China Pharmaceutical Regulatory Updates

Pacific Bridge Medical

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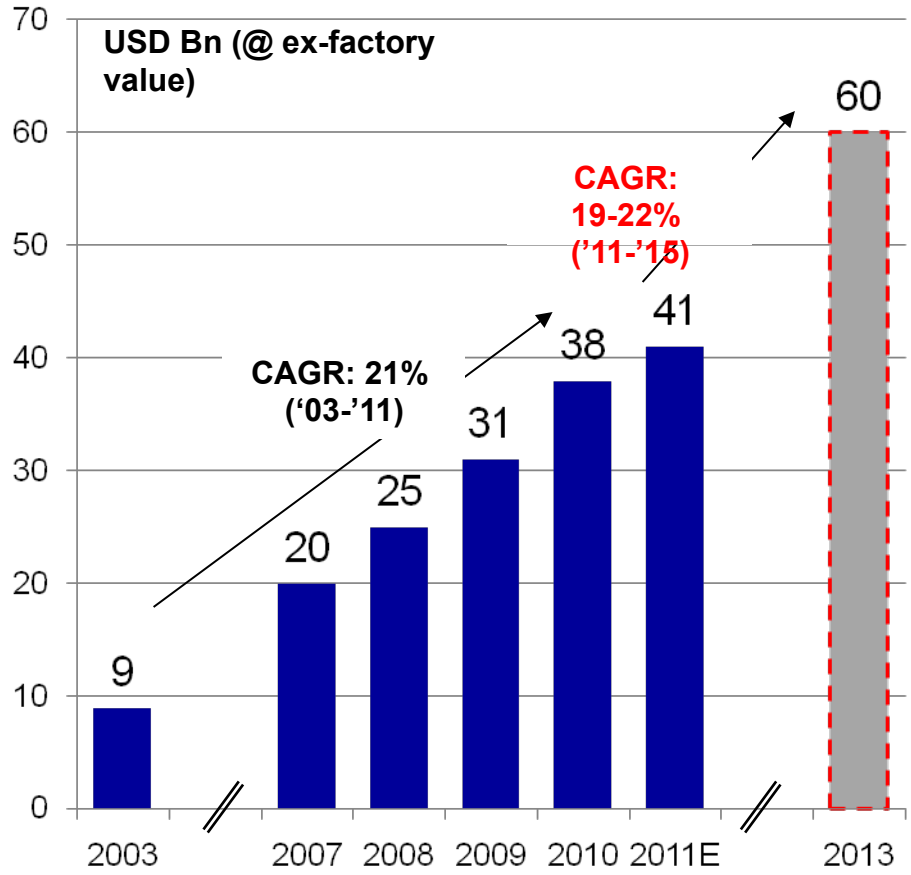
Agenda

- Pharmaceutical Operating Environment
  - Market Overview
  - Drug Approval
  - Pricing and Reimbursement
  - Tendering and Bidding
  - Hospital Listing

China has become the 3rd largest pharma market globally since 2010

China pharmaceutical market size



Source: IMS Health, MENET China

Top 4 pharmaceutical markets, 2011 (Estimated)

1. US	$310 billion
2. Japan	$102 billion
3. China	$41 billion
4. Germany	$40 billion

Note: IMS data tends to under-estimate China's market

The impetus for the growth is a timely combination of macro-environmental and industry-driven factors

Macro trends shaping China's healthcare space

Rapid economic growth (GDP, disposable income, urbanization)

Aging population and increasing prevalence in chronic and "western" style diseases

Healthcare delivery system expansion and HC reform

Sustained growth over 20% CAGR since early 2000s

Pharma industry structural changes globally and at home

New World Orders with emphasis on pharmerging markets*

MNCs** stepping up investment and best practice in China in full value chain

Local players moving 'up' the value chain & attempting "innovative" categories

: Pharmerging markets – Brazil, China, India, S. Korea, Mexico, Russia, Turkey

**: MNC - multi-national company*

Navigating the market in China is no easy task, as the value chain involves a complex set of stakeholders

