Developing a successful China regulatory strategy for market entry and beyond

February 22, 2024

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Agenda

- Recent registration trends
- Regulatory framework overview
- Registration pathways
- NMPA Legal Agent requirement
- Drug classification
- Device risk classification
- Clinical trials
- Hot topics
- Maintaining compliance in China
- About Cisema & how we can help

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Recent registration trends

NMPA Approval Trends: Medical Devices & IVDs

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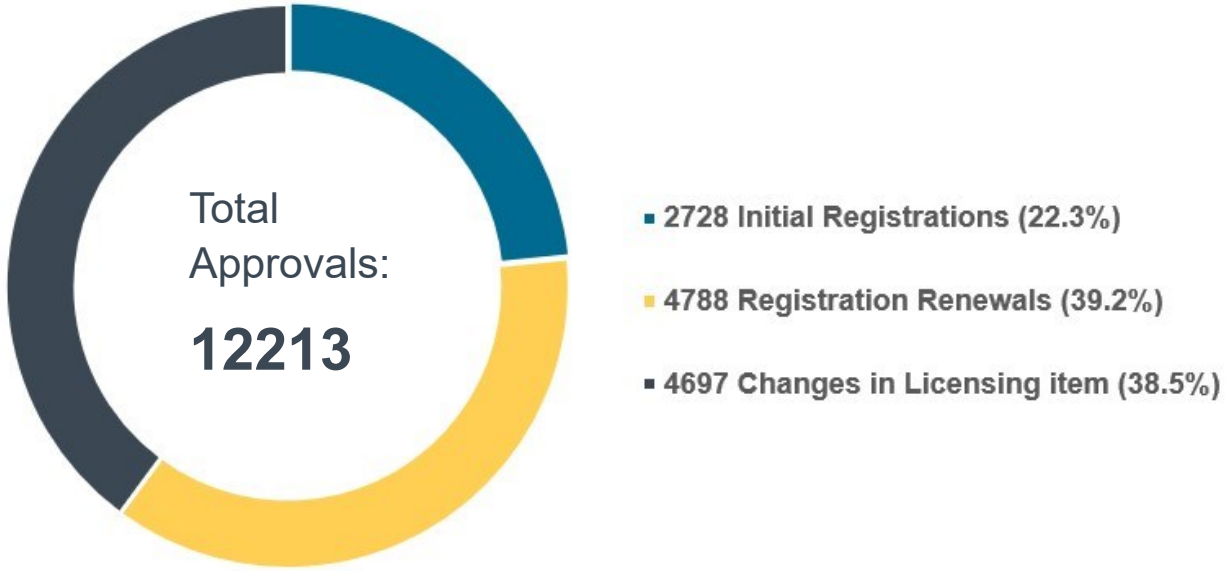
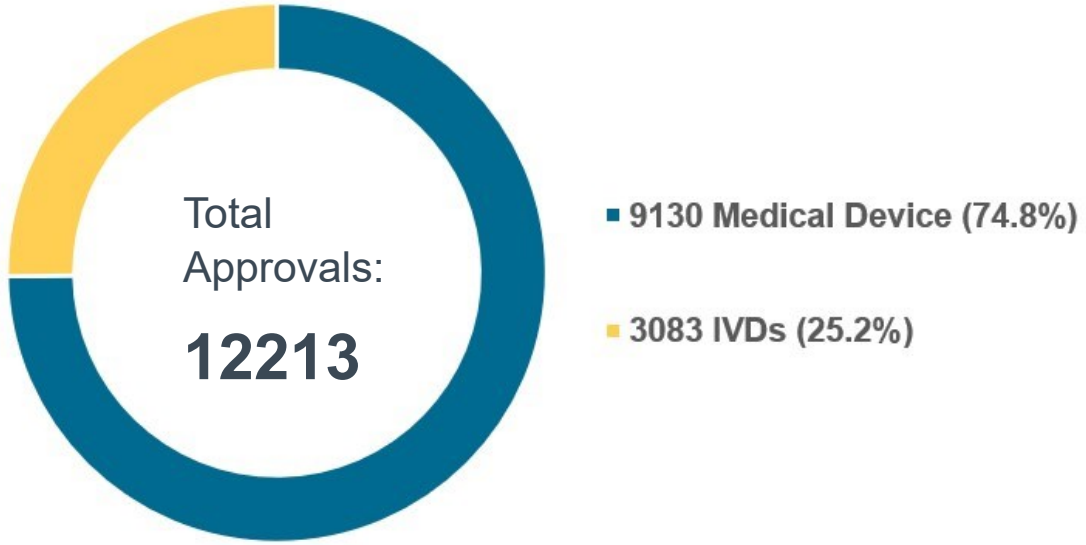
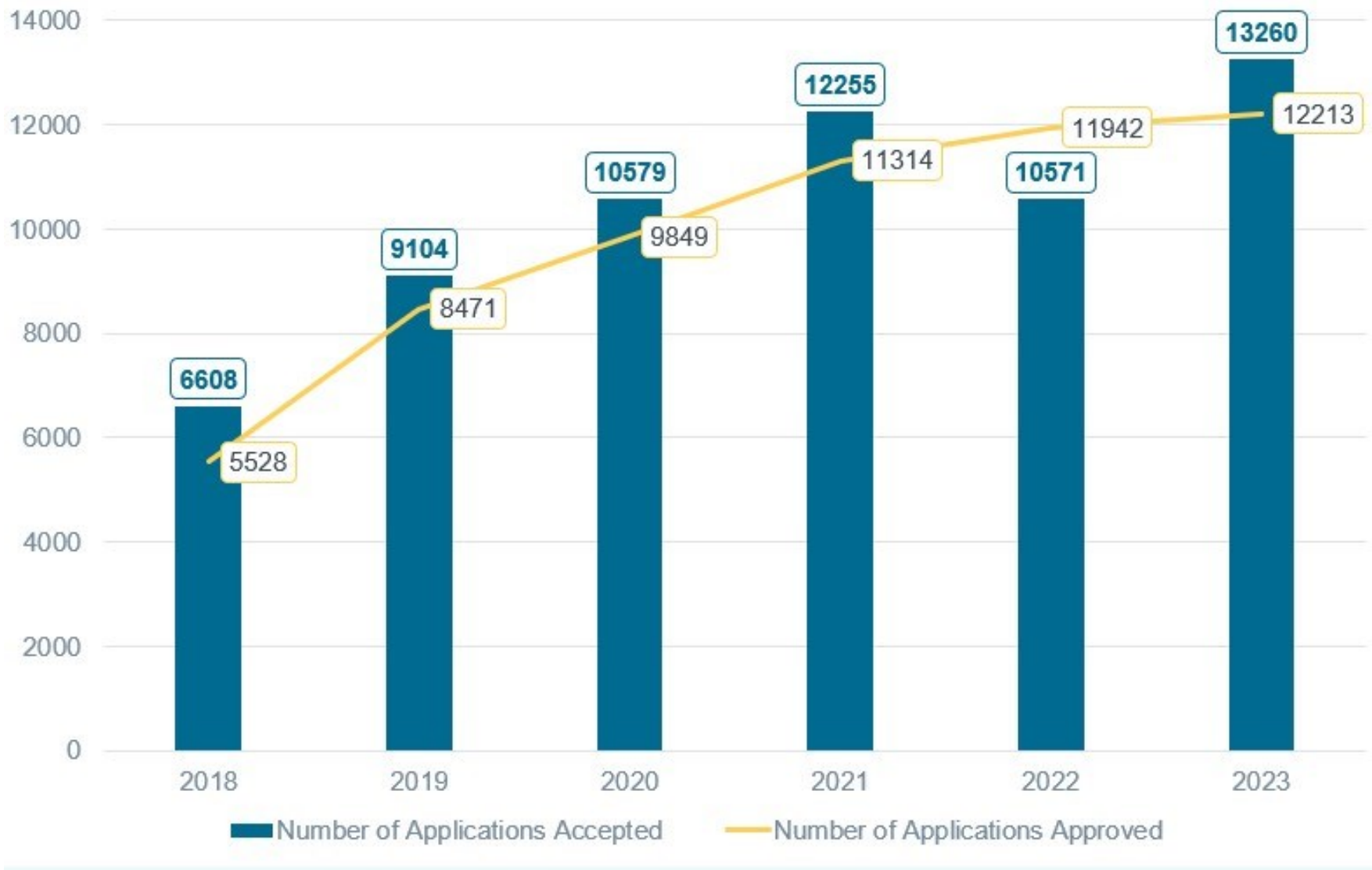
- NMPA handles applications and approvals for Domestic Class III and **all overseas approvals**





NMPA Approval Trends: Medical Devices & IVDs



Top 10 Registering Countries: Medical Devices & IVDs

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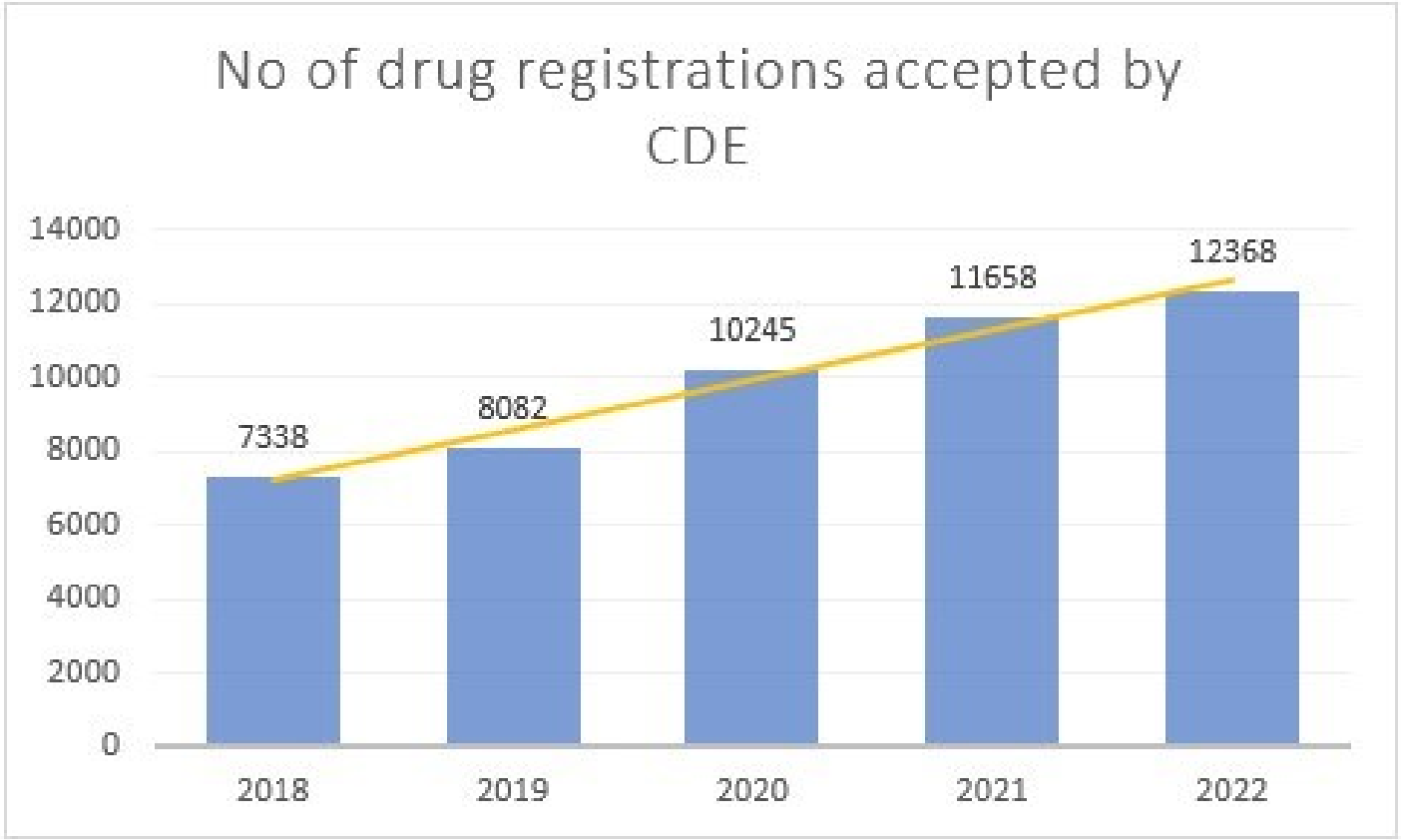
2020	2021	2022	2023
1. USA	1. USA	1. USA	1. USA
2. Germany	2. Germany	2. Germany	2. Germany
3. Japan	3. Japan	3. Japan	3. Japan
4. South Korea	4. South Korea	4. South Korea	4. South Korea
5. Switzerland	5. Switzerland	5. France ▲	5. France
6. Taiwan	6. Italy ▲	6. Switzerland ▼	6. Italy ▲
7. France	7. France	7. United Kingdom ▲	7. Switzerland ▼
8. Sweden	8. United Kingdom ▲	8. Italy ▼	8. Ireland ▲
9. Netherlands	9. Sweden ▼	9. Sweden	9. Sweden
10. Israel	10. Israel	10. Israel	10. Israel

NMPA Approval Trends: Drugs

- 12 000+ drug registration applications accepted by Center for Drug Evaluation in 2022 (6% YOY growth) :
- Drug clinical trial application
- Marketing authorization application
- Re-registration application
- Other supplementary applications.
  - Traditional Chinese medicines
  - Chemical drugs
  - Biological products
  - Drug-device combination products



NMPA Approval Trends: Drugs

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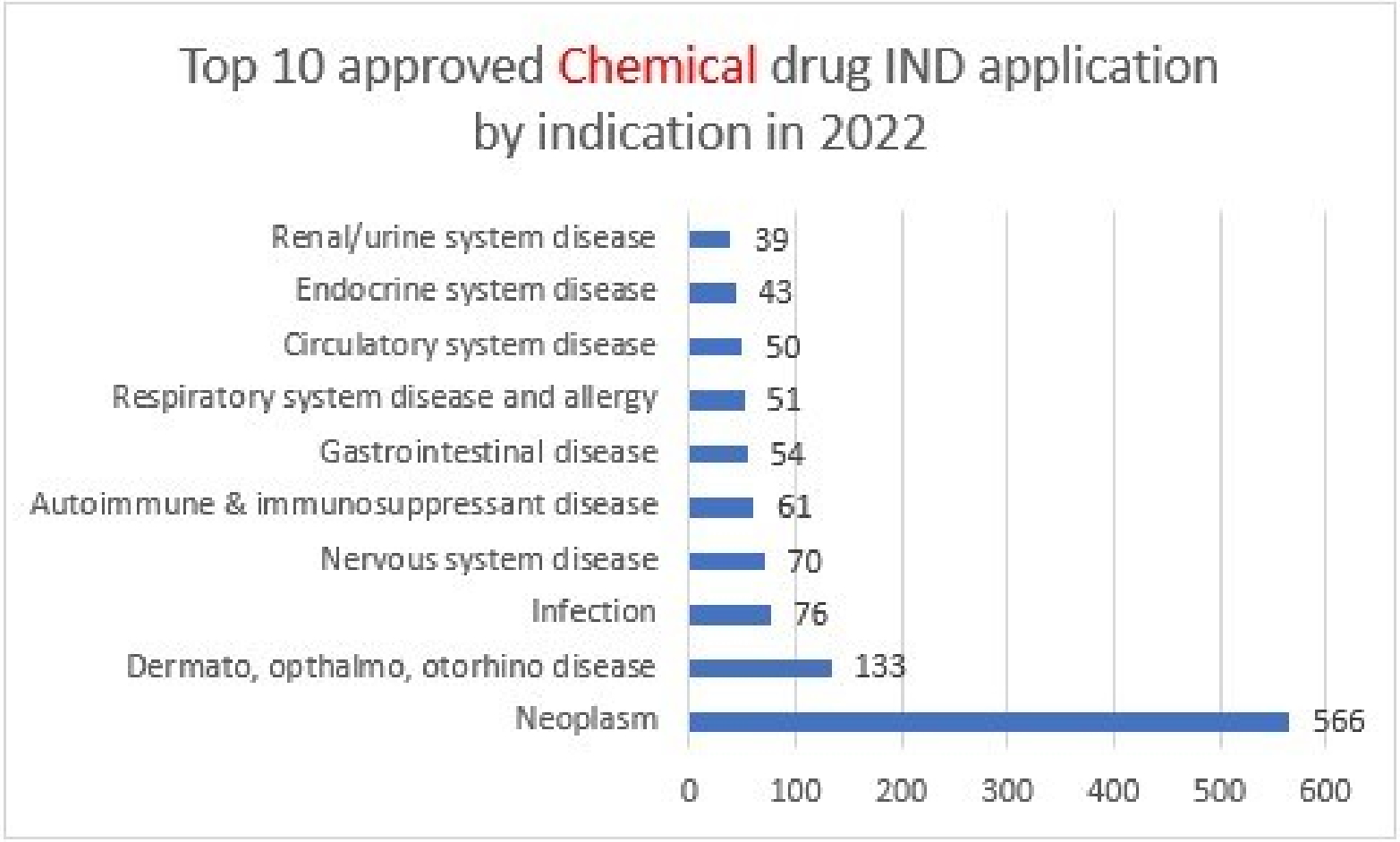
Chemical drug Investigational New Drug (IND) applications approved by CDE in 2022 decreased slightly YoY by 3% from 1327 to 1286.

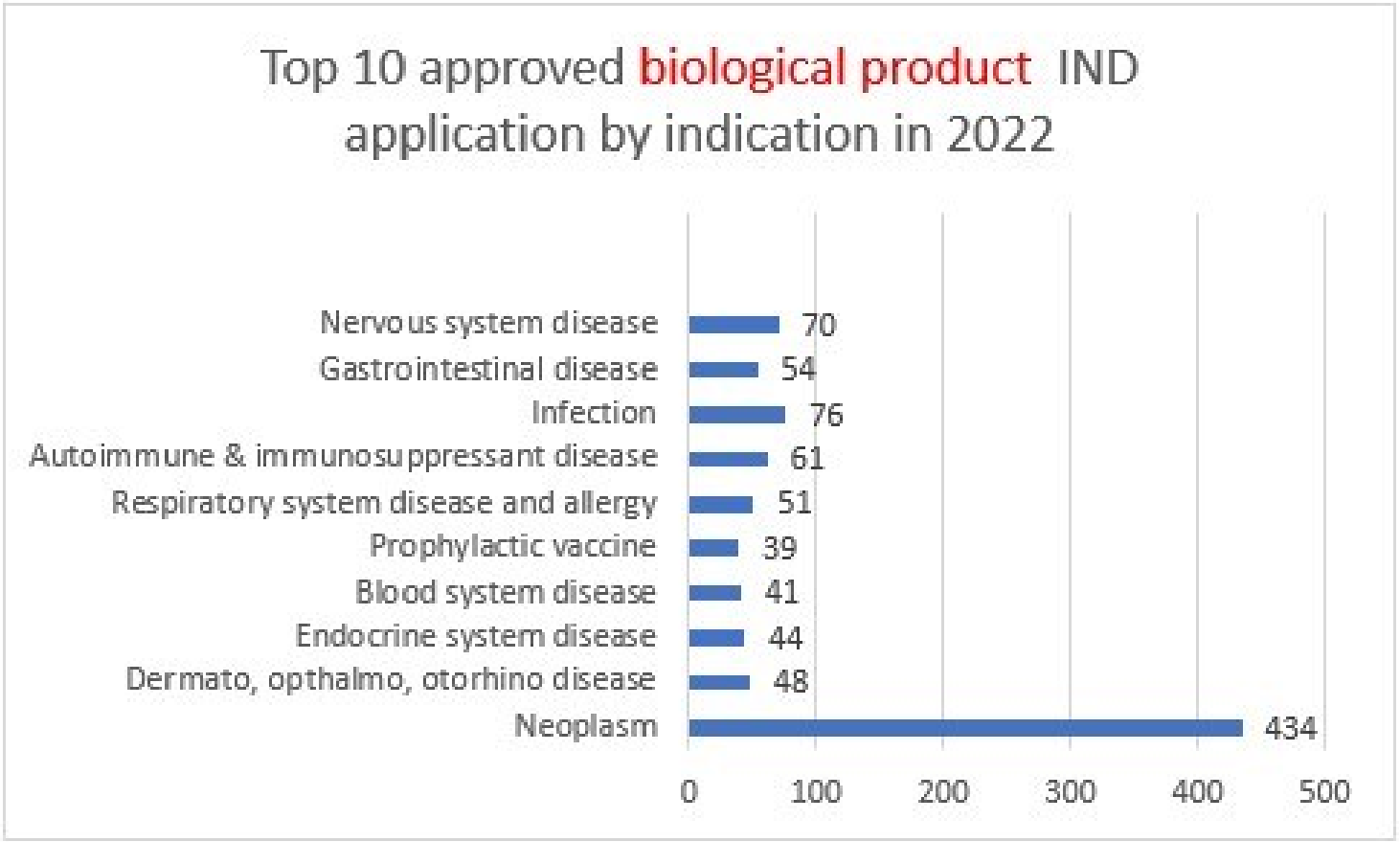


55%

NMPA Approval Trends: Drugs

Biologic drug IND applications approved by CDE in 2022

- 40 IND approvals for preventive biological products of which 18 were innovative
- 729 IND applications for therapeutic biological products of which 533 were innovative



56%

Regulatory Framework & Pathways

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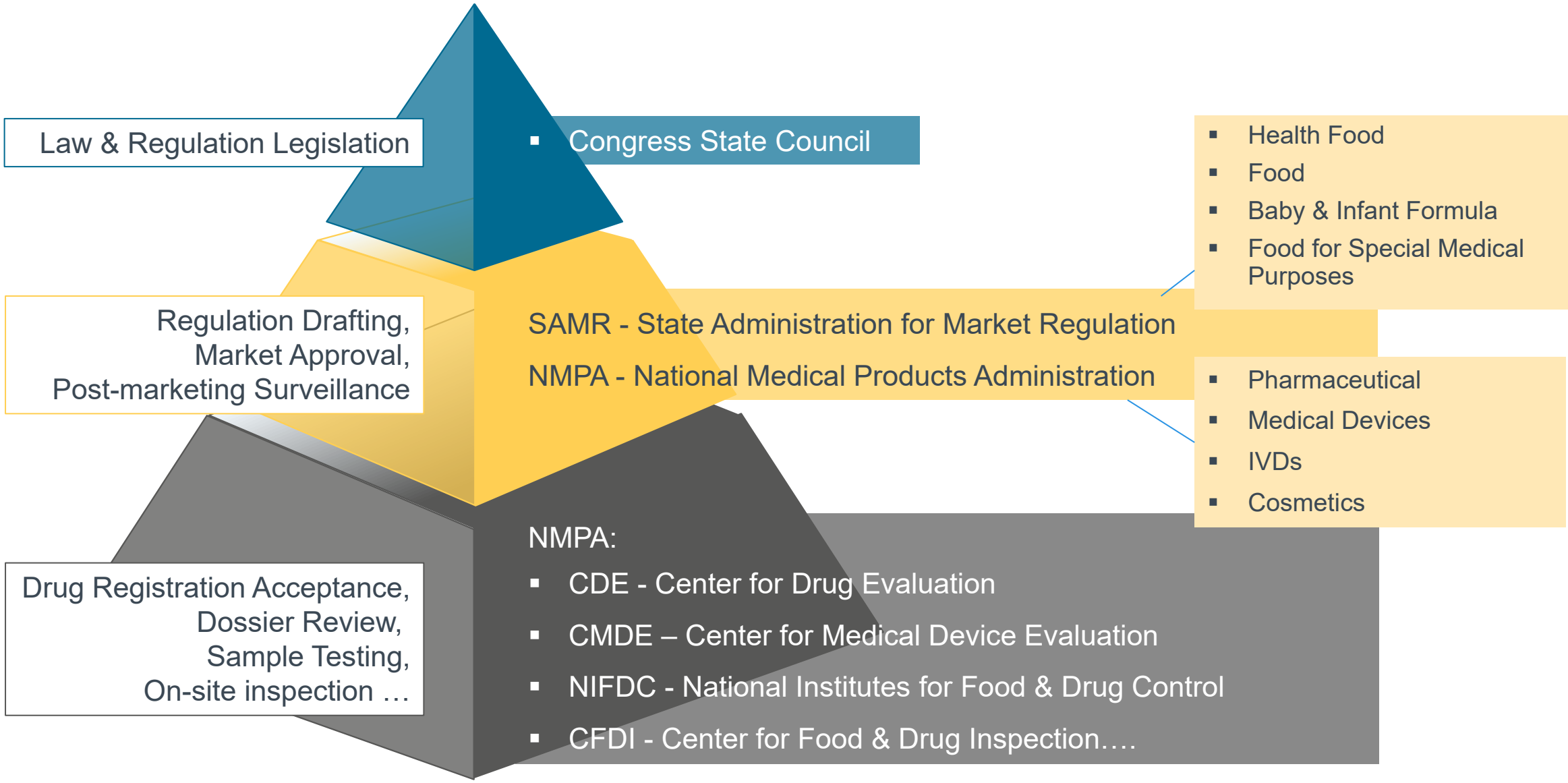
Authorities & Regulation Framework – 3 Levels



Select the Optimal Registration Pathway

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Mainland China

NMPA Standard Application

- Requires home-country approval (e.g. CE, FDA, UK CA)
- Requires Clinical Evaluation Report or Clinical Trial

- NMPA Priority Review
- NMPA Emergency Approval
- NMPA Conditional Approval

NMPA Innovative Medical Device Application

- NMPA Innovative Medical Device Application: approved or not
- Requires China patent

Parts of China

Hong Kong & Greater Bay Area

- Registration is voluntary into Hong Kong at present; relies on home country approval
- Hospital sponsor in GBA then required
- Enables collection of RWD on Chinese ethnic population

Hainan Boao Lecheng International Medical Tourism Pilot Zone

- Requires home country approval (e.g. CE, FDA, UK CA)
- Hospital sponsor
- Enables collection of RWD on Chinese ethnic population

Hainan Pilot Zone: 2nd Boao RWS Conference

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- Currently, there are 13 products certified through Hainan RWD/RWE: 4 drugs & 9 devices
- Pre-submission process being introduced in Hainan for RWE
- Seeking to bolster role of RWE in evaluation of medical devices
  - Specific guidelines being drafted
  - At this stage, RWE still cannot replace clinical evidence / evaluation

- Vision:
  - High-risk products: clinical trial (primary evidence) + RWE (complementary evidence)
  - Medium & low-risk products: same-variety comparison / non-clinical (primary evidence) + RWE (complementary evidence)
  - Product iteration: non-clinical + RWE
- For RWS, treatment cost for patients is usually not borne by sponsor
  - Follow up an issue in practice
  - But cost is much lower than clinical trials.

Hong Kong Listing

- Voluntary system for product safety approvals of medical devices and IVDs
- Now **required** for tenders and sales to public hospitals
- Recent announcements making listing mandatory

Process:

- Identify **Local Responsible Person** (LRP) in Hong Kong
- Classification according to Hong Kong standards (uses IMDRF)
- Submission dossier for listing with Hong Kong Medical Device Administrative Control System (MDACS)
- Compliance with post-approval requirements

Other opportunities:

- **Greater Bay Area applications**
- Real World Data generation for mainland China registration

Hong Kong & GBA market size

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2021	Hong Kong	Switzerland	Greater Bay Area	United Kingdom
Population (m)	7.5	8.7	78	67.8

(**Source:** worldometers.info)

Hong Kong 2021	Public hospitals and institutions under HA	Private hospitals	Correctional institutions
No. of facilities	43	13	20
Number of hospital beds	30105	5147	874

(**Source**: Hong Kong Department of Health)

- Nov 10, 2023: **14,513** registered pharmaceutical products of which **106** were registered in Q1/2023
  (Source: Hong Kong Drug Office database)
- October 26, 2023: **4,663** medical devices & IVDs actively listed
  (Source: MDACS database)

Drugs: Accelerated pathways

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Pathway	Applicable scope of drugs		Technical review time
Normal review	Drugs not eligible for priority review		200 working days
Priority review	Drugs must meet 1 of the following conditions: 1. **Shortage of drugs** urgently needed in clinical practice (NHC Catalogue) 2. Innovative new drugs & improved new drugs for prevention & treatment of major infectious & rare diseases 3. New varieties, dosage forms, and specifications of **paediatric drugs** 4. **Vaccines** & innovative new vaccines urgently needed for disease prevention and control 5. Drugs included in the **breakthrough therapy** programme 6. Drugs eligible for **conditional approval**		130 working days OR 70 working days for **rare disease drug** urgently needed for clinical use that has been listed overseas but not domestically
Breakthrough Therapy	▪ Innovative new drugs OR modified new drug (globally) ▪ Adequate evidence show obvious clinical advantages ▪ Prevent or treat diseases seriously life-threatening/affect quality of life, no effective prevention/treatment available		
Conditional Approval	**Drugs:** ▪ Urgently need for public health ▪ Used to treat seriously life-threatening diseases for which no treatment method is available	**Vaccines:** ▪ Urgently need for major public health emergencies ▪ As determined by NMPA	
Special approval	Drugs for public health emergencies		Format check 24H Approval 3 WD

Key considerations

Legal Agent, Classification, Clinical Trials

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Legal Agent / MAH / Authorised Person

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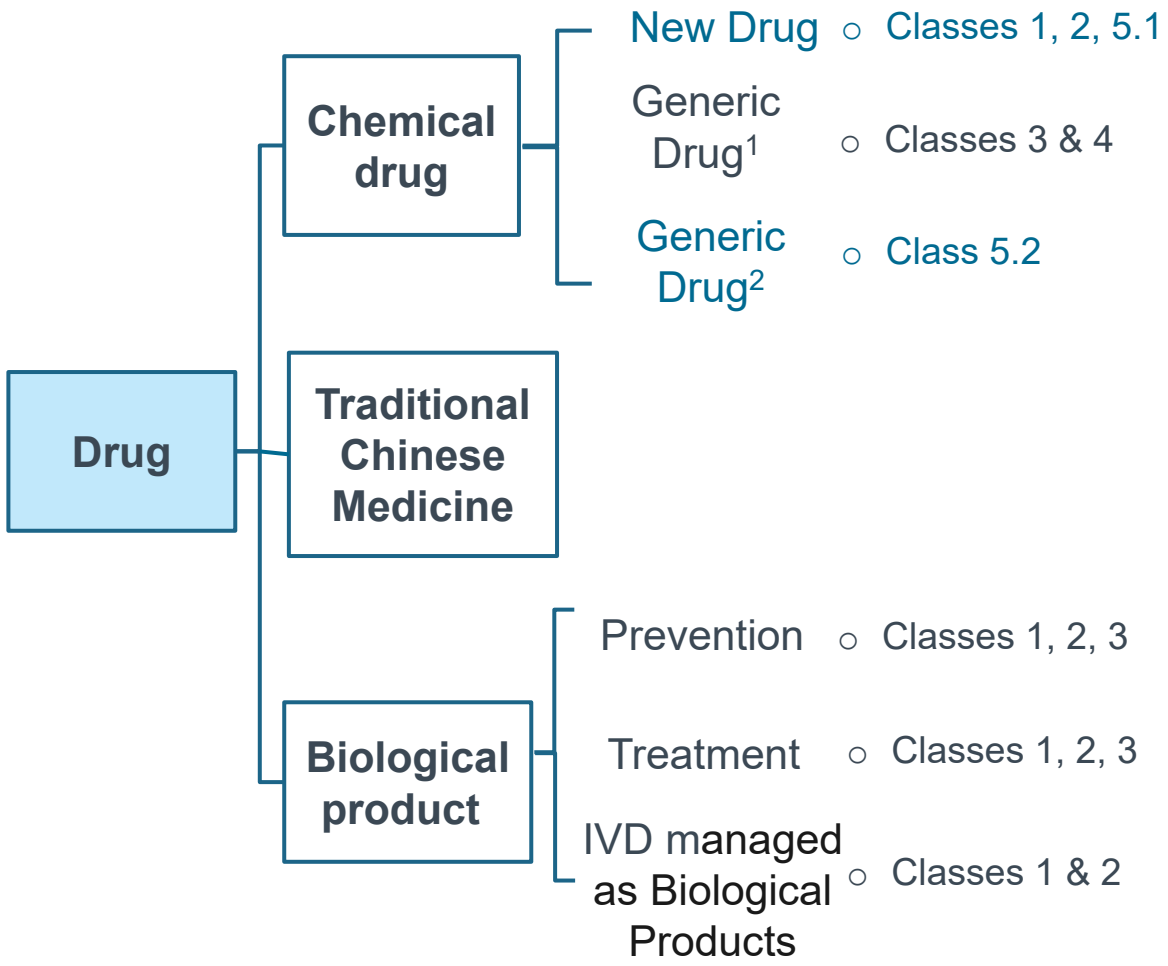
Distributor	Own subsidiary	Consulting firm
+ Distributor may offer to cover upfront investment required to register in return for lower transfer price	+ Retain full control of certificates and therefore flexibility in choosing as many channel partners as required	+ Qualified and experienced regulatory and quality experts available immediately to register your product and undertake Post-Market Surveillance
- Possible IP violation as the Distributor has access to sensitive information as part of the registration process	- Requires an established and well-functioning Post-Market Surveillance system in China to conform with NMPA requirements	+ Retain full flexibility in choosing or replacing channel partners as required
- Distributor retains control of registration certificates which can impact imports, change notifications and renewals	- Considerable investment required to set up a company, find and hire qualified and experienced regulatory experts	+ Retain full control of certificates
- No other Distributor can be added without their approval; it can also be difficult to replace Distributor		- Annual representation fees/costs

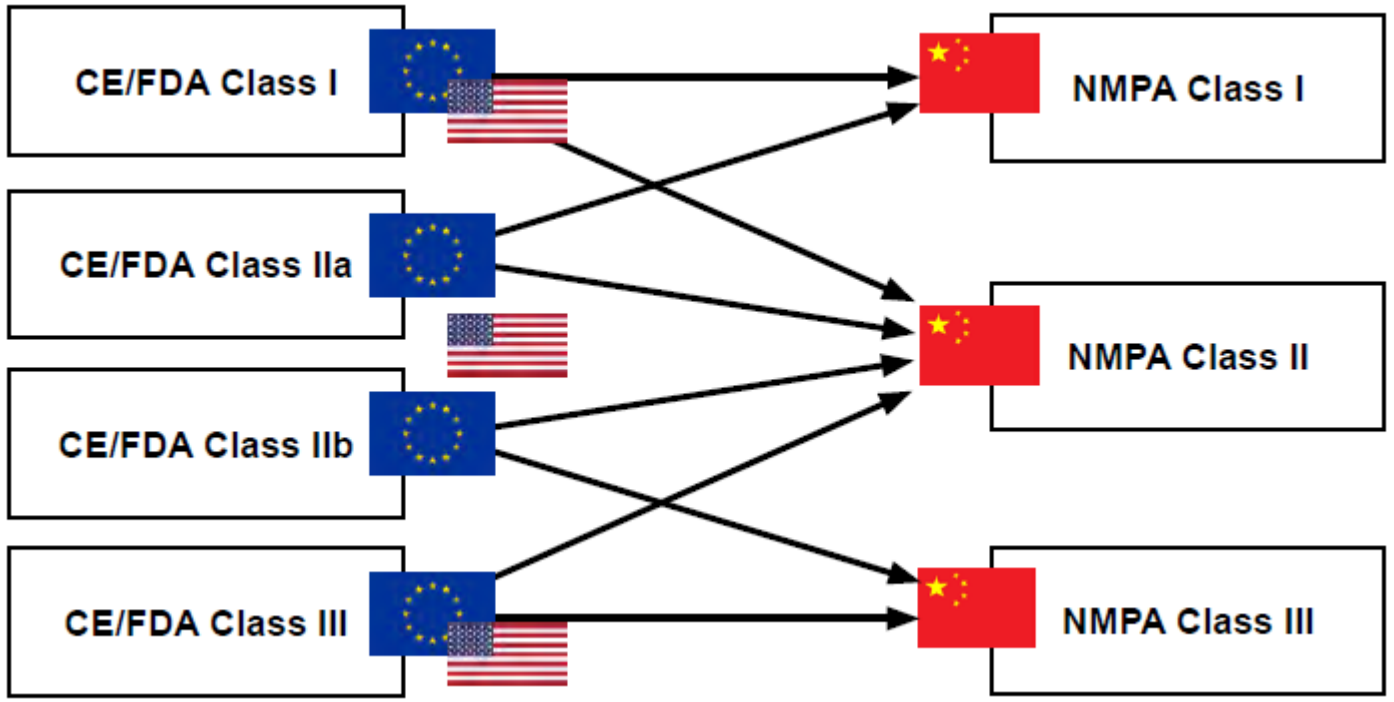
Classification of Drugs in China



No.	Chemical Drug Registration (Imported)
1	Innovative new drugs not marketed anywhere in the world.
2	Improved new drugs not marketed anywhere in the world. E.g. New dosage form, new indication.
5.1	New drugs or improved new drugs that have been marketed in other countries, but not yet in China.
5.2	Generic drugs that have been marketed in other countries, but not yet in China.

No.	Prevention Biological Product & Therapeutic Biological Product	IVD (Imported)
1	Innovative and not marketed anywhere in the world.	Innovative IVD reagents.
2	Improved and not marketed anywhere in the world.	IVD reagents marketed overseas apply for marketing in China.
3.1	Produced & marketed overseas but not marketed in China, apply for marketing in China.	N/A
3.2	Produced & marketed overseas but not marketed in China, apply for production & marketing in China.	N/A

Device Risk Classification



How to classify a medical device

Check the latest version of the "Classification Catalogue"

If no clear result, judge according to the "Rules for Medical Device Classification"

Apply for an official classification from the NMPA

- Class I
- Class II
- Class III

Medical Devices: Class II & III Registration Process

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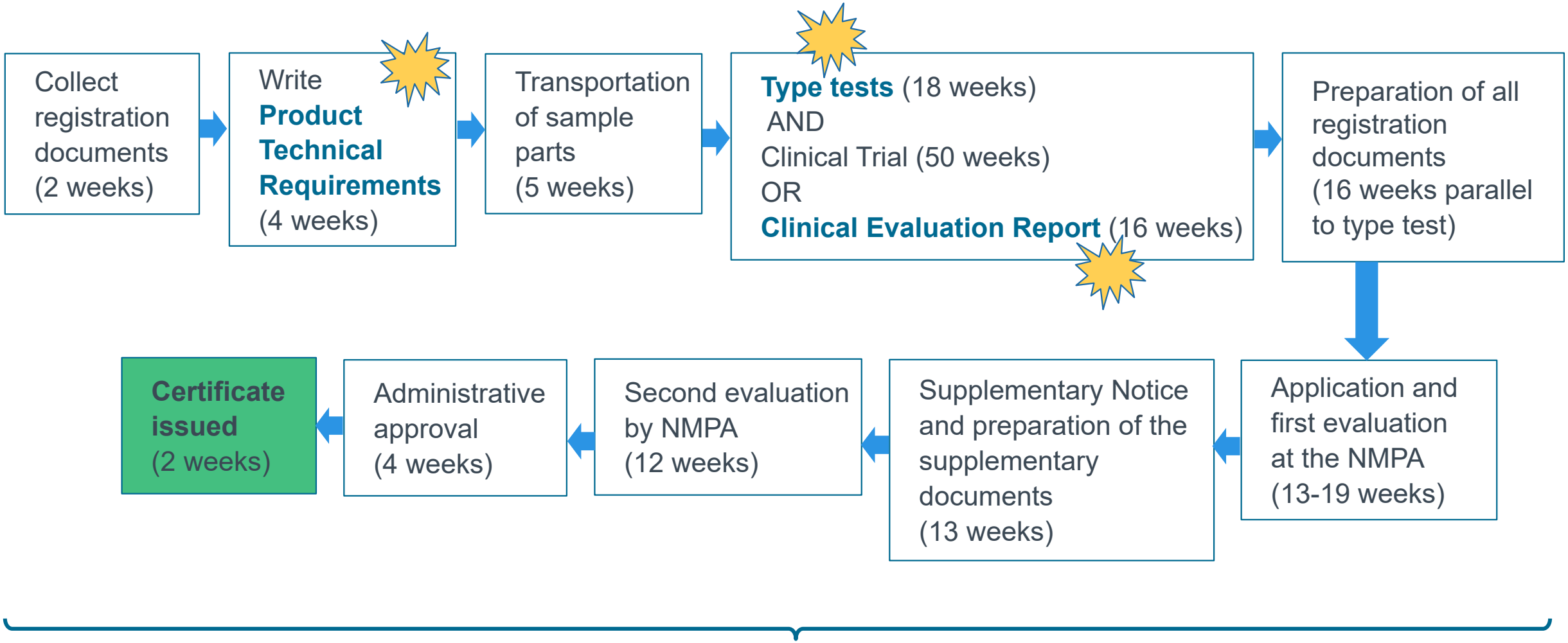

Expected registration time frame: About 18 months for class II and 21 months for class III without clinical trials

Medical Devices: Is a Clinical Trial Required?

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		Clinical Trials Necessary?
Q1. Is this product high risk?	Yes	Clinical trial more likely required.
	No	Move to next question.
Q2. Is the product on the "Clinical Trial Exemption List"?	Yes	Clinical evaluation and/or trial not required.
	No	Move to next question.
Q3. Is there sufficient qualifying overseas clinical trial data?	Yes	China clinical trial not required.
	No	Move to next question.
Q4. Do predicate devices exist, which have already attained NMPA registration?	Yes	Move to next question.
	No	China clinical trial required.
Q5. Is enough clinical data of the predicate device legally accessible?	Yes	Clinical trial not required
	No	Clinical trial required

Write a CER based on Overseas Clinical Data

Write a CER based on Predicate Device

IVDs: Is a Clinical Trial Required?

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- Previous to 2018 all IVDs were required to undergo a clinical trial in China.
- **2018 No.94 Notification by NMPA: IVD Clinical Evaluation Exemption Catalogue**
- Applicants can skip clinical trials if in Exemption Catalogue & only when IVD reagent meets both of the following conditions:

  (1) IVD reagent has:

  a) clear work mechanism & fixed design & is produced with mature technologies

  b) same type of previously approved product has been clinically used for years with no record of severe adverse events

  c) new IVD reagent's functions are the same as standard ones for this type of IVD reagent.

  (2) New IVD reagents can be proved to be safe and effective by methodological comparison with same type of products.

- IVD reagents meeting conditions, clinical trial evaluation documents are still required for submission
- Necessary documents include:
  - analysis & data of comparison between new IVD product and same type of approved product
  - analysis of relevant literature and empirical data, etc.

Drugs: Is a Clinical Trial Required?

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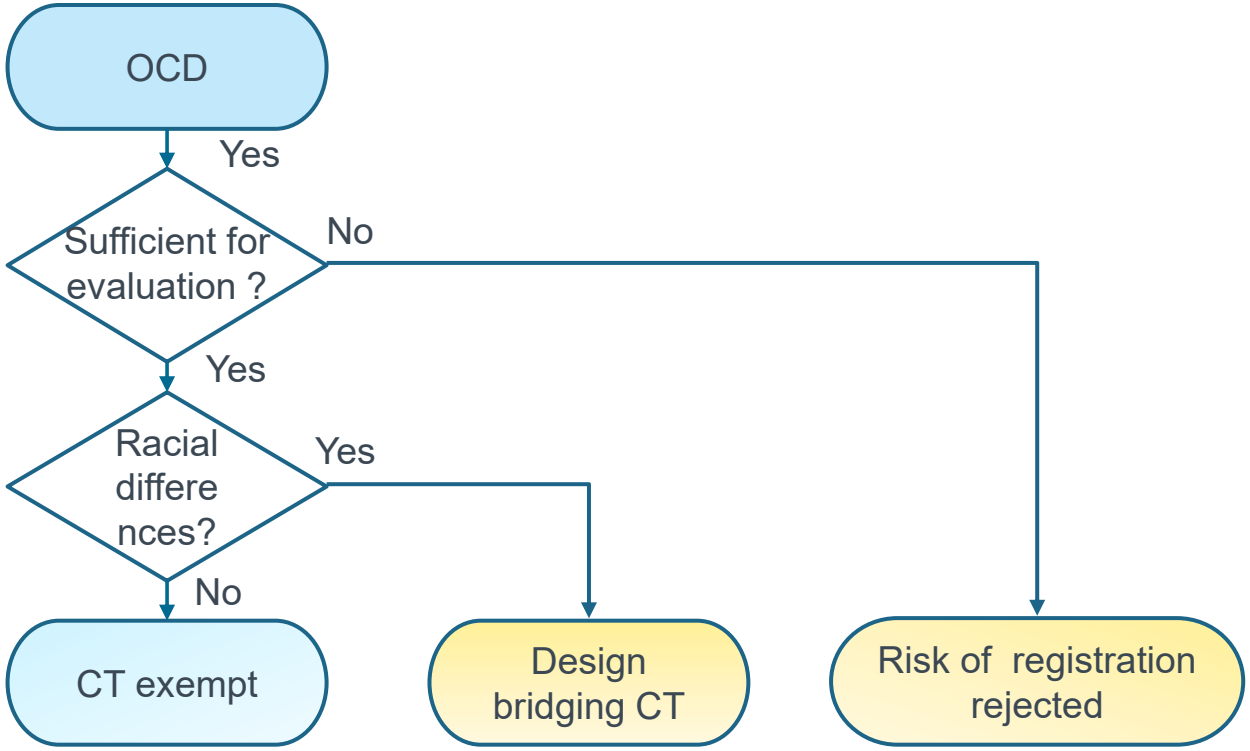
- Class 1 (Innovative new drug) and Class 2 (Improved new drug) not marketed anywhere in the world, clinical trials shall be completed before MA application in China.

- CTs conducted overseas with no Asian/Chinese ethnic population, a bridging trial needs to be designed to reflect pharmacodynamic or clinical data in the Chinese population on:
  - efficacy
  - safety
  - dose
  - dosing regimen,
- so that overseas clinical data can be extra-polated to Chinese patients.



Hot Topics

Localization, Medical Device Master Files

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Hot Topic: Localization Trends

- For high-end medical devices, foreign companies remain as dominating market players in China
- Headwinds:
  - Buy “Made in China” & localization trends
  - Bidding platform practical difficulties
- Key recent trend we are seeing: distributors approaching their manufacturer suppliers and insisting they must be local agent in order to operate on the bidding platforms.
  - But this is not correct! There are solutions available to retain your independence from your distributor.

Hot Topic: Localizing Production in China

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Market Authorization Holder (MAH)

- Establish own entity in China to act as MAH = relatively fast
- Find Chinese partner as OEM
- Local product registration certificate
- Cost of entry lower and controllable
- “Made-in-China” products can be sold in a short timeframe

Wholly Foreign-Owned Enterprise (WFOE)

- Find location for factory
- Create WFOE and build factory
- Local product registration certificate
- Best way to protect IP
- Independent from any Chinese partner
- Better control of product quality and PMS
- Better control of planning and scheduling

Hot Topic: Medical Device Master Files (MDMF)

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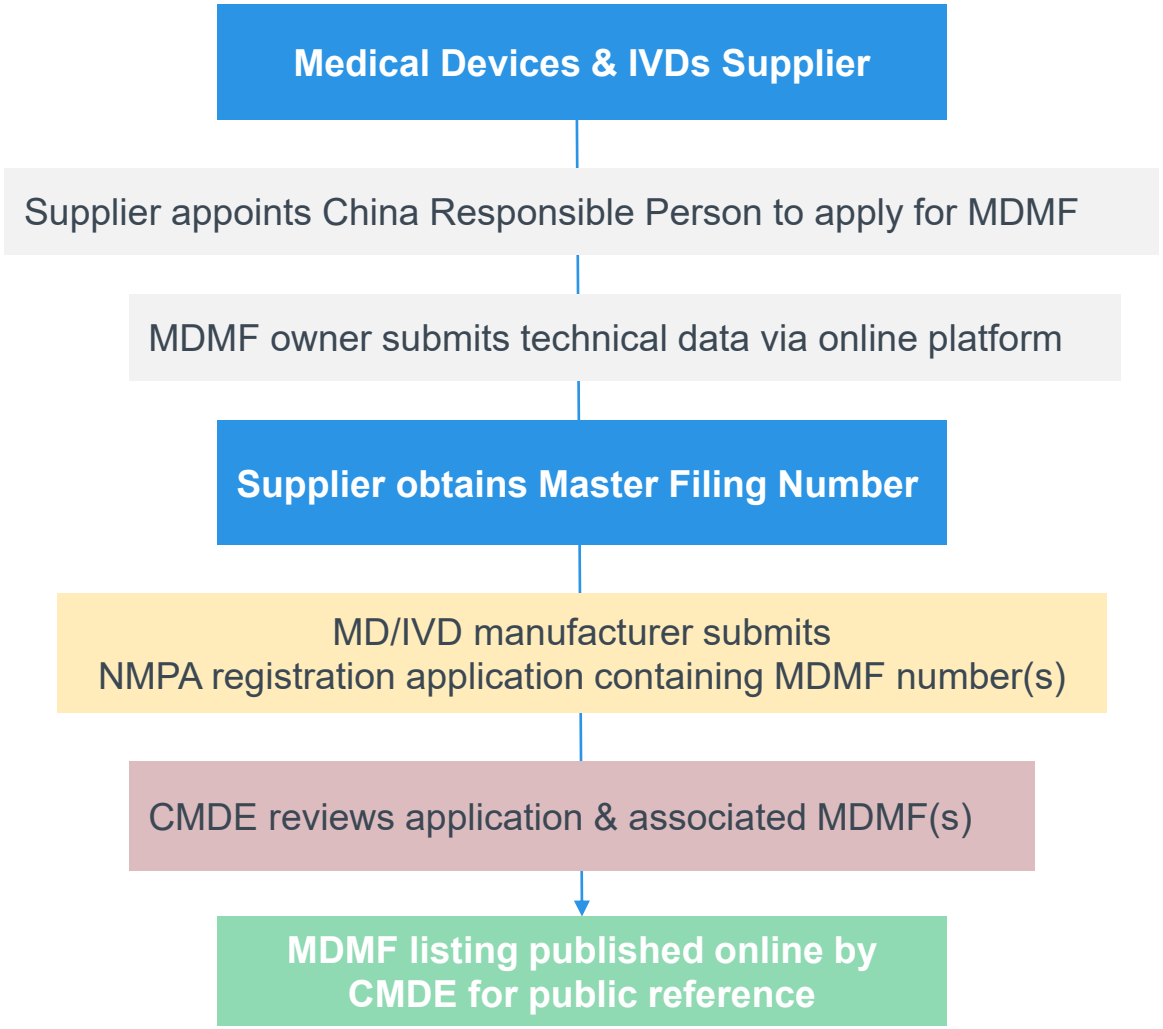
NMPA Announcement No. 36-2021: MDMF

- Relevant for **all** suppliers to medical device & IVD manufacturers, incl but not limited to:
  - raw materials, packaging materials, components, etc.
  - apply for MDMF at China's NMPA
- Voluntary (no obligation)

Why?

- Protect production & raw material **confidential information** from being disclosed to any third parties during NMPA registration process of end products

MDMF Process



Maintaining Compliance in China

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China Audits and Quality Control

- Trend of factory audits in China driven by increasing regulatory requirements and supply chain strains over the last few years
- Return to physical factory inspections overseas
- Audit types:
  - ISO9001
  - ISO13485
  - GMP
  - NMPA/SAMR **overseas factory** inspections
  - IEC
  - IATF16949
  - VDA 6.3
  - APQP, FMEA, PPAP, SPC, MSA
  - Run & Rate
  - Formel Q
  - QRQC

Inspection Triggers

- Issues identified when **filing/registering products** or existing certificates cancelled due to issues found in documents
- Potential risks of QMS are found in the review of product registration or filing
- Failing sampling tests indicating that there is risk in the QMS
- **Adverse event** indicating that there is risk in the QMS and product safety
- Product recalls
- **Complaints** or other clues indicating the existence of illegal activities
- Major non-conformities by the audit of **overseas regulatory agencies**
- Required second on-site inspection to confirm rectification measures have been undertaken correctly
- Random inspections conducted by NMPA/SAMR to complete annual indicators.

How Cisema can help

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How can Cisema help?

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Pre-Registration

- Regulatory Pathway Strategy
- Feasibility Studies
- Clinical Trial Protocol Design
- CRO China Clinical Trials

Registration

- Legal Agent
- Filings
- Registrations
- Special Pathways
- Type Testing
- Labelling Support
- …

Post-Registration

- Post-Market Surveillance
- Advertisement Support
- Post-Market Clinical Followups & Observational Studies
- In-China audits
- Pharmacovigilance audits
- Overseas Factory Inspections
- GMP, QMS, SOP Adaptation
- Certificate Localization in China

China approvals are realistic & achievable

Thank you for your attention. Questions?
Please **contact us** for a copy of the **slides** or detailed **whitepapers**.

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Enabling Compliance in China

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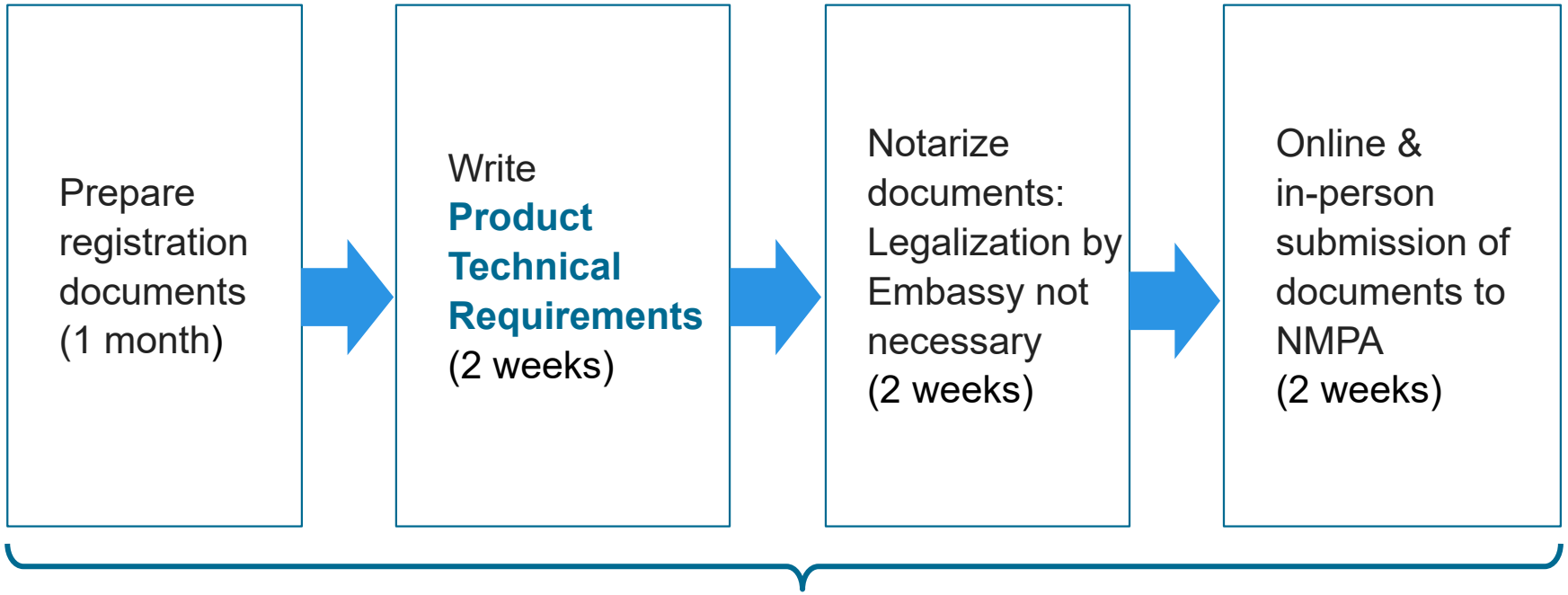
Class I Registration Process Overview



- The documents must be submitted in person to the NMPA counter.
- If they are complete and meet the formal requirements, the certificate for the filing with NMPA stamp will be issued immediately.

Hainan: Expediting Approvals

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Timeline for RWD pathway of Rezum®

Rezum® thermal ablation system for treating benign prostatic hyperplasia