What to know from Lessons learned and how to Drive Faster Market Access to China

AdvaMed Virtual Workshop, Dec 7, 2016

- Overview of CFDA regulations and device registrations
- What to know from Lessons learned
- How can we drive faster product market approval
- Basic Pre-requisite for entering into China market
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Retrospection of CFDA Regulation Development

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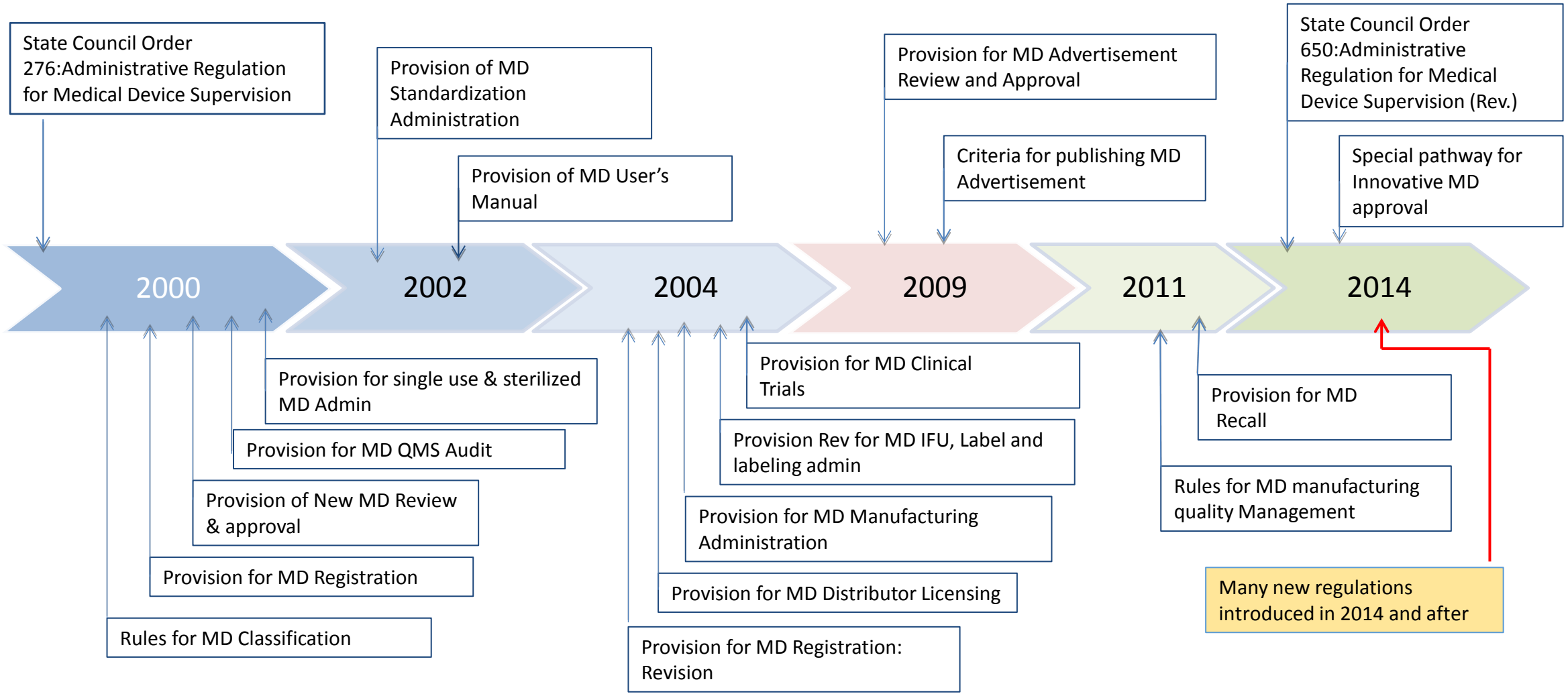
There were 3 waves of device regulations releases in past 20 years, and now the 3rd generation is being implemented



3rd Generation of device regulations, and Impact

BioHan Consulting

China Food and Drug Administration

Pre-Market

Post-Market

State Council: Regulation for MD Supervision and Administration, June 2014

- **Provision for AE Report and Recall, 2011**
- **Innovative product Registration, 2014**
- **Provision for MD Registration, 2014**
- **Product IFU, Labeling, 2014**
- **Manufacturing Quality, 2014**
- **Distribution/Sales, 2014**
- **Guidance for MD Clinical Evaluation, 2015**
- **Quality Administration of MD in Clinical Use, 2016**
- **Provision for Clinical Trials Quality Control (GCP), 2016**
- **MD Classification and Nomenclature Rules, 2016**
- **2nd Batch of MD Exempted from Clinical Trial, 2016**
- **Preferential Approval Process for Priority MD , 2016**