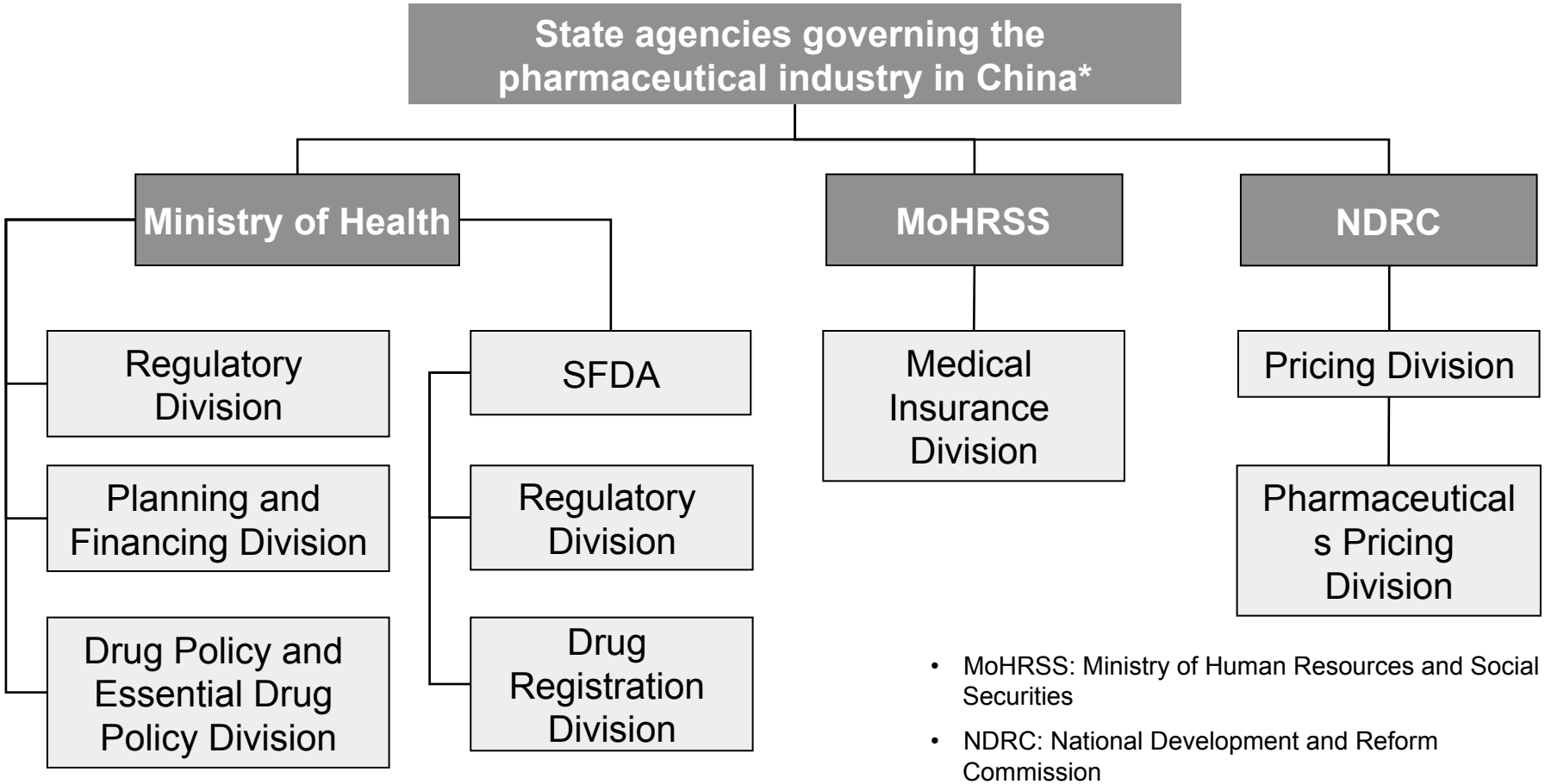
Illustration of the business of Rx commercialization in China

Key constituents -

- Drug manufacturers
- Distributors
- Central government: various agencies
- Provincial governments: various agencies
- Hospitals: various classes and levels
- KOLs and physicians

*: RDL – Reimbursed Drug List

Multiple government agencies are responsible for policy-making and for monitoring the industry



- MoHRSS: Ministry of Human Resources and Social Securities
- NDRC: National Development and Reform Commission
- SFDA: State Food and Drug Administration

∗ This org structure is replicated at provincial level

Various agencies and their responsibilities

	MOH (Central) & Provincial Health Bureaus	SFDA	NDRC	MOHRSS (Central & Provincial)
Drug registration	◔	●		
GMP monitoring		●		
Pricing & price review	◔		●	●
Reimbursement / RDL	◔	◔	◔	●
Essential drug list	●		◔	
Tendering	●			
Clinical trial		●		
Post-market surveillance		●		

Level of Influence

Low ○ → ● High

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A series of provisions and guidelines regulate drug development and approval in China

Scope of Regulations

- Approval for conducting clinical trials (IND)
- Approval for new drug manufacturing
- Approval for marketing license (NDA)
- Registration supplements
- Renewal of license

Types of Drugs

- New drugs
- Generic drugs
- Imported drugs

New drug classifications – chemical drugs are classified into 6 broad Classes

Traditional Chinese Medicines and Botanical Drugs

- 11 classes

Chemical Drugs

1. Molecule has not been approved anywhere globally
2. New route of delivery which has not been approved anywhere globally
3. Molecule has been approved overseas but not in China yet
4. New salts of an approved molecule
5. New dosage forms of an approved molecule
6. Generics

Biologics

- 15 classes

- Also sub-classes within each broad class
- Since 2010, Class 6 has been separated out and subject to independent review and approval process under Generic Drugs

Generic drug applications

- Generic applications can be used for drugs that already have National Standards in China or are listed in the Chinese Pharmacopoeia
- Class 6 of chemical drugs, Class 15 of preventative biological products, Class 15 of therapeutic biological drugs, and Class 9 of traditional Chinese medicine and natural drugs fall into this category

Imported drug applications

- All drugs manufactured outside China must be registered via the imported drug application, even if they are new drugs.

Registration supplements

- For changes to already-approved drugs
- Total of 33 kinds of supplements
  - 17 of these require the SFDA's approval
  - 10 situations require approval from the provincial drug authority (PDA), or alternatively can just be filed for record (without approval) with the SFDA
  - Final 6 situations can be filed for record with the PDA.

Application documents for New drug registration

- The SFDA has issued a detailed documentation list for chemical drugs, biological products, and traditional Chinese medicine
- The SFDA has issued technical guidance for some document sections
  - Adopted CTD format for submission since 2010
  - If the products are imported, the SFDA will also accept drugs prepared in accordance with ICH guidelines

Data requirements are itemized according to drug classification designated by SFDA

	Class 1		Class 2			Class 3		Class 4		Class 5			Class 6
(Sub-classes)													
Pharmaceutical Research Data (incl. CMC)													
Pharmacology and Toxicology Data													
Clinical Data (incl. size of trials)													

Illustrative

Chemical Drugs – required application documents

Summary Materials:

1. Drug name.
2. Certified Documents (Drug Manufacturing License, GMP Certificate, patent status, business licenses, etc.).
3. Drug discovery and current status of the drug, including R&D and summary of the use and production of the drug both domestically and overseas.
4. Summary and evaluation of main research results including a comprehensive analysis of the safety, efficacy, and quality controllability of the drug.
5. Product insert, drafting notes, and latest literature.
6. Package and label design.

Chemical Drugs – required application documents (2)

Pharmaceutical Research Materials:

7. Pharmaceutical research material summary (i.e. summary of experimental literature about the study, synthesis process, and dosage selection).
8. Manufacturing process.
9. Experimental data for confirming chemical structure and components (i.e., physical-chemical properties and purity validation).
10. Experimental data for quality validation.
11. Product specification and notes, including product reference standard.
12. Sample testing report.
13. Source, specification, and testing report for active ingredients and excipients.
14. Drug stability research data.
15. Specification of immediate packaging material and container.

Chemical drugs – required application documents (3)

Pharmacological and toxicological research materials:

16. Summary of pharmacology and toxicology research materials.
17. Primary pharmacodynamics research data.
18. General pharmacology research data.
19. Acute/single-dose toxicology research data.
20. Long-term toxicology research data.
21. Special safety research data and references on irritability (topical, systemic, phototoxicity), hemolysis and local irritation (blood vessels, skin, mucous membranes, muscle, etc.), and other special safety experiments as appropriate.
22. Research data on interactions of combination drug in terms of pharmacodynamics, toxicology, and pharmacokinetics.
23. Mutagenicity research data.
24. Reproductive toxicity research data.
25. Carcinogenicity research data.
26. Drug dependence research data.
27. Pre-clinical pharmacokinetics research data.

Chemical drugs – required application documents (4)

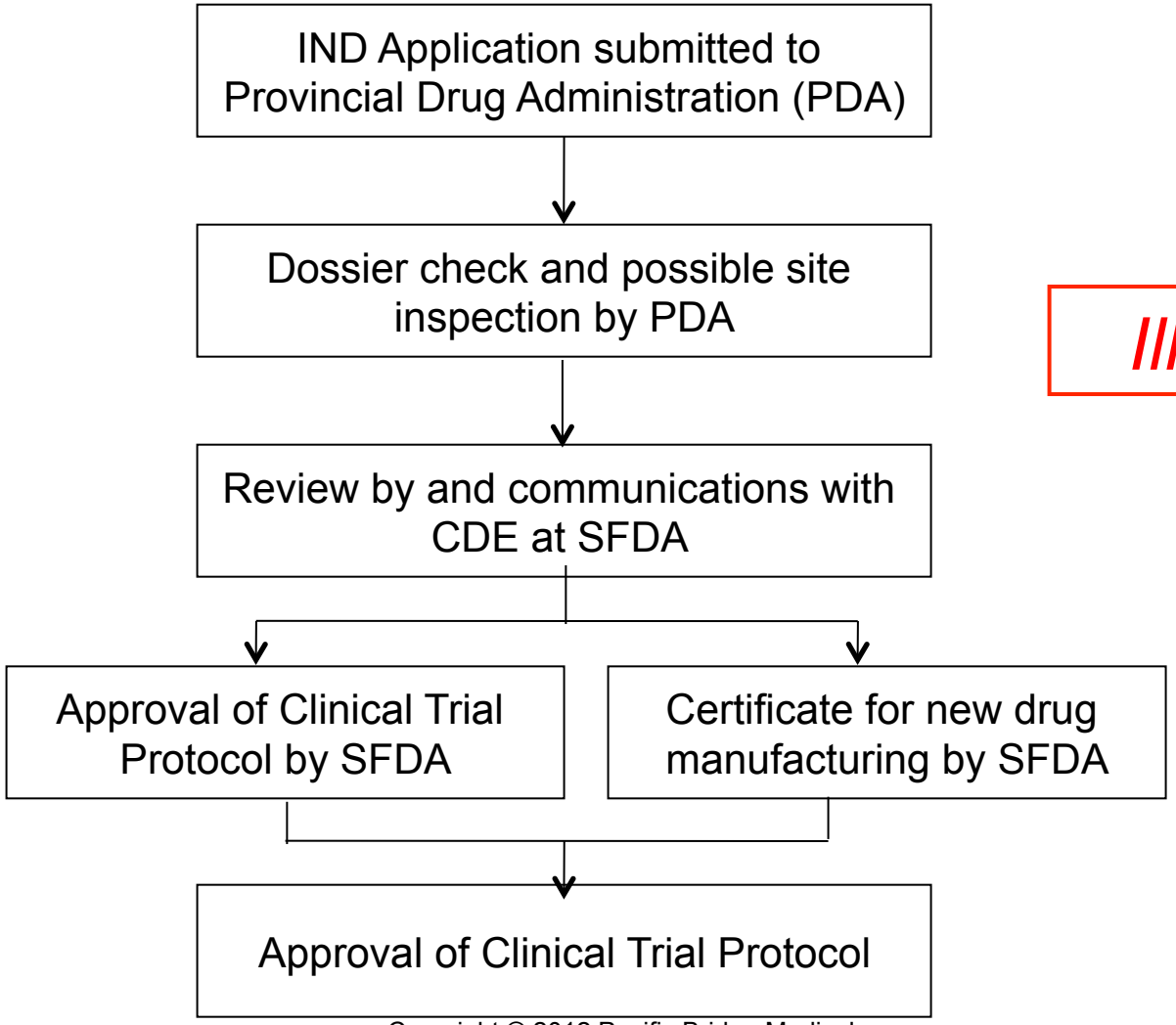
Clinical development materials:

28. Summary of global clinical development.
29. Clinical trial protocol to be conducted in China.
30. Investigator's Brochure for clinical trials to be conducted in China.
31. Draft of Informed Consent Form and Institutional Review Board (IRB) approval document.
32. Clinical development report.

Registration requirements - summary

- Companies should not encounter problems with different data requirements in China and foreign countries
- Chinese registration document requirements follow ICH guidelines, so requirements are fairly similar for China versus the United States and the European Union
- Problems arise when a drug company does not wish to submit sensitive, confidential data for drug registration in China
- Discuss the case informally with experts from the Center for Drug Evaluation to ascertain the minimum requirements for your therapeutic area.

Application and approval procedure for conducting clinical trials in China



Illustrative

Application and approval procedure for conducting clinical trials in China - summary

- IND review and approval takes 7-9 months
- IND approval and new drug manufacturing certificate are carried out in parallel
- For locally produced products, the application process begins at PDA level and approvals are issued by the SFDA
- For imported drugs,
  - It begins with SFDA
  - The standard review time is 3-4 weeks longer than local products
  - However, the actual time varies greatly, pending upon complexity and quality of data overseas

For an imported new drug, it takes approx 36– 42 months from IND submission to NDA approval

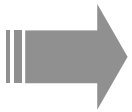
Step 1:

Application for conducting clinical trials (IND Application)

Takes 7 - 10 months (SFDA, NSCPBP)

Step 2:

Conducting clinical trials



Timeline pending upon the scale of clinical development, which in turn depends on the New Drug Classification (Applicant)

Step 3:

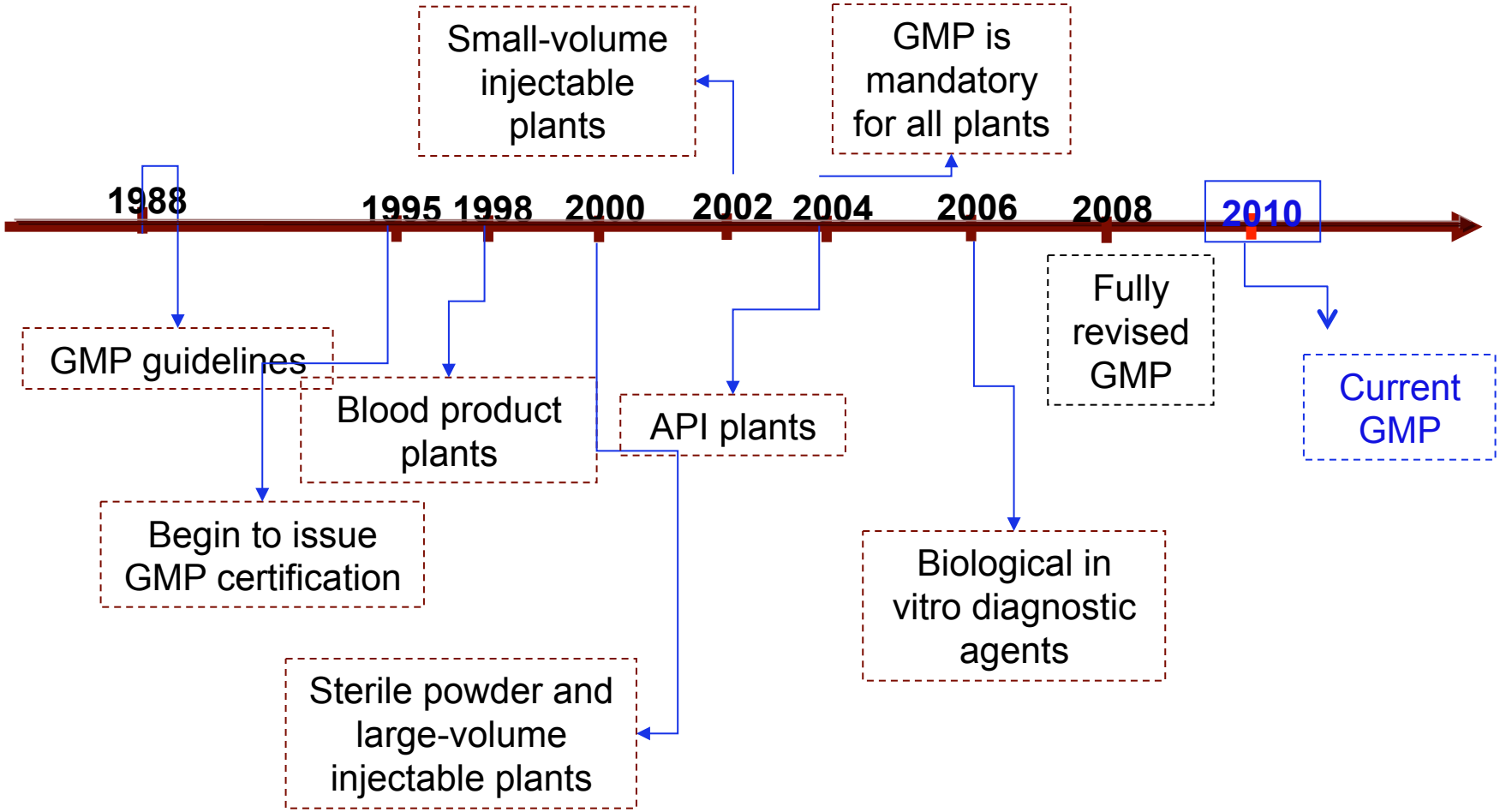
Application for imported drug registration(NDA Review & Approval)

Takes 7 - 15 months (SFDA; NSCPBP)

Expedited Approval is now possible in China, with eligibility criteria poorly defined

Regulatory Pathway	Drivers/Barriers
Special Registration Path (Green channel)	▪ The SFDA issued guidance for the Special Registration Path in 2009, which may apply to • Products have never been marketed anywhere in the world • New therapeutic advantages in AIDS, cancer or “rare diseases” • New drugs to treat diseases for which no effective therapies exist ▪ The Green Channel can reduce review time by a few months ▪ However, eligibility criteria are ill-defined thus far
Standard approval	

GMP: the modernization of drug manufacturing in China (1)



Source: Team analysis

GMP: the modernization of drug manufacturing in China (2)

- Relatively short history
- The number of manufacturers were reduced to around 4,500 in 2010 from 7,000+ in 2000
- The 2010 Version GMP began in March 2011
  - Adoption of ICH
  - All plants to obtain new GMP certification by end 2015
  - Local industry expected to spend billions of dollars
  - Significant number of plants will likely close
- Some local manufacturers have chosen to pass cGMP, aiming at the global market

Source: Team analysis

Drug development in China – IND approvals

IND Approvals in China

	2006	2007	2008	2009	2010
New molecules/ formulations (local)	N/A	N/A	N/A	288	141
Generics (local)	N/A	N/A	N/A	196	153
Imported drugs	N/A	N/A	N/A	320	308
Total	**1,426**	**758**	**581**	**804**	**602**

Anti-corruption reforms in 2006-2007 began to set more globalized standard

Sources: SFDA publications

Drug development in China – clinical trial sites

Sources: SFDA

Drug development in China - summary

- 433 clinical trial sites certified by the SFDA as of 2011
  - All affiliated with hospitals
- SFDA intends to cut IND review and approval timeline
- SFDA encourages more international multi-center clinical trials
- Exploring Regional collaboration: China, Japan, and S. Korea
- Adopted CTD format for submission since 2010
- 2010 GMP: all local players to obtain new certification by end 2015

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It takes up to 15 months for a brand to be prescribed after receiving SFDA's approval

Approval of Drug Price

4-5 months

- A drug must obtain its approved retail price before entering the bidding process
  - If the drug is on the NRDL, its price is set by NDRC
  - If the drug is not on NDRL, the manufacturer must get its retail price approved by provincial government s (The Pricing Bureau)
- Approx. 3 months to get price approval at the province where the company is registered
- Additional 1-2 months to get price at other provinces
  - The process needs to be carried out at each province individually

Provincial Bidding

3-5 months

- Each Province will select a few (2-5 suppliers) for each drug (molecule, dosage form, dose strength) – the bidding process
- The bidding schedule s(a few times a year) are set by provincial governments
- Whether or not the drug is or not on RDL, bidding process is a MUST before entering hospitals
- Manufacturers need to go through the bidding process province by province
- Each bidding process takes approx. 3 months

Hospital Listing

3-5 months

- Once a product wins bidding at a province, it will then need to obtain listing by hospitals
- Hospital Listing is the contract that a hospital has agreed to carry the product

Drug pricing in China is based on a combination of free-market and state- control mechanisms (1)

Essential Drug List – EDL

- Issued by MOH
- Mainly old generic drugs
- 100% reimbursed by the government
- Retail price set by NDRC

List A drugs – NRDL

- Issued by MoHRSS
- Mainly old generic drugs, over-laps with EDL
- 100% reimbursed by the government
- Retail price set by NDRC

List B* drugs – NRDL and PRDL

- MOHRSS proposes National RDL List B, consisting of innovative and premium-priced drugs
- Provinces may substitute 15% of List B to address local need
- Retail price set by NDRC and Provincial Pricing Bureau (PB)
- Patient's co-pay ranges 10%-90%

Drug pricing in China is based on a combination of free-market and state- control mechanisms (2)

Products not on NRDL

- Manufacturers can set their own retail prices within reasonable levels, as long the price can be approved by local Pricing Bureau
- For certain very expensive drugs, getting onto RDL might not be a profit-maximizing strategy

Imported drugs

- Price is calculated using a formula to arrive at a 'reasonable' retail price based on the CIF (cost-insurance-freight) price, which is registered with the pricing bureau of the first entry point of the product
- Imported drugs are eligible to be included in RDL

A 5-step price-setting process for RDL drugs by NDRC has been in place since March 2007

Step 1

- Regulators visit the manufacturer
- Evaluate the cost of the product's raw materials
- Propose a price

Step 2

- A new expert group on drug pricing will assess the proposed price

Step 3

- A public hearing to solicit public comments on the proposed price

Step 4

- Group discussions

Step 5

- Completion of the group examinations

- The revised system is intended to secure the integrity of the pricing process, with regulators selected at random and rotated on a five-year basis to minimize conflicts of interest
- NDRC might be given expanded responsibility in the future to control prices of all prescription drugs and not just those on the NRDL

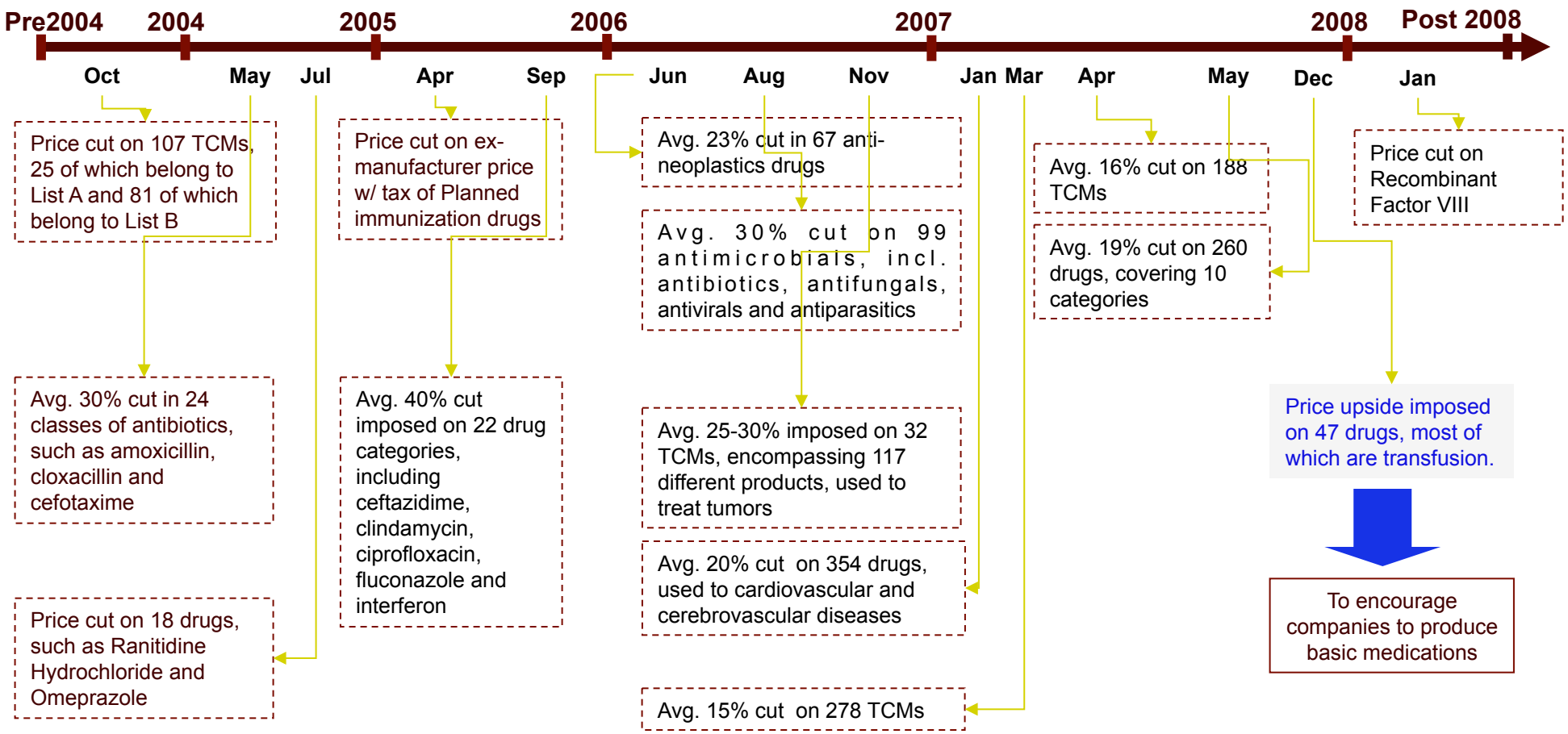
For non-RDL drugs, proposed retail price has to be approved by local Pricing Bureau

Materials required for pricing application - Shanghai example

- **Product general information** – generic name, brand name, dosage, specification, indication, estimated annual sales, patent information (if have), drug license, country of origin
- **Cost information** – CIF (cost, insurance and freight), exchange rate, tariff, VAT, port charges(drug test fee, administration fee, customs clearance fee, and other cots) , port price, retail price applied
- **Retail price in the country of origin and surrounding countries*** – country, brand, dosage, specification, retail price
- **Competitors (similar products) price in China** – brand, dosage, specification, retail price, place of production
- **Backup materials** (not officially required, but need to prepare if there are challenges) – efficacy, safety summary; product value dossier (health economic data)

*Surrounding countries usually include Hong Kong, Taiwan, Korea, Japan, Thailand and Singapore, etc. Asia countries

NDRC initiated several rounds of price adjustments, lowering the drug price about 20% since 2004 to 2009



Source: NDRC New Releases

NDRC implemented 2 price-cuts in 2011, which was very unusual

1st price-cut in 2011

- In late March
- 162 molecules and close to 1,300 dosage form specs
- Infectious, cardiovascular and circulatory diseases, antibiotics
- Approx. 20% cut on retail price

2nd price-cut in 2011

- In September
- 80 molecules
- Hormones, endocrine and nervous system disorders
- Approx. 14% cut on retail price

New pricing mechanism is under discussion aiming at control of all drugs with highly specified criteria

	Current Situation	Proposed Policy
Coverage of Price Control	• RDL drugs are under government's control	• Majority drugs controlled by central and local governments
Price Structure	• Only retail price is set. No clear control on the ratio of profit and cost of sales/marketing and financial expenses) • No clear regulation on imported drugs' markup	• Detailed provisions on price structure to control profit margin • A range of acceptable markups for imported drugs
Off-patent and generic drugs	• The price of an off-patent drug is set by its manufacturer • First generic does not have price advantage over followers	• 25% price cut required for innovative drugs after patent expiry • Generic price set according to order of entry (1st, 2nd, 3rd, and all afterwards)

Source: Team analysis

The development of the Reimbursed Drug List (RDL) is "top-down", without drug-makers' participation

National RDL

- Central government entities
  - MoHRSS*
  - NDRC**
  - Ministry of Finance

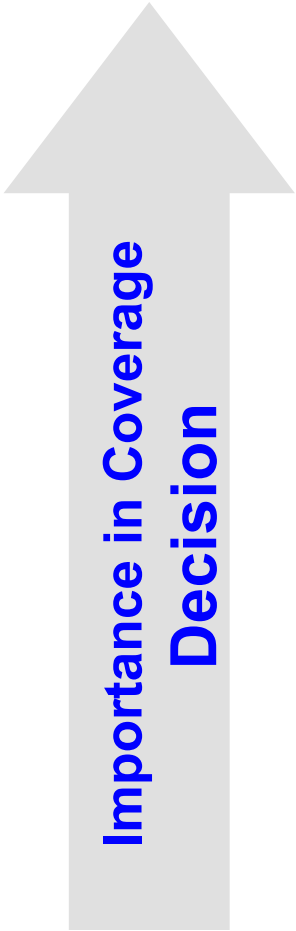
Provincial RDL

- Provincial government entities
  - Pricing Bureau
  - Provincial Bureau of HRSS
  - Provincial Finance Bureau

- National and provincial expert committees and advisory boards
  - Clinical KOL's
  - Pharmacy KOL's
  - Health economics KOL's
  - Pharmacology KOL's
- Experts are randomly selected to participate in reviews from established Expert Databases
  - As soon as selected, experts are grouped together and stay "quarantined"

Advocacy development with KOLs is crucial in moving products to RDL

RDL: clinical need is the stated main-driver, with cost-containment as another obvious goal



Clinic need/Utilization

Efficacy & Safety

Reasonably priced (compared to other drugs in same TA)

Average total cost

Years on the market

Cost effectiveness (Health-economics)

MoLSS updates the National RDL approx every 4 years

Step 1: Draft list

- Gov't officials (SFDA, MoLSS, NDRC & MOH) compile a list of RDL candidates
- Applications from drug makers are not necessary

Step 2: Advisory Board review

- The Advisory Board reviews the list of pre-selected drugs, to categorize and to confirm the rationale of the therapeutic classifications (clinical benefits, health-economics, etc.)

Step 3: Expert review

- KOLs in different therapeutic areas will be randomly selected to participate in the voting

Step 4: Final list

- The final list will be finalized and published by MOHRSS
- NDRC will then proceed to set prices for RDL drugs
- And Provincial BoLSSs will develop their own Provincial RDLs, with the ability to substitute up to 15%

Materials required for NRDL evaluation

- **Disease**
  - Epidemiology
  - Disease burden
- **Product**
  - General information
  - Efficacy
  - Safety
  - Guideline recommendation (if have)
  - Pharmacoeconomic data
  - Budget impact
- **Reimbursement status (historical)**
  - Domestic
  - International

- There is no official process to submit the application materials and the company need to submit the application materials to key reimbursement officials and 'experts' informally.

NRDL evaluation process

Illustrative

1 Qualification: deadline for NDA approval

2 Actions need focus on this step.

3 4 Closed-door and difficult to manage

1 Candidate drugs

- SFDA provides candidate drug profiles
- Retail prices and prices per treatment cycle are considered
- Prioritized candidates for evaluation are:
  - Drug launched after the last national reimbursement list release
  - Drugs regions adapted in their current reimbursement list
  - Other drugs recommended by evaluation experts

- Decide on level of usage and funding of reimbursed drugs according to insurance type, clinical guidelines, evidence-based analysis
- Explore mechanism of including more expensive drugs in the reimbursement list via negotiation

4

Leading group

Led by MoHRSS and cosist of representatives of relevant authorities (NDRC, MoH, SFDA, etc.)

2 Consultants ≈ 300

Pre-selection catalogue

3 Selection experts ≈ 2000

Physicians, pharmacists, health economists, pricing experts, …

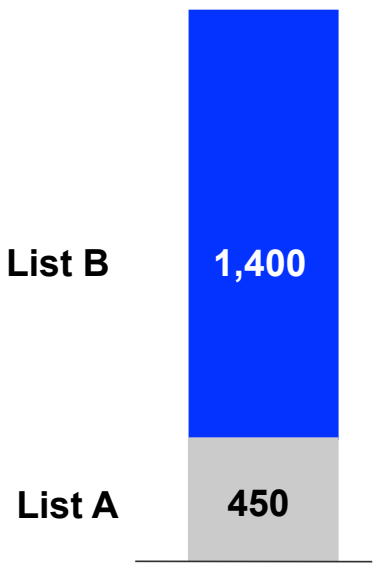
- Recommended by professional associates
- Provide consultancy in drug classification and data analysis
- Decide on evaluation criteria and recommend the pre-selection catalogue

- A pool of experts recommended by provincial reimbursement authority
- Selection group randomly drawn from the experts pool for each drug class
- Vote for drugs to be included

‘Consultants’ are very important for RDL listing

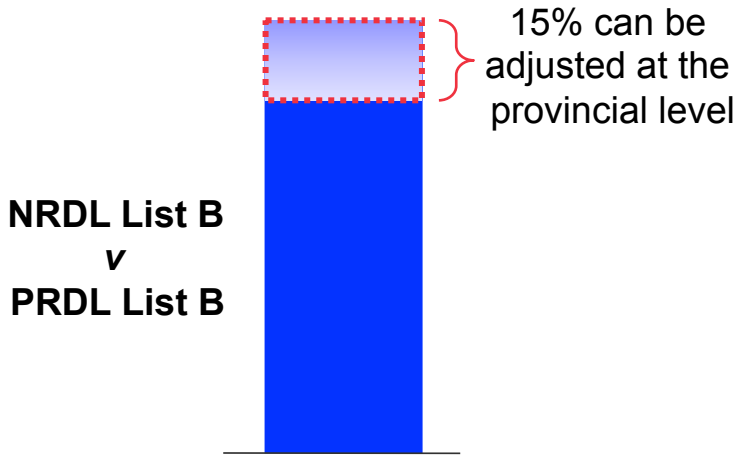
- ‘Consultants’ are served as advisors for NRDL evaluation and very important for the decision making, usually including:
  - top pharmacists
  - top KOLs in different disease areas
  - Health economists
  - Health insurance expert
  - Drug pricing expert;
- Key reimbursement officials from MOHRSS
- The lobby for support from ‘Consultants’ need to be planned and initiated at least one year before the start of NRDL renewal

The current NRDL was published in late 2009



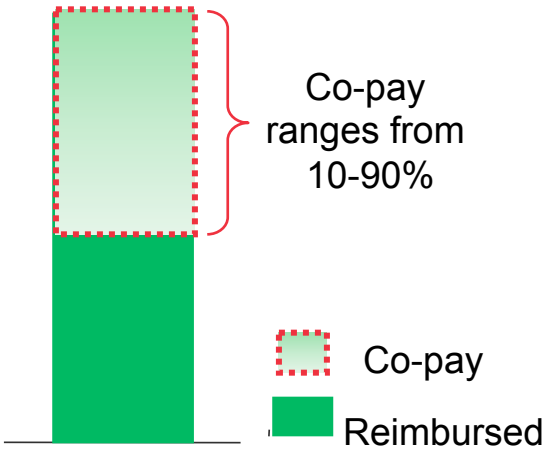
NRDL

- List A consists of mainly generic drugs, and are 100% reimbursed
- NRDL:
  - 2,127 drugs: 1,140 western drugs and 987 TCMs
  - In List A, 349 western products and 154TCMs
  - In List B, 791 western drugs and 833 TCMs



List B

- List B can be adjusted at the provincial level – up to 15%
  - To meet unique need in that Province
  - Usually applied to "high profile" drugs such as for highly prevalent diseases, oncology, and rare diseases



List B

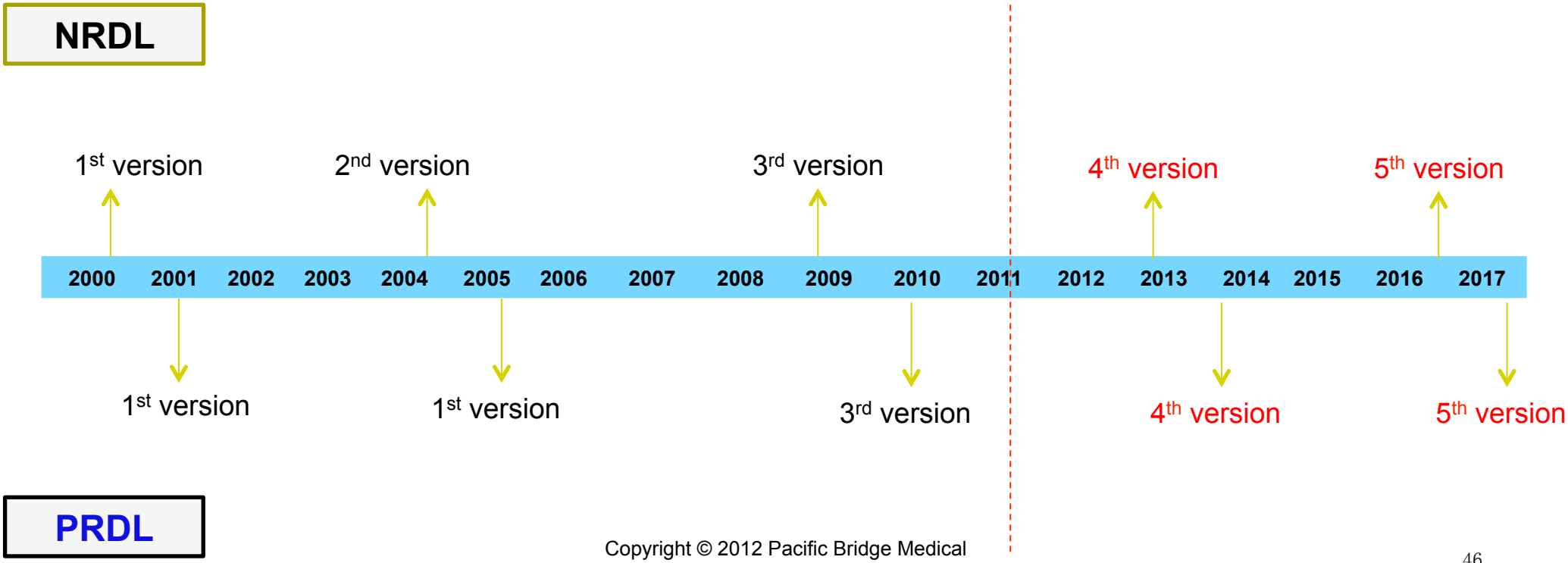
- Reimbursement rate (reimbursed v. co-pay) for drugs on List B is not 100%
  - Provinces also have the freedom to adjust reimbursement rates
- Putting some drugs on List B is a symbolic gesture, as the provincial governments can make the co-pay as high as 90% for some drugs

PRDL evaluation

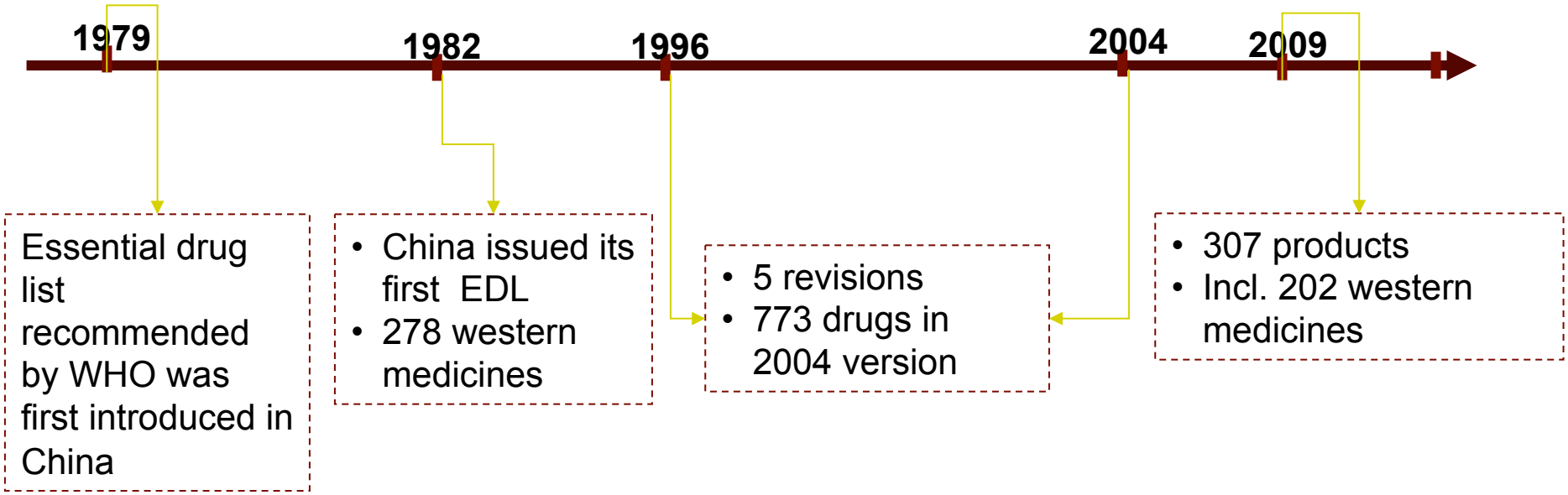
- If a product missed the NRDL, it may try PRDL List B.
  - Need to approach 31 provinces one by one
  - May have advantage with your host province
- Process and materials required are similar to NRDL; ‘consultants’ are mainly provincial top experts;
- Focus on the 15% adjustment of List B
  - e.g. 2009 NRDL list B has 791 western drugs, which means PRDL can adjust 119 drugs (adding or removing)

NRDL/PRDL renewal timeline

- Estimation based on historical experience
- The N/PRDL is estimated to be renewed every 4 years.
- NRDL is followed by PRDL, