
Herbal Products	6.43	5.31	9.39	76.65	4.69
Surgicals	8.21	12.52	9.29	-25.77	4.65
Vaccines	3.26	5.83	0.50	-91.34	0.25
Total	145.58	145.45	200.02	37.52	100.00

China's Top ten formulation Importing partners $ Million						
Rank	Country	2015	2016	2017	Gr%	Share%
1	Germany	4474.61	5603.25	6935.43	23.78	27.14
2	USA	3272.11	3228.27	3797.70	17.64	14.86
3	France	1621.11	1795.73	2352.11	30.98	9.20
4	Italy	1566.03	1704.63	1848.95	8.47	7.23
5	Switzerland	1073.01	1261.99	1409.29	11.67	5.51
6	Sweden	795.24	860.45	1291.57	50.10	5.05
7	United Kingdom	1119.70	1048.19	1189.93	13.52	4.66
8	Japan	716.14	758.83	949.86	25.17	3.72
9	Ireland	584.30	600.13	821.30	36.85	3.21
10	Denmark	528.64	605.40	624.80	3.20	2.44
30	India	21.50	36.80	27.74	-24.62	0.11
	World	19190.58	21001.33	25558.22	21.70	100.00
Source:UNcomtrade						

REGISTRATION AND LICENSING REQUIREMENTS

➢	Regulatory Authority	:	**NATIONAL MEDICAL PRODUCTS ADMINISTRATION (NMPA)**
➢	Website of regulatory Authority	:	http://www.nmpa.gov.cn
➢	Fees for Drug Registration	:	367.6 Thousand RMB (57169 USD)
➢	Normal time taken for registration	:	3-5 Yrs
➢	Registration Requirement [Dossier Format]	:	CTD
➢	Whether plant inspection is mandatory	:	Yes
➢	Requirement of Local agent/ Subsidiary	:	Local Agent is sufficient

国家药品监督管理局
National Medical Products Administration

Recent activities:

- In June 2017 NMPA joint ICH as 8th regulatory member.
- CFDA renamed as National Medical Product Administration on 1st Sep 2018.
- Administered by the State Administration for Market Regulation (SAMR).
- Registrant needs to use this name for future fillings.

Functions Includes:

- Registration, review and approval of APIs, FDFs, Medical devices, Biologics and Cosmetics.
- Review and publication and of national pharmacopeia's (CP).
- Drug classification based on the therapeutic category.
- Supervise and control registration procedures.
- Inspection for domestic and outdoor facilities.
- Promotion of national essential medicines and traditional medicines.
- Established recall and disposal procedures.

NMPA reforms and actions

- New employment for the technical staff (assessors).
- Efforts to become ICH members.
- Implementation of new policies.
- Waiver for the clinical trials and bio studies (BE) for fast approvals and to suffice market needs.

Regulatory authorities relating to Drug Administration:

- National Institutes for Food and Drug Control (NIFDC): Verify the drug specification and test the samples
- Center for Food and Drug Inspection(CFDI) :Inspect the manufacturing facility of the drug
- Central For Drug Evaluation(CDE): Conducts Drug evaluation
- Centre for Drug Re-evaluation (CDR)

Laws, Regulations and Guidelines:

(1) Drug Administration Law of the People's Republic of China: Order of the President of the Peoples Republic of China (No. 45)

- First amendment on Dec. 28th, 2013
- Second amendment on Apr. 4th, 2015
- Draft amendment released to **Public hearing** stage （1st Nov.,2018 to 1st Dec.,2018）

(2) Basic regulation of drug registration in China

- Provisions for Drug Registration SFDA Order No. 28
- Service guide
  - 30024-1 Service guide for approval of IDL
  - 30024-2 Service guide for approval of Re-registration of IDL
  - 30024-3 Service guide for the approval of changes specified in IDL with it's attachments

(3) Good Manufacturing Practice for Drugs (2010 Revision) (MOH Decree No. 79)

(4) Registration dossier's requirements: Announcement of Dossier's requirements for chemicals drug registration with new classification (No. 80 , 2016)

Drug Classification System:

Class-1 - New chemical entity
Class-2 - New chemical entity with new therapeutic indication
Class-3 - Generic drug for the innovator not marketed in China
Class-4 - Generic drug of innovator marketed in China
Class-5 - Imported drugs
Class 5.1 - For the innovator drugs enter into China
Class 5.2 - For the generic drugs enter into China

Note: Current registration system falls under the class 5.2

Difference between prior and current registration policies for APIs

Previous	Current
Import Drug Licence (IDL) Country specific requirement	Joint application policy (Effective from 1St January 2017) Similar to USFDA system.
Use to be valid for 5 years	Valid till entire product life cycle
Long review cycle and approval	Fast review cycle and quick approval
No initial assessment	Formal initial assessment (as per No.80 order)
No need of customer activation	Needs customers activation

CTD Modules:

- ✓ Based on the quality safety and efficacy.
- ✓ The content is equivalent to the ICH module.
- ✓ Based on number 80 article by CFDA.

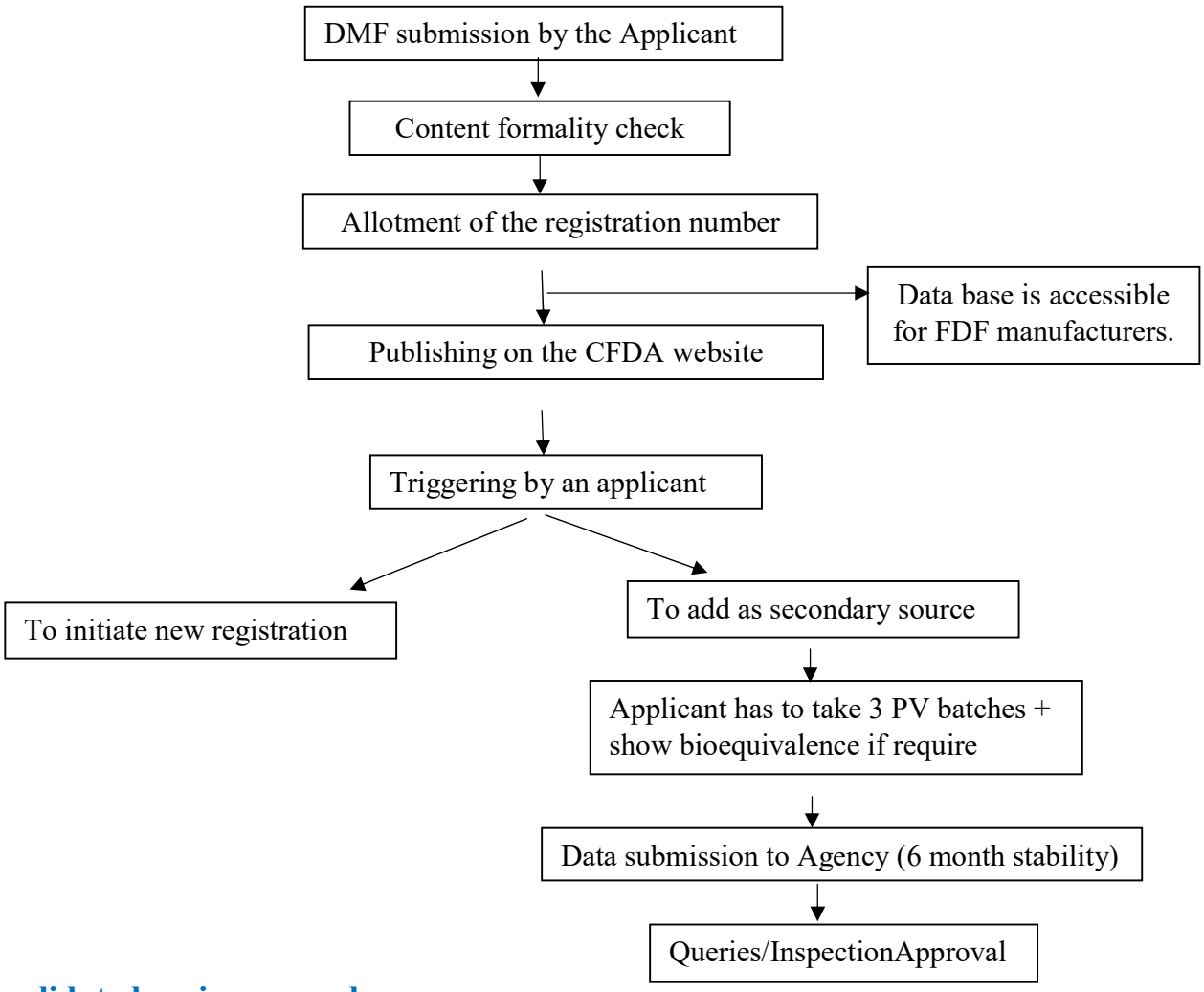
NMPA's expectations for importers:

- Appointment of local agent for easy communication (if applicable).
- Regional requirements should be strictly followed.
- Stringent controls should be adopted irrespective of the CP pharmacopeia.
- Supply of samples and documentation support during sample evaluation.
- Cooperation from supplier during port inspection and sampling (if required).
- Extension of the USDMF and CEP to China market sometimes cannot be considered.

Dossier assessment criteria:

- Should comply with the no.80 article requirement by NMPA.
- Administrative/regional requirements should be suffice.
  Ex., Administrative documents should be legalise and notarised.
  Specification should not be less than the local standards.
- Formality check should pass

Registration Cycle



Consolidated review procedure

- Firstly, submit registration dossiers and get a unique registration number by holder/Manufacturer of API or agent.
- Secondly, try to associate with DPs by holder/Manufacturer of API (or) DP or agent
- Thirdly, consolidated review by CDE
- Finally, activate the status of API depending on the result of DP evaluation by CDE

Status of APIs

- **A -** Approved for using in marketed DPs.
- **A* -** Has passed the technical evaluation independently but not joint with DPs.
- **A# -** API has approved for using in marketed DPs, but have major changes (major changes on manufacturing process, changes on manufacturing facility) that impact the quality of product and has not passed consolidated review.

- ☐ I - Has not passed consolidated review with DPs.

DMF sections with some special requirements:

Section 3.2.S.1.3

- Polymorphism report should be provided (If applicable)

Section 3.2.S.2.2

- Process should at least have 3 chemical conversions. (CMO acceptable)
- (Purification and salt formation cannot be considered as chemical step).
- If process has reprocess and recovery (solvent, reagent and API), then the detailed discussion, validation and batch equivalency data should be provided.

Section 3.2.S.2.3

- KSM should be justifying in accordance with ICH Q7.
- It should procure from at least GMP compliant facility.
- Audit and compliance report of vendor should be provided.
- Quality indicative methods (RS/Assay) should be added in KSM spec (As applicable).
- Complete AMV should be carried out. Partial validation shall not be considered.
- KSM should be well characterized.
- CMC information of KSM (If required).

Section 3.2.S.2.4

- All in-process and intermediate specs should be quality compliant
- AMV (complete/partial) should be performed.
- Critical process parameters should be justified (Negative experimental studies)

Section 3.2.S.2.5

- Executed process validation protocol and report should be provided.
- Blank Master Batch Production Records should be provided.

Section 3.2.S.2.6

- Rational for selection of the manufacturing process from lab, pilot, commercial batches.
- Supported with literatures/ patents should be included.

Section 3.2.S.3.1

- API had better be characterized against the pharmacopeial standards for UV, NMR, XRD etc.

Some specific regional requirement (Special requirements from NMPA)

(1) Master blank manufacturing records:

- For all the APIs, blank BMRs should be provided

- Except for sterile DPs and DPs manufactured by special process, BMRs should be provided
- For the samples used for Clinical trial and BE studies, the BMRs should be provided

(2) Complete validation

- For API, provide the validation documents of each test method one by one, tabulate the validation results, and provide validation data &chromatograms
- For DP**,** the requirements for method validation are the same with API's

(3) Comparison with innovators

- For API, compare the Assay, Related Substances (including specified impurity, unspecified impurity, total impurity), Polymorphism and so on.
- For DP, compare the design, screening & optimization and determination of formulations. Compare the quality characteristics (including Assay, related substances, packing conditions). If it's an oral DP, compare the dissolution and so on.

(4) The information on KSM (s)

- Audit reports for outsourced KSM(s): For outsourced KSMs, audit plans should be established, and audit reports should be provided.
- **Control of KSM (s)**
  Detailed manufacturing process, In-house specifications, Related substances, Specified impurities, Unspecified impurities, Total impurities, Assay, Residual solvents and Other tests
- **Necessary method validation**

(5) Reaction steps of production of API :

- **At least three steps acquiescently (**Note: Reactions of salt formation and purification are not counted)
- The production of KSMs should also conforms to GMP
- The requirements of quality control on KSM almost the same as that of final API

(6) Stressing test/Affecting factors testing

a. **Stress testing (API)**
   Purpose: elucidate the intrinsic stability of the API.
   Conditions: under more severe conditions than those used for accelerated testing.
b. **Affecting factors testing (API)**
   Purpose: investigate the intrinsic stability of the API.
   Conditions: under more severe conditions than those used for accelerated testing.
c. **Stress testing (DP)**
   Purpose: assess the effect of severe conditions on the drug product.

Conditions: include photostability testing and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

d. **Affecting factors testing (DP)**
Purpose: investigate the rationality of the formulation, manufacturing processes and packing conditions.
Conditions: as specified in corresponding sections for drug substances.

e. **Except for intensity of stress, others are the same.**

Degradation conditions	High temperature testing	High humidity testing	Photostability testing
Stress Testing From ICH guidelines	10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing	75% RH or greater	NLT1.2 million lux hours NLT200 watt hours/square meter
Affecting factors testing Form ChP2015	60°C for ten days (test at 5th, 10th day) 5% Assay loses, conducted at 40°C	90±5%RH for ten days (test at 5th, 10th day) 5% weight increase conducted at 75±5%RH	4500 lx ± 500 lx for 10 days (test at 5th, 10th day)

(7) Audit and compliance report.

(8) No use of nitrogen purging during packing and storage

(9) In-voices, leaflet and photographs of the reference standards.

Drug Registration Requirements

How to Obtain Marketing Authorization

1. Definition of Marketing Approval:

Marketing Approval for Chinese local enterprises includes Drug Registration Approval letter, Drug Registration and Drug License.

For imported drugs, Marketing Approval includes Drug Registration Approval letter, Drug Registration Specification, and Drug registration license (General called IDL). These documents are released at the same time when IDL is issued, so in pharmaceutical industry, marketing approval documents are usually called IDL. IDL is issued by NMPA (previous called CFDA). The process from application to IDL being issued is called drug registration license transaction or IDL application. IDL includes some information like name and address of manufacturer, etc, but no information of agent.

2Applicant of Marketing Approval

Drug Registration Regulation was put into effect by NMPA on Oct.1st, 2007, in which the clause No.10 stipulates that applicant of Marketing Approval (referred to as applicant) refers to institution who makes the application for drug registration and is responsible for related legal liability.

Domestic applicant should be the institution who has legally registered in China and is independently responsible for civil liability.

Foreign applicant should be legal pharmaceutical manufacturers abroad. Regarding the import drug registration of foreign applicant, it should be its China's branch office or appointed distributors in China to do such registration.

3The management of Marketing Approval and import & export

Active ingredient can be directly used for manufacturing formulation called Bulk Drug. (Also known as API.) API can be sold only after get approval. API cannot be directly used for manufacturing formulation called intermediate, like Amlodipine Base.

Marketing Approval is used for managing the purchase and sales of products in China in the form of drug. Some examples as below:

3.1 Except specially requested drugs, (such as Ephedrine contained drugs) Marketing Approval is not required for formulation export from NMPA, but GMP certificate from NMPA for related forms (tablet, capsule, injection) is required, and it must be recorded in provincial Drug administration every time when accepting orders and exporting.

3.2 Except specially requested drugs, (such as Ephedrine contained drugs) Marketing Approval is not needed when bulk drug is purchased for manufacturing formulation which is only for export, (formulation is not sold in China.) but related proofs from Chinese sellers should be submitted.

3.3 Except specially requested drugs, (such as Ephedrine contained drugs) Marketing Approval is not needed when the bulk drug is purchased only for research. But Chinese sellers should have proofs like contract or invoice to limit end user's usage.

3.4 Except specially requested drugs, (such as Ephedrine) bulk drug export does not need Marketing Approval, GMP from NMPA and it does not need to make record to province Drug administration either.

3.5 Except specially requested drugs, (such as Ephedrine) Marketing Approval is not needed when bulk drug is not purchased to manufacture formulation directly. For example amino acid API is bought to produce food and Domperidone is bought to produce Domperidone Maleate.

3.6 Marketing Approval has no direct relation with customs management for goods. Customs manages goods import and export according to HS code. HS code has related supervision conditions, and if the condition code is Q, *Drug CustomsClearance Form* is required to be submitted to customs. Drug Customs Clearance Form is issued by local port FDA. IDL or filed records from provincial Drug administration (like for research or formulation export only) is needed when issuing. For example, Cetirizine and Metoprolol do not need Drug Customs Clearance Form, but Cefradine and Reserpine do.

Registration classifications of chemical drugs

New registration classification of chemical drugs, classification description and coverage

Registration classification	Classification description	Coverage
1	Innovative drugs never sold in domestic and overseas market	The bulk drugs and preparations thereof containing new chemicals compound with clear structure and pharmacological effect and with clinical value.
2	Improved new drugs never sold in domestic and overseas market	2.1 The bulk drugs and preparations thereof containing optical isomer of known active ingredients prepared with resolution or synthesis method, or esterified known active ingredients, or salified known active ingredients (including salt with hydrogen bond or coordinate bond), or with the changes in acid radical, basic group or metal elements of known salt active ingredients, or form other non-covalent bond derivatives (such as complex, chelate or clathrate compound), and with significant clinical advantages.
		2.2 Preparations containing known active ingredients, of new dosage form (including administration system), new formulation and

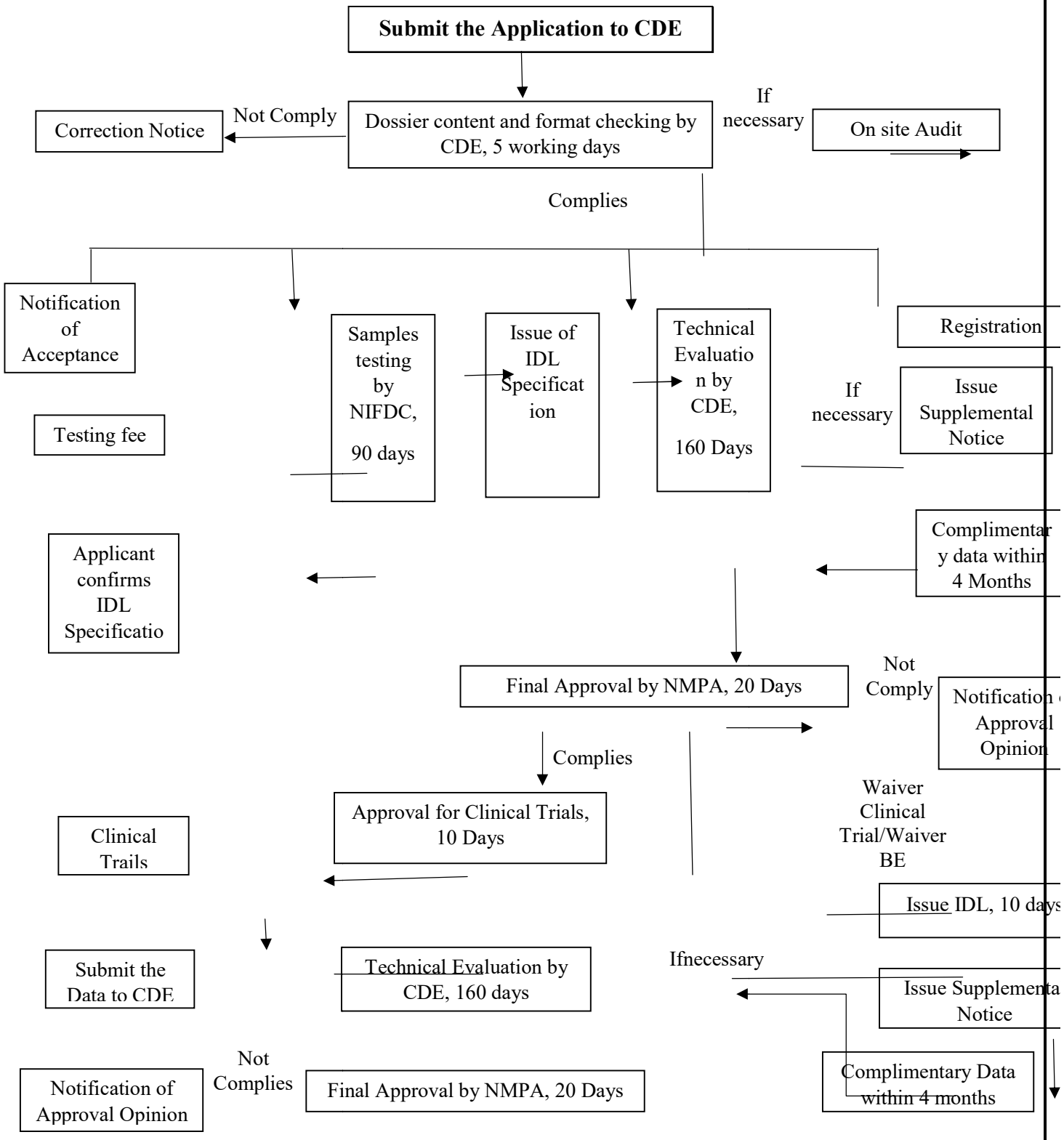
		technology and new administration route, and significant clinical advantages.
		2.3 New compound preparation containing known active ingredients, and with significant clinical advantages.
		2.4 Preparations containing known active ingredients and of new indications.
3	Generic drugs produced based on originators sold in overseas market but not yet in domestic market	The bulk drugs and preparations thereof with the same active ingredients, dosage form, strength, indications, administration route and dosage and usage with originators.
4	Generic drugs produced based on originators sold in domestic market	The bulk drugs and preparations thereof with the same active ingredients, dosage form, strength, indications, administration route and dosage and usage with originators.
5	The drugs marketed overseas under application for being listed in China	5.1 Originators (including bulk drugs and preparations thereof) marketed overseas under application for being listed in China
		5.2 Non-originators (including bulk drugs and preparations thereof) marketed overseas under application for being listed in China.

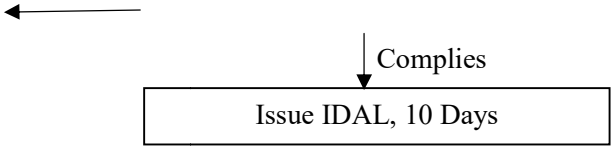
Note: 1. "Known active ingredients" refer to "active ingredients of the drugs sold in the market".

2. Registration Classification 2.3 excludes "new compound preparation containing unknown active ingredients".

Remark: data from NMPA website http:// nmpa.gov.cn/WS04/CL2042

Procedure for Generic Drug IDL Application





Reference timetable for IDL application of Generic Drugs

CDE, as the subordinate of CFDA is responsible for the evaluation work for application documents. Currently CDE arranges applications in queue according to drug categories. The queuing number, date of documents arrival, status of application in CDE for all applications are published in CDE official website.

Currently there are only 17 examiners in CDE who are responsible for evaluation of generic drugs. There is a serious shortage for examiners comparing to a large number of the applications for generic drugs in China market, which restricts and hampers the development of generic drugs. CFDA are studying relevant solutions and policies.

Because the actual time for IDL application is different from the time which is showed on CFDA official website, (please refer to *Procedure for Generic Drug IDL Application.*) We have incorporated an actual time table for IDL application based on working experience for reference.

1 No need to conduct BE study

Time table of IDL application for drugs not required for clinical trial or BE (e.g. Bulk drugs) is as below:

Items	Descriptions	Period (Months)	Remarks
Preparing dossiers		3	Translation and reorganization.
Format Checking by CDE	Checking whether the content and the format of documents is as per CFDA's requirements.	1	If dossiers are acceptable, registration fee shall be charged.
Specification verified by NIFDC	Sample testing and proposing IDL specification.	4	Preparing 3 batches of samples, standards and column etc.
Evaluation by CDE	Evaluating technical dossiers.	12	Some products may need 30 months.
NMPA issues IDL		3	

CSC reservation time	In case CDE needs supplementary dossiers.	5	
Total		24	

2 Need to conduct BE study

Time table of IDL application for drugs required to conduct BE study is as below:

Items	Descriptions	Period (Month)	Remarks
Preparing dossier		3	Translation and reorganization.
Register in CDE web site		1	
BE test or Clinical Trials	The enrolment information of subjects shall be submitted in 2 years		Refer to notice No. 257 of 2015
Preparing for Data after Clinical Trials or BE		1	
Audited by CDE	Checking whether the content and the format of documents is as per CFDA's requirements.	1	Pass review, pay the registration fee
Specification verified by NIFDC	Confirm the specification and test samples	4	Preparing 3 batches of samples, standards, Column etc.
Evaluation by CDE	Evaluating technical dossiers.	12	Decide whether IDL shall be issued.
NMPA issues IDL		3	
CSC reservation time	In case CDE needs supplementary dossiers.	6	
Total		31	

The standards of Certified Documents for IDL application

1 Registration agency

1.1 When the registration is conducted by a foreign manufacturer's resident branch office in China, a copy of ***Registration Certification of Resident Office of Foreign Enterprise***or copy of business licenseshould be provided.

1.2 When the registration is conducted by a Chinese company, business license of the agent, letter of authorization from manufacturer, master copy of notarization for letter of authorization and master copy of certification from Chinese embassy for manufacturer's letter of authorization and relevant Chinese version should be provided.

2FSC (Free Sales Certificate) and GMP

FSC refers to the free sales certificate issued by drug administration institution of manufacturer's country for the product which applies for IDL.

GMP refers to the certificate which can prove the product proposed to apply for IDL is as per GMP, issued by drug administration institution of manufacturer's country.

2.1 WHO-COPP format

The master copy of COPP (Certificate of APharmaceutical Product) in format that recommend by WHO.

Other formats or documents should not be provided if the countries or regions can issue WHO- COPP. This is what NMPA prefers to accept.

2.2 Non WHO-COPP format

For the countries which cannot provide WHO-COPP, copy of FSC and GMP, master copy of notarization and master copy of notarization from Chinese embassy should be provided.

3 Patent

Master copy of declaration of manufacturer does not make infringement to others with manufacturer's company stamp.

4 Others

The relevant certificates should be provided if the drug proposed to apply for IDL has been or will be sold in EU, USA, Japan market. Copies of such certificates submitted should be stamped by the manufacturer.

For bulk drug, CEP, DMF No. of API & certificate of market approval of using the API's formulation, the GMP of Drug manufacturer

For formulation, the acceptance for ANDA application from FDA or EMA can be provided.

These certificates will enhance NMPA's confidence in manufacturers who are truly producing the products and strictly comply with GMP, which shall increase the possibility to attain IDL.

5 The attested certified documents should not be detached (separated) by any individual.

6 All the documents should be within their validity.

Remark: This article is compiled according to the official website of NMPA. http://www.nmpa.gov.cn

Documents needed for the first time IDL application of classify 4 & 5.2

Parts	Serial No.	Content	Remark
One		**(I) Summary**	
		Drug Registration Application Form in triplicate If API, registration form in One	
	1	**Drug name**	
	2	**Certified documents, LOA, COPP and Patent declaration**	
	3	**Project purpose and basis**	
	4	**Self-evaluation report**	
	5	**MAH (marketing authorization holder) information**	
	6	**Innovator information**	
	7	**Package insert, draft instruction and References**	
	8	**Draft of package and label**	
Two		**(II) API**	
	9. (2.3.S)	**Quality Overall Summary**	
	2.3.S.1	General Information	
	2.3.S.2	Manufacture	
	2.3.S.3	Characterization	
	2.3.S.4	Control of Drug Substance	
	2.3.S.5	Reference Standards or Materials	
	2.3.S.6	Container Closure System	
	2.3.S.7	Stability	
	10. (3.2.S)	**Quality**	
	10.1. 3.2.S.1	General Information	
	3.2.S.1.1	Nomenclature	
	3.2.S.1.2	Structure	

	3.2.S.1.3	General Properties	
	10.2 3.2.S.2	Manufacture	
	3.2.S.2.1	Manufacturers	
	3.2.S.2.2	Description of Manufacturing Process and Process Controls	
	3.2.S.2.3	Control of Materials	
	3.2.S.2.4	Controls of Critical Steps and Intermediates	
	3.2.S.2.5	Process Validation and/or Evaluation	
	3.2.S.2.6	Manufacturing Process Development	
	10.3 3.2.S.3	Characterization	
	3.2.S.3.1	Elucidation of Structure and other Characteristics	
	3.2.S.3.2	Impurities	
	10.4 3.2.S.4	Control of Drug Substance	
	3.2.S.4.1	Specification	
	3.2.S.4.2	Analytical Procedures	
	3.2.S.4.3	Validation of Analytical Procedures	
	3.2.S.4.4	Batch Analyses	
	3.2.S.4.5	Justification of Specification	
	10.5 3.2.S.5	Reference Standards or Materials	
	10.6 3.2.S.6	Container Closure System	
	10.7 3.2.S.7	Stability	
	3.2.S.7.1	Stability Summary and Conclusions	
	3.2.S.7.2	Postapproval Stability Protocol and Stability Commitment	
	3.2.S.7.3	Stability Data	
Three	**2.3.P**	**(III) Drug Product**	NA for API
	11. (2.3.P)	**Quality Overall Summary**	NA for API
	2.3.P.1	Description and Composition of the Drug Product	NA for API
	2.3.P.2	Pharmaceutical Development	NA for API
	2.3.P.2.1	Components of the Drug Product	NA for API
	2.3.P.2.1 .1	Drug Substance	NA for API
	2.3.P.2.1 .2	Excipients	NA for API
	2.3.P.2.2	Drug Product study	NA for API

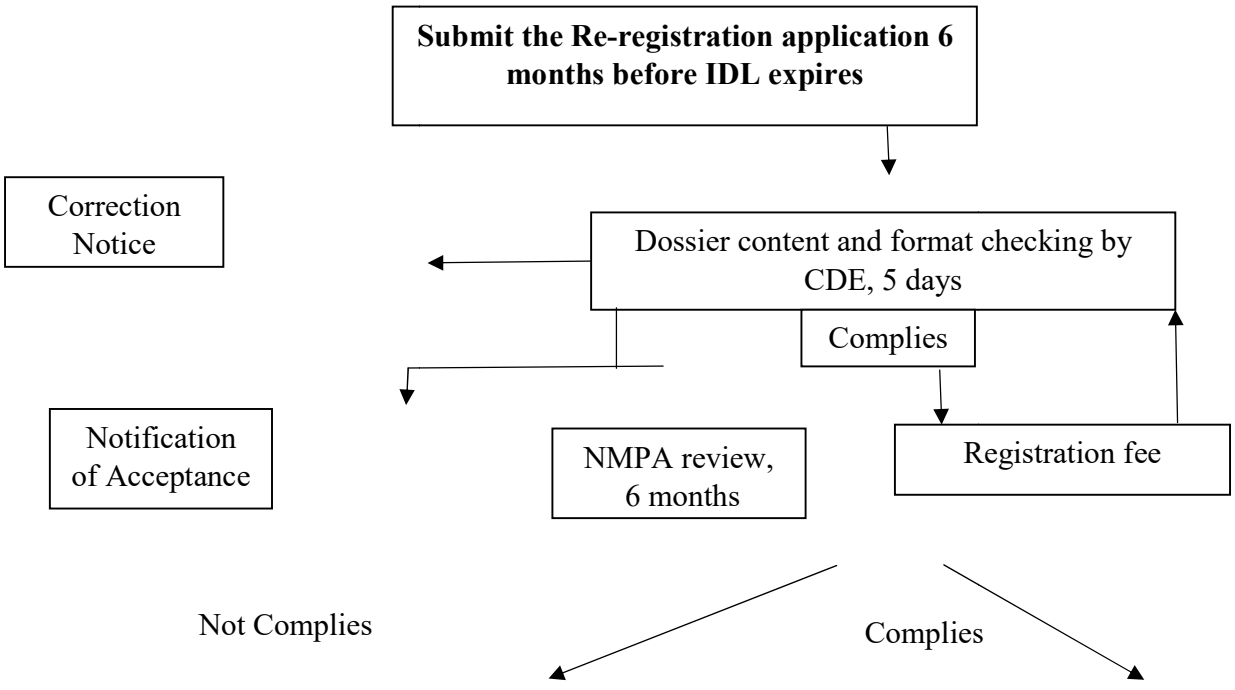
	2.3.P.2.2 .1	Components development process	NA for API
	2.3.P.2.2 .2	Drug product property	NA for API
	2.3.P.2.3	Manufacturing Process Development	NA for API
	2.3.P.2.4	Container Closure System	NA for API
	2.3.P.2.5	Compatibility	NA for API
	2.3.P.3	Manufacture	NA for API
	2.3.P.3.1	Manufacturers	NA for API
	2.3.P.3.2	Batch Formula	NA for API
	2.3.P.3.3	Description of Manufacturing Process & Process Controls	NA for API
	2.3.P.3.4	Control of Critical steps & Intermediates	NA for API
	2.3.P.3.5	Process Validation and / or Evaluation	NA for API
	2.3.P.3.6	Production status of test samples for clinical / BE	NA for API
	2.3.P.4	Control of API and Excipients	NA for API
	2.3.P.5	Quality control of Drug Product	NA for API
	2.3.P.5.1	Specification(s)	NA for API
	2.3.P.5.2	Analytical Procedures	NA for API
	2.3.P.5.3	Validation of Analytical Procedures	NA for API
	2.3.P.5.4	Batch Analysis	NA for API
	2.3.P.5.5	Impurities	NA for API
	2.3.P.5.6	Justification of Specifications	NA for API
	2.3.P.6	Reference Standards or Materials	NA for API
	2.3.P.7	Stability	NA for API
	2.3.P.7.1	Stability Summary and Conclusions	NA for API
	2.3.P.7.2	Postapproval Stability Protocol and Stability Commitment	NA for API
	2.3.P.7.3	Stability Data	NA for API
	12. (3.2.P)	**Drug Product**	NA for API
	12.1. 3.2.P.1	Description & Composition of Drug product	NA for API
	12.2 3.2.P.2	Pharmaceutical Development	NA for API
	3.2.P.2.1	Components of drug product	NA for API
	3.2.P.2.1 .1	Drug Substance	NA for API
	3.2.P.2.1 .2	Excipients	NA for API
	3.2.P.2.2	Drug product	NA for API
	3.2.P.2.2	Components development process	NA for API

	.1		
	3.2.P.2.2 .2	Drug product property	NA for API
	3.2.P.2.3	Manufacturing process development	NA for API
	3.2.P.2.4	Container Closure system	NA for API
	3.2.P.2.5	Compatibility	NA for API
	12.3 3.2.P.3	Manufacture	NA for API
	3.2.P.3.1	Manufacturers	NA for API
	3.2.P.3.2	Batch Formula	NA for API
	3.2.P.3.3	Description of Manufacturing Process & Process Controls	NA for API
	3.2.P.3.4	Control of Critical steps & Intermediates	NA for API
	3.2.P.3.5	Process Validation and / or Evaluation	NA for API
	3.2.P.3.6	Production status of test samples for clinical / BE	NA for API
	12.4 3.2.P.4	Control of API and Excipients	NA for API
	12.5 3.2.P.5	Quality control of Drug Product	NA for API
	3.2.P.5.1	Specification(s)	NA for API
	3.2.P.5.2	Analytical Procedures	NA for API
	3.2.P.5.3	Validation of Analytical Procedures	NA for API
	3.2.P.5.4	Batch Analysis	NA for API
	3.2.P.5.5	Impurities	NA for API
	3.2.P.5.6	Justification of Specifications	NA for API
	12.6 3.2.P.6	Reference Standards of Materials	NA for API
	12.7 3.2.P.7	Stability	NA for API
	3.2.P.7.1	Stability summary and conclusion	NA for API
	3.2.P.7.2	Post-Approval Stability protocol and Stability commitment	NA for API
	3.2.P.7.3	Stability Data	NA for API
	13(2.4.P)	**Nonclinical Quality Overall Summary**	NA for API
	14	**Nonclinical Overview**	NA for API
	14.1(4.2. 1)	Pharmacokinetics	NA for API
	14.2(4.2. 2)	Toxicology	NA for API
	15 (2.5.P)	**Clinical Quality Overall Summary**	NA for API

	16	**Clinical Overview**	NA for API
	16.1 (5.2)	**Clinical Studies Summary**	NA for API
	16.2 (5.3)	**Reports of BE studies**	NA for API
	16.2.1 (5.3.1.2. 1)	**Reports of FastingBE studies**	NA for API
	16.2.1 (5.3.1.2. 2)	**Reports of Postprandia BE studies**	NA for API
	16.2.3 (5.3.1.4)	**Methodological validation and biological sample analysis report**	NA for API
	16.3 (5.3.5.4)	**Other Clinical Studies Reports**	NA for API
	16.4 (5.4)	**Literature References**	

Remark: Data from No. 80 order of IDL registration documents in 2016.The detailed requirements refer to the above No. 80 order.

Procedures for Re-registration of IDL



Notification not to approve	Issue new IDL

Remarks: This procedures is limited to the Re-registraion application which has no change of process, specification, etc since the previous registration. If there is any major change to manufacturing process and specification, then the procedure will be complicated.

Documents for IDL Re-Registration

The IDL valid period is 5 years. Manufacturer can submit the application of Drug IDL Re-Registration to CDE 6 months before expired date of IDL. The previous IDL of API will not be renewed.

1. Certified documents

1.1 Original IDL, original Drug registration approval letter, original imported drug registration specification, if supplementary application is accepted by CDE within valid period of IDL, original approval letter from CDE should be provided.

1.2 Manufacturer's letter of Authorization for registration to agent, master copy of notarization and master copy of certification from Chinese embassy.

1.3 When the authorized agent is different from original one, master copy of *Letter of Registration Agent Waiver*, master copy of notarization and master copy of certification from Chinese embassy should be provided.

1.4 Copy of agent's business license.

1.5 FSC (Free Sales Certificate) and GMP

FSC refers to the free sales certificate issued by drug administration institution of manufacturer's country for the product which applies for IDL.

GMP refers to the certificate which can prove the product proposed to apply IDL is as per GMP, issued by drug administration institution of manufacturer's country.

1.5.1 WHO-COPP format

Master copy of COPP (Certificate of Pharmaceutical Product) in the format that recommend by WHO.

Other formats or documents should not be provided if the countries can issue WHO- COPP. This is what CDE prefers to accept.

1.5.2 Non-COPP format

For the countries which cannot provide WHO-COPP, the copies of FSC and GMP, master copy of notarization and master copy of certification from Chinese embassy should be provided.

2. The batch formula, manufacturing process, drug specification and analytical procedures should be provided. Any changes of batch formula, manufacturing process, drug specification and analytical procedures from last time application should be pointed out, and certificate documents from manufacturer's country, master copy of notarization and master copy of certificate from Chinese embassy should be provided.

3.The source of bulk drug for formulation. Certificate documents from manufacturer's country, master copy of notarization and master copy of certificate from Chinese embassy should be provided if there is a change to the source of bulk drug.

4.Summary of the drug importation and marketing in China during the past five years. Further explanation with regard to non-compliance batches is required if any. Manufacturer's seal shall be affixed.

5.Summary of clinical trial and adverse reaction of the sold drug during the past five years. Manufacturer's seal shall be affixed.

6 First time of IDL re-registration

6.1 When obtaining IDL for the first time, if Phase IV clinical trial is required by CDE, the summary report of Phase IV clinical trial should be provided with manufacturer's company stamp.

6.2 When obtaining IDL for the first time, if CDE requires work to be completed as required, a work summary report should be provided with relevant data provided as well. Manufacturer's seal shall be affixed.

7 The sample of the current packing, label and insert sheet of smallest retail package used in China.

8 The current version of the insert sheet in the original language from the original manufacturer approved by the competent drug authorities at the local country or region where the manufactured is located and the Chinese translation.

9 Government certificate, notarization and certificate from Chinese embassy should be provided at the same time. Government certificate, notarization and certificate from Chinese embassy should not be unsealed without permission.

10 All documents should be in the period of validity.

Change Management

Regulations relating to Change Management

- **Article 110**: A supplemental application should be filed for changes of items in the approval certificate or the content of its attachment of new drug research, drug production and drug importation.
- **Annex 4**: Registration Items and Application Information Requirements of Supplemental Application of Drug Registration.

Classification of Change

1. **Class IMinor change:** Almost have no impact on the safety, efficacy and quality control of production. Examples are
   - Change the process parameters between control range, eg. Stir time, stir speed.
   - Change the source of KSM, but don't change it's synthesis route and specification.
   - Change the source of solvents, reagents, but don't change their specifications
   - Change the supplier of excipients, but the type and grade are the same. If the change cause significant variation on dissolution, which should be considered as medium change.
   - Non-solid preparations: change the supplier of excipients, which is a single chemical entity(Assay is NLT 95%)

2. **Class II Medium change:** Need corresponding studies to prove
   - Extend the mfg. process, and treat the KSM as intermediate.
   - Change the specifications of KSMs, solvents, intermediates, but impurity profile of intermediates and final products is the same or equivalent.
   - Add or instead in-process controls because of safety and quality
   - Change the source, type and grade of excipients, eg, corn strach is instead of wheat starch, microcyrstalline cellulose PH200 is instead of microcyrstalline cellulose PH101 .
   - Add colorants, add or not use fragrances,flavoringagents,which are not more than 2%(w/w) (w/v).
   - Add water soluble film coating material or appearance polishing material for solid preparations

3. **Class III Major change:** Need systematic studies to prove
   - Change one and more reaction steps, even the whole mfg. process, treat an intermediate as a KSM.
   - Change the synthesis process to fermentation process.
   - Change the critical steps and critical parameters

- Change the granulating solvent, eg, water is instead of ethanol.
- There are huge change on the type and quantities of excipients, eg., add 5% of microcyrstalline cellulose cause the weight increase.
- Change the equipment having important impact on the quality of final product, eg., wet granulator is instead of dry granulator , or vice versa

4. **General information change:**
   - Change the expression of manufacturer's name and facility's address, but actual facility address doesn't change.
   - Change the agent.

Application of API's change:

- Submit supplemental dossiers under the unique registration number of this API
- Annual report should be provide for APIs
- Associate with DPs
- Consolidated review
- Activate the status of API

Application of DP's change

- Submit supplemental dossiers to CDE
- Evaluated by CDE
- Approved/disapproved by CDE

Expenses of IDL application

1. The drug registration fee is calculated based on one API or one preparation. If another specification is added, the registration fee will be increased by 20% according to the corresponding category.
2. No supplementary application registration fee is charged for the drug supplement application filed by the provincial food and drug supervision and administration department or directly filed by the food and drug supervision and administration department of the State Council as per the Drug Administration Regulations. If such an application is reviewed and the application content requires technical review, the applicant shall pay the fee in accordance with the charging standard for the supplementary application requiring technical review.
3. 2000RMB will be charged if the applicant applys for one time drug import permit.
4. The import drug registration fee standard is based on the corresponding domestic registration fee standard plus the difference between domestic and international inspection of transportation, accommodation and food expenses.
5. The registration fees for drug registration in Hong Kong, Macao and Taiwan are subject to the registration fee for imported drugs.
6. The fee for the registration of the drug registration expedited fee shall be separately formulated.

Charge Standard Regulations

2.1 The charging justification: as per【2015】 No.2 (Notice concerning the repromulgation of administrative institutional fee items of food and drug regulatory departments under the administration of the central government) and 【2015】 No. 1006 (Notice on the issuance of "administrative measures on drug and medical device registration fee standard ") documents issued by Ministry of finance, national development and reform commission.

2.2 The charging standard: as per【2015】 No. 53 (Notice of the China food and drug administration on the promulgation of drug and medical device registration fee standards) and 【2016】 No. 124 (Notice concerning the new classification fee standard for chemical drug registration) documents issued by NMPA.

Charge standard(Unit: 10K RMB)

Types of section		Made in China	Imported
New drug registration fee	Clinical Trials	19.20	37.60
	Production / listing	43. 20	59. 39
Generic registration fee	Clinical trial not required for Production / listing	18. 36	36. 76
	Clinical trial required for Production / listing	31. 80	50. 20
Supplementary application registration fee	General item	0. 96	0. 96
	Technical review required	9. 96	28. 36
Drug re-registration fee (each five year)		Developed by provincial price and finance department	22.72

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Details of importing country embassy in India: http://in.china-embassy.org/eng/

Contact details of Indian Embassy abroad: http://indianembassybeijing.in/