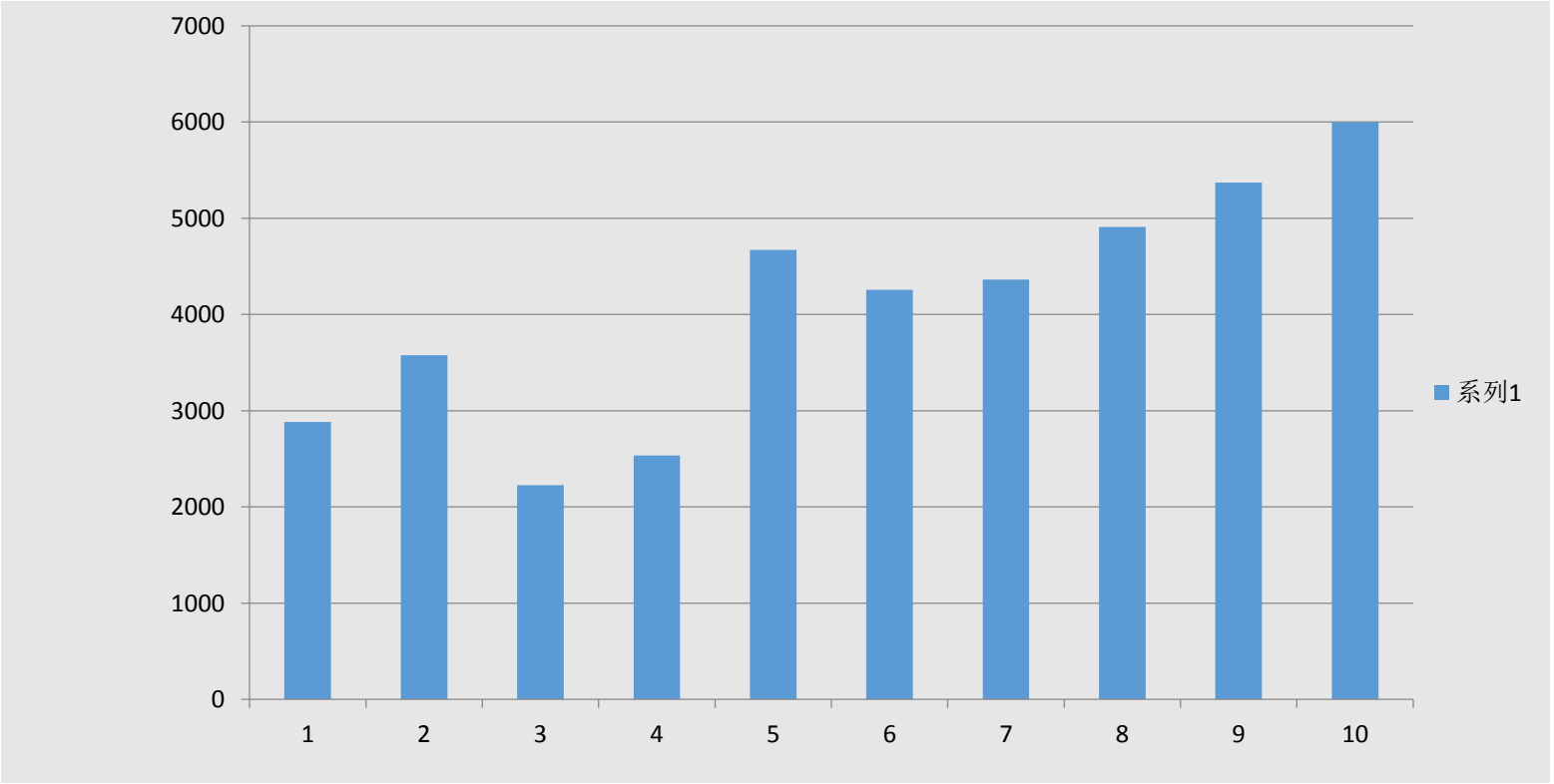
A whole set of regulatory system has been completed

- More strict control on high risk devices;
- Addressing clinical evaluations;
- Requiring clinical trial for imported device, the same as for domestic device;
- Introducing quality controls on device in clinical use;
- Preferential policies to devices with innovation & for unmet clinical need

Overview of CFDA Registrations (2004-2013)

CFDA Registrations increased steadily in that 10 years before CFDA regulatory reform in 2014, with exception in Year 06 & 07due to internal political fluctuation

	Year	No.
1	2004	2883
2	2005	3578
3	2006	2226
4	2007	2536
5	2008	4671
6	2009	4257
7	2010	4362
8	2011	4910
9	2012	5370
10	2013	5999

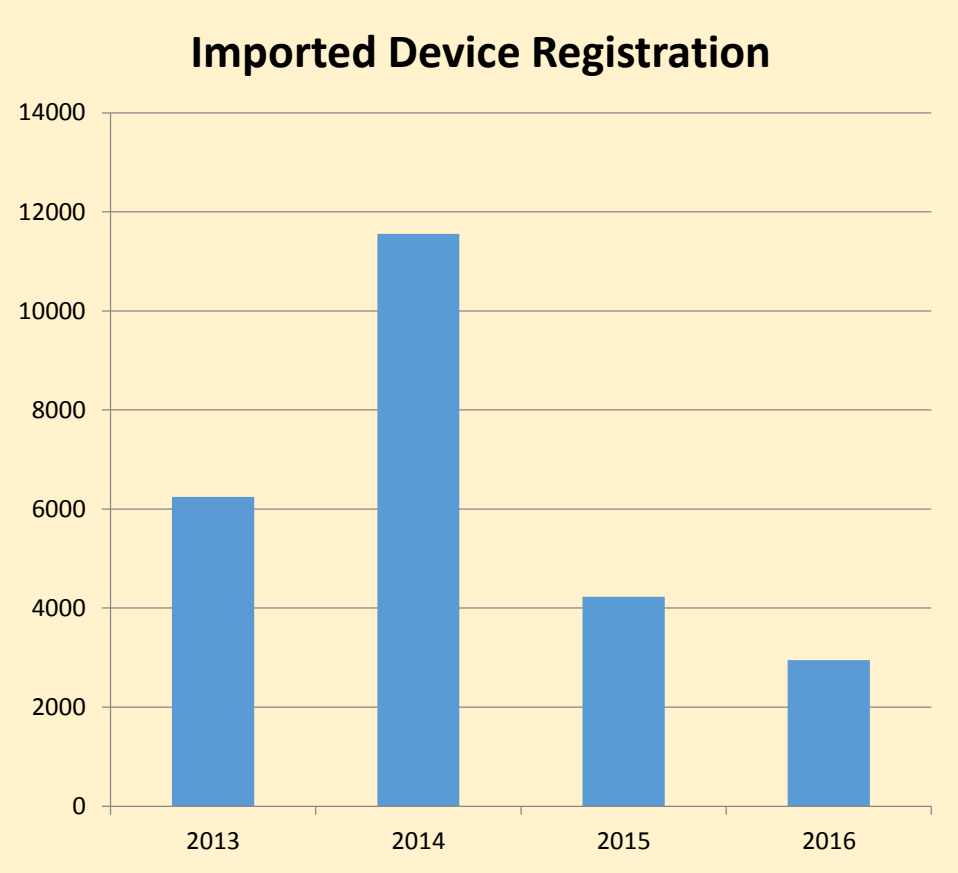


- The number of import registration increased very steadily in 10 years
- There was a drop in 2006-07, but rebounded in 2008/09, the reason is because of CFDA political leader's turmoil

Impact of New Regulations on Registration in Recent Years

Regulatory Reform caused obvious fluctuation of registration

Year	Imported	Domestic
2013	6242	20459
2014	11556	19584
2015	4230	12288
2016.9	2950	6169



- Significant increase of registration in 2014 before the new regulations introduced for enforcement in 2015;
- Sharp decrease in registration number in 2015 due to the complication of new requirements, clinical trials, delay, higher costs, also exclusion of class I;
- It seems to recover in 2016 and future as expansion of clinical trial exemption

Comparisons of Registration with Domestic Devices

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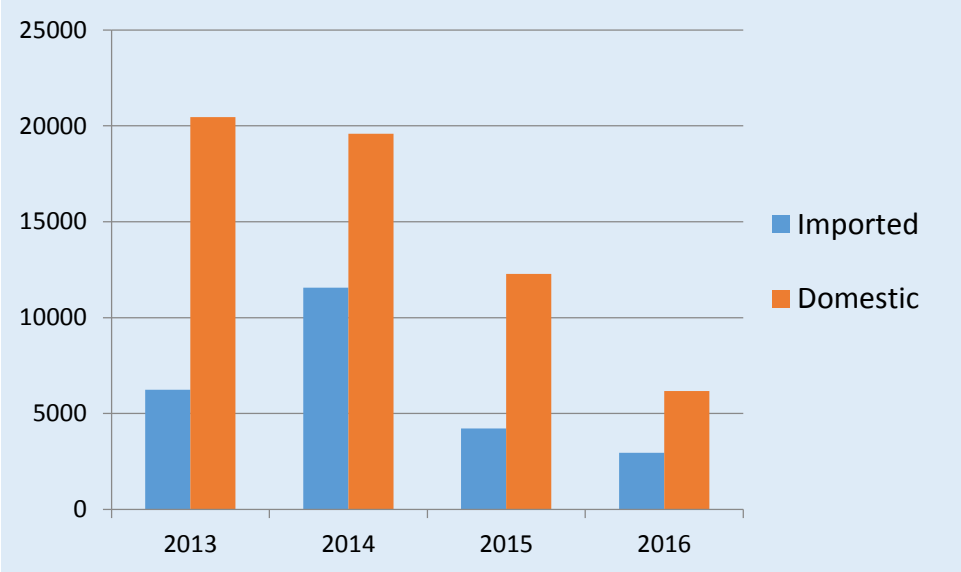
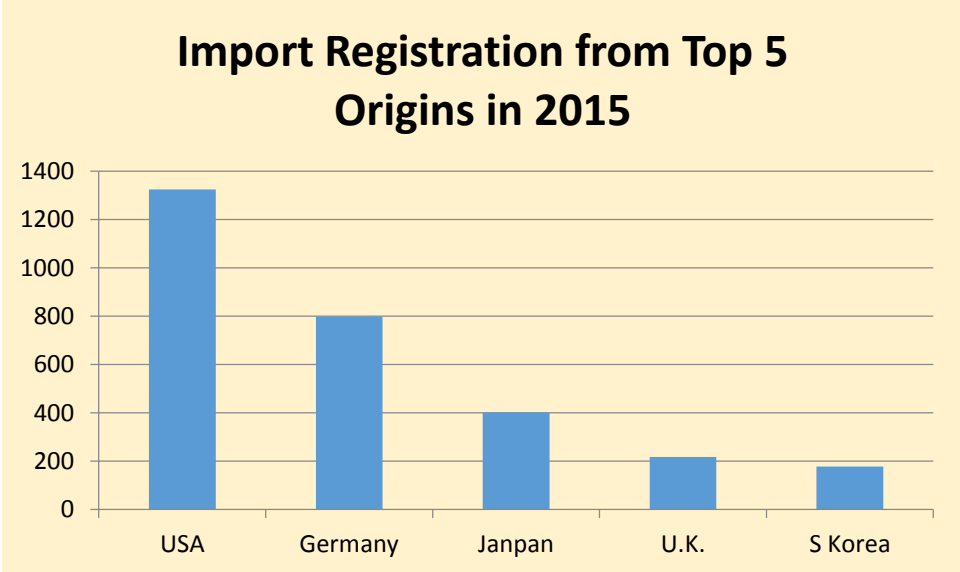
New regulatory requirements have impacted on both import and domestic device registration, but impact more on import device



- Different from imported registration, no increase of domestic device registration in 2014 because almost no impact from the new regulation;
- Decrease in 2015 mainly because of complication from new regulatory requirements;
- Impact of the new regulations is significant for both imported and domestic, but more on import



- 31% of all import registration from USA;
- 18% from Germany;
- 10% from Japan.

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Number of submissions that CFDA rejected

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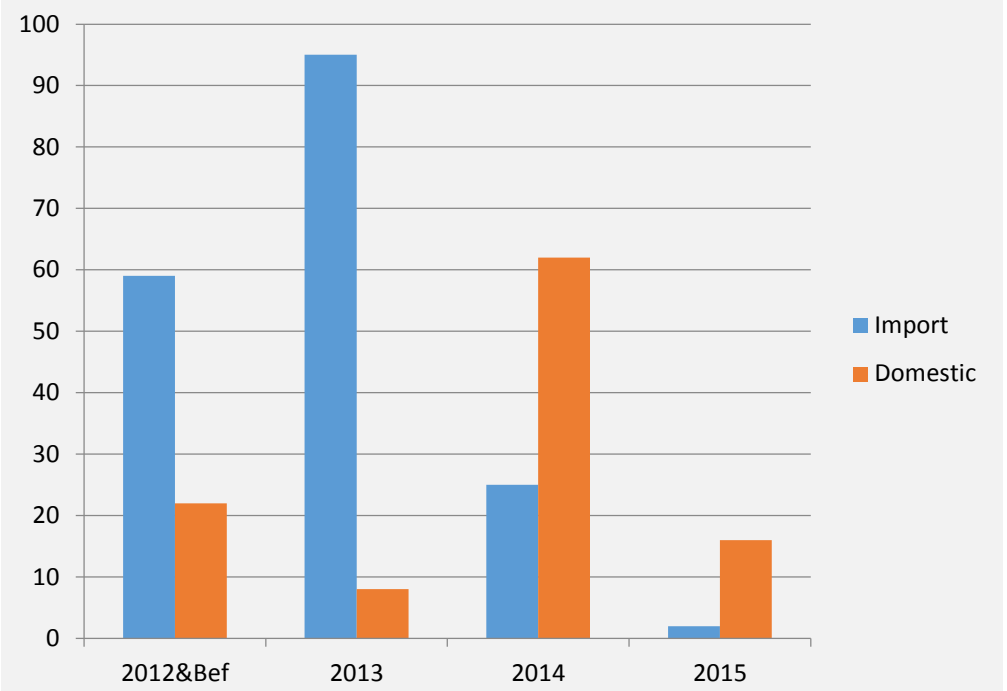
289 rejections in 2015



① Deadline for re-submission missed out

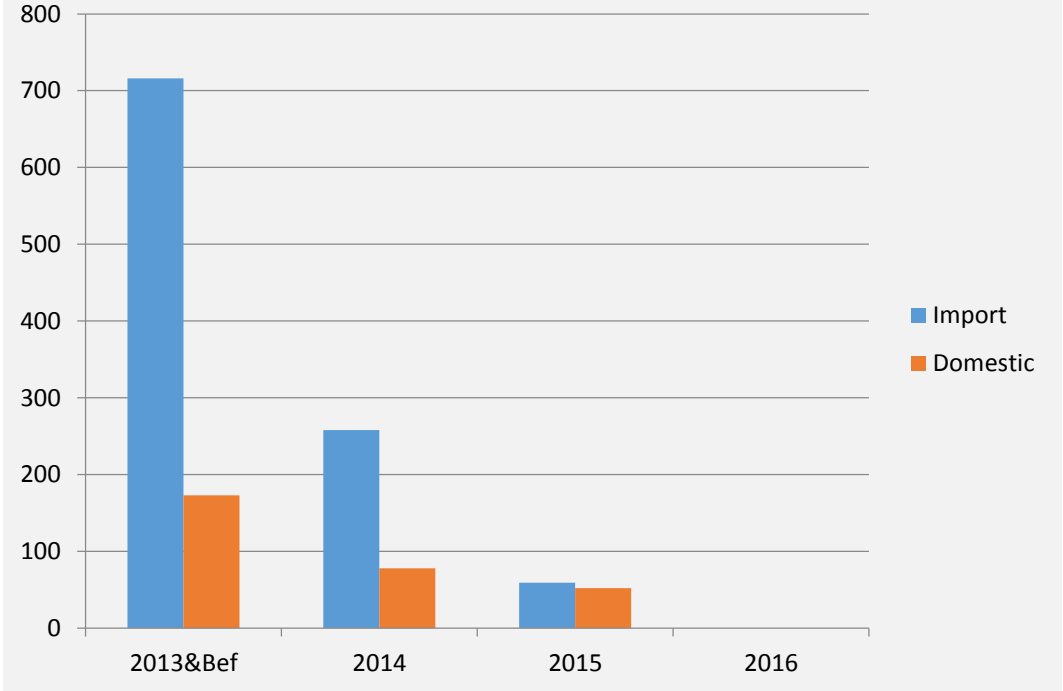
② Information e.g. certificate of a 3rd party tester, requested not provided;

③ Test information, e.g. biocompatibility, not provided;

④ Clinical evidence not fulfilled;

⑤ Additional test, e.g. EMC requested not completed;

1342 rejections in 2016



① Clinical evidence not sufficient or not meet the new GCP ;

② Information e.g. certificate of a 3rd party tester requested not provided;

③ Test information, e.g. biocompatibility, not provided;

④ Additional test, e.g. EMC requested not completed;

⑤ Deadline for re-submission missed out

⑥ Applicant given up, not to pursue, too costly, wait for new list of exempt

What to learn from lessons learned

BioHan Consulting

Case #	Scenario	Root Cause	What to learn
Company A	Contracted with a local distributor A1 for submission and sales, A1 has good sales network, but had an office administrator to work on RA. It took almost 5 years but was still pending because device failed to meet a mandatory standard. Finally the A used very experienced senior consultant to work out with a solution, but time for market was very much delayed.	A1 has no expertise in RA and no good access to key CFDA officials, could never figure out a solution	Do not rely on distributor for product registration
Company B	Contracted for many years with an only local distributor B1 for submission and sales, but recently found B1 has developed its own device, which is similar to B, then becoming the competitor. And the submission for product license renewal in 2013 by B1 for B was rejected by CFDA in 2015 due to missing CFDA deadline for additional request. Now B needs to re-submit as initial according to new regulations which is more difficult and costly.	B1 has no RA expert, did not make full efforts to get the renewal, or had no ability to work it out.	Do not use sole distributor who could be potential competitor to work for registration
Company C	Contracted for many years with an only local distributor C1 for submission and sales, C1 got the product license at beginning. But C recently learned that one only distributor can never increase market share of sales, wanted to add more local dealers to expand. C wanted to get license renewal recently, but could not do so as C1 did not agree to give to C the early license, which must be returned to CFDA for license renewal.	C1 wanted to be sole distributor, and did not agree to return the product license it helped and held in hand.	Use an independent consultant to work on product registration

What to learn from lessons learned

BioHan Consulting

Case #	Scenario	Root Cause	What to learn
Company D	Contracted with a certain scaled regulatory service company D1 to work for its product registration. It took 3 years but no good progress. This was partially because that CFDA has increased requirement and level of hardness. D1 has got a lots of clients with cheaper price and hire many new staff from graduates. Since D1 has a big client base and cheap staff, it can still make good profit. But recently D1 reluctant to work continuously on the submission already made due to the increased difficulties that junior staff could not handle under the price contracted.	Service price contracted could no longer cover the working requirement increased. Junior staff was supposed to do secretary job only, not as an expert.	Do not use service provider which is too cheap and staff on project has little experience.
Company E	Contracted with an international CRO to do clinical trial for device registration. The CRO has rich experience with drug clinical trials and used drug quality standard to run the study with drug level (million $ high) price, but failed to pass CFDA device technical review.	The CRO has weak relation with CFDA device groups and did not catch up the new , device special requirements	Good access to communication with device groups can lead to a better fitting protocol with lower price.

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How to deal with the new regulations for faster pre-market approval

When one door shuts, another opens:

1. Special Process of approval for Innovative Medical Devices;
2. Preferential Approval for Priority Device;
3. Shifting manufacturing of imported device to China;
4. High competency of an RA team and CRO.

1. Special Process for Innovative Medical Device Review and Approval

The manufacturer/applicant that meets all of the following conditions can apply for eligibility of enjoying special approval process:

(1) The applicant,

a) through technological innovations which it leads, holds by law in China, **indigenous intellectual properties of core technologies** of the product, or

b) through the transferring in accordance with the Chinese law to **obtain patents for inventions** or their right to use in China, or

c) the application to the authorities of intellectual properties (Inventive Patent) of China for the ownership or right of the patent for invention has been **published (announced)** by the patent authorities of China.

(2) The main working principle/function mechanism of the product must be that it is **original (the newest and leading) within the country (China).** The product properties or safety must have **fundamental improvement** compared with similar products. The technology must be **internationally advanced**, with significant **clinical application values.**

(3) The applicant must have finished preliminary studies of the product, and **produced basically finalized product** (prototype). The research process is real and controllable, and the research data is complete and traceable.

CFDA Special Process for Innovative Product

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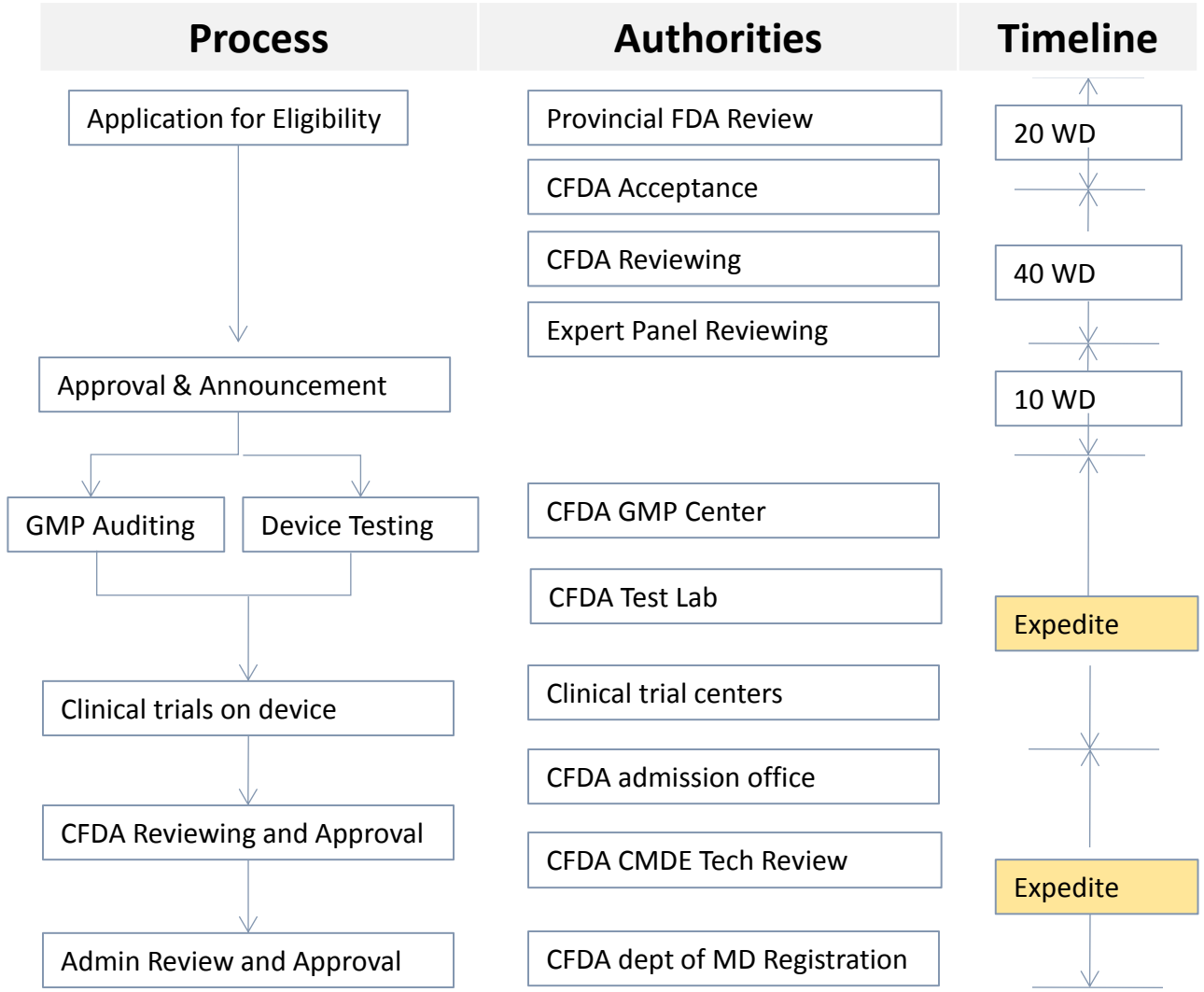


- CFDA earlier involvement
- Designated reviewer
- Instruction for RA & Tech requirements
- Faster processing without waiting time

2. Preferential Review and Approval Process

① Diagnosis or treatment **of rare diseases**, and has obvious clinical advantages;

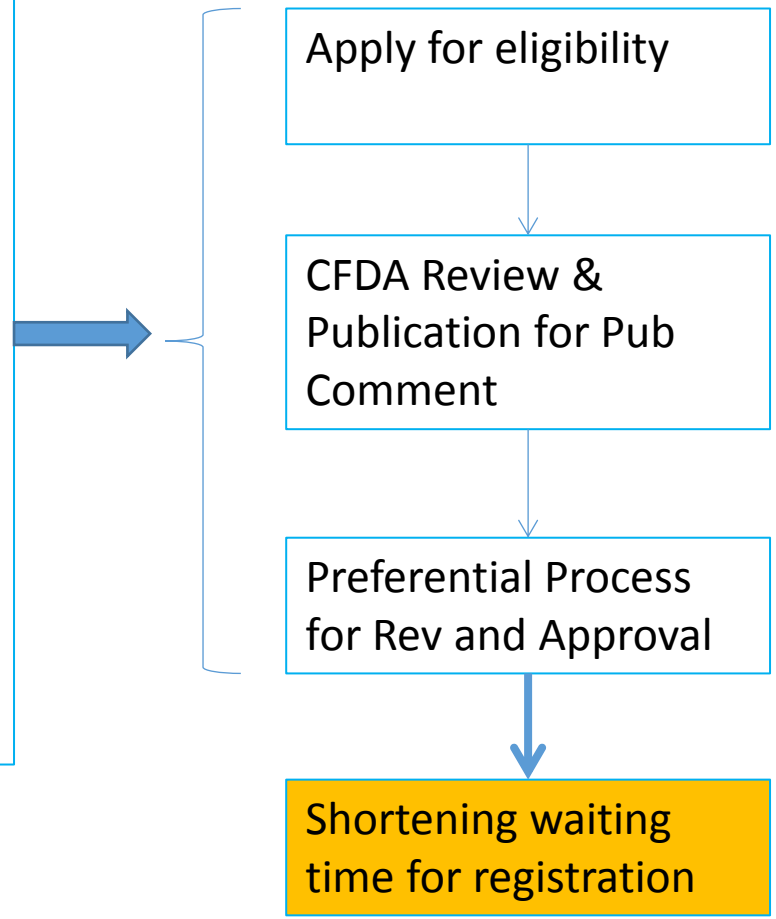
② Diagnosis or treatment of **malignant tumors**, and has obvious clinical advantages;

③ Diagnosis or treatment of **elderly-specific and multiple diseases**, and no effective diagnosis or treatment available;

④ Dedicated to **children**, and has obvious clinical advantages;

⑤ Clinical **urgently needed**, and in China there is no same species of products approved for market.

⑥ Others that CFDA considers as priorities



3. Shifting manufacture of previous registered import device to China can get approval faster

BioHan Consulting

Aspects	Imported Product, e.g.	Developed in China, e. g.	Assembled/manufactured in China for already registered import device
Requirements in general	Almost the same, but QMS audit only if necessary	Quality system audit;	Same as developed in China
Time to market (if no clinical trials required)	18 +/-3 months: -wait for US FDA approval before submission; - need to test unit imported	15 +/-3 month: - can start earlier; - no need to wait for pre-approval from country of origin	Same as developed in China
Time to market (if Clinical trials required)	30 +/-3 month (12 month for clinical trials)	27 +/-3 months (12 months for clinical trials)	No need for clinical trial in China, but evaluation on existing data
Benefit from special approval of Innovative Device if eligible	Some benefit: - Need waiting for pre-approval from COO; - Need IP registration in China;	More benefit: - Earlier entering into CFDA review process from development.	Same as left
Establishment of manufacture	No need in China	Manufacturing license: - Wholly Foreign owned - Joint Venture	Manufacturing license: -Wholly Foreign owned - Joint Venture
Cost for registration	Translation fee; CFDA user fee doubled vs local	Less user fee	Less user fee

4. High Competency of an RA team or CRO

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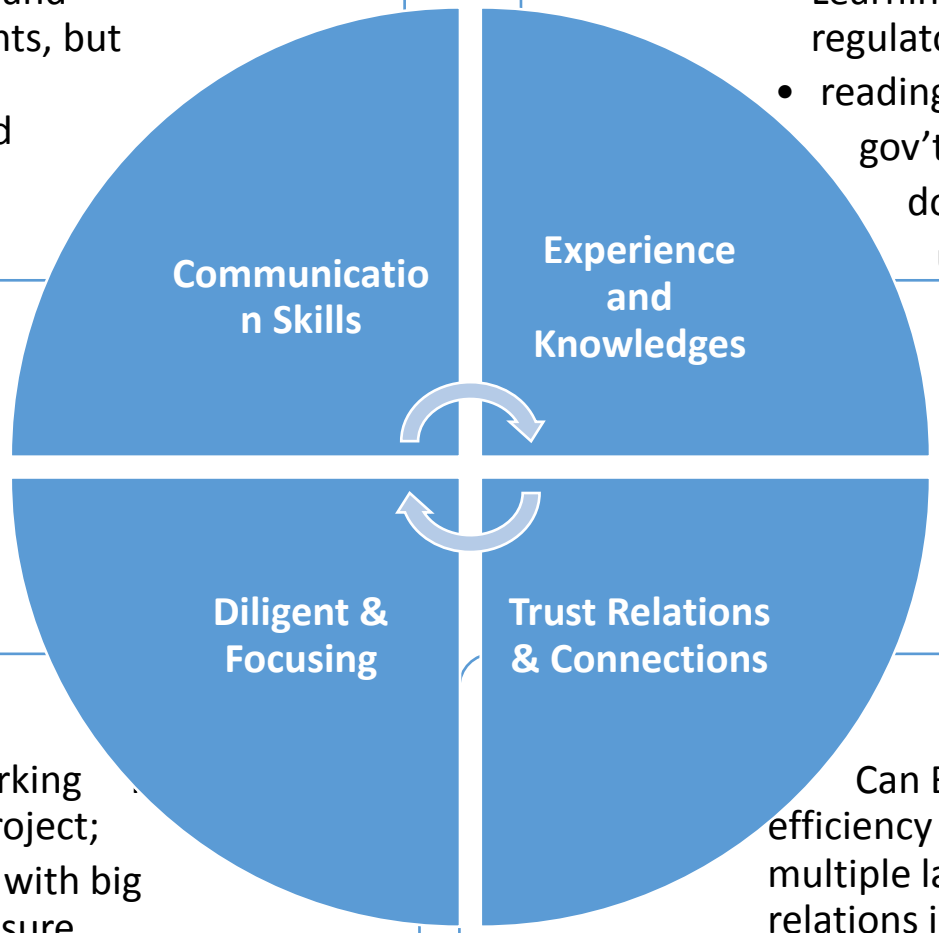
- Not just receive and deliver documents, but exchange ideas, perspectives and proposal



- Learning product and regulatory requirement,
- reading through gov't documents does not mean full understanding

- A must when working RA and clinical project;
- Work intensively with big amount and pressure

Can Build work efficiency when with multiple layers of trust relations internally and externally

Any one of these competencies does make difference to got faster pre-market approval

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Pre-Requisite: Requirement and Roles

BioHan Consulting

A foreign manufacturer must have pre-requisites and roles by itself or some one it assigns

	Who & What	Requirement	Roles	Remark
1	Agent to submit for CFDA registration	Legal entity registered in China	Submitting on behalf for product registration	The roles and responsibility can be taken cared by one or more legal entities in China as long as the qualification is satisfied.
2	Medical Devices product	• Approved in COO* such as US FDA 510K or PMA • CFDA Registration	As a pre-requisite For safety and efficacy	
3	Importer or China Branch	Import license	Importing product to China	
4	Dealer/distributor	Medical Device Distribution License	Selling product to users	
5	Agent for post-market regulatory compliance	Legal entity registered in China	Taking legal or regulatory responsibility jointly for product sold	

Note* COO: Country of Origin may be the country where the legal manufacturer or physical production factory is located

Comparison of Pre-Requisite with a manufacturer in China

BioHan Consulting

Domestic manufacturer needs neither to get market approval by a foreign country, and nor an importer for importation. But the same mandatory requirements in other aspects, in particularly CFDA registration for product

	Who & What	Foreign	Domestic	
1	Agent for pre-market approval	Legal entity in China	Yes	The roles and responsibility can be taken cared by one or more legal entities in China as long as the qualification is satisfied.
2	Medical Devices product	• Approved in COO such as US FDA 510K or PMA • CFDA Registered	No need to have market approved already by the Country Of Origin	
3	Importer or China Branch	Import license	No need to have an importer	
4	Dealer/distributor	Medical Device Distribution License	Yes	
5	Agent for post-market regulatory compliance	Legal entity in China	Yes	

A few advices in general

To work with good business partner(s) in China is the key for success.

1) Good agent for regulatory affairs including product registration & post market compliance

- Industry working experience, knowledge in product and manufacturing operation;
- Good internal and external communication skills and efficiency;
- Good trust relations & networking with authorities;
- Intelligent and diligent;

Consider to build an RA team when the business in China becomes large enough, but team may not be stable because of shortage of RA professionals in China

2) Good distributor(s) is critical for business success

- Use multiple distributors for different locations, even if you have own sales team in China;
- Setting up branch office in China when business is expanded large enough;
- Exploring a long term strategy to establish manufacturing or JV in China.

Thanks for Listening !
Welcome any questions or emails

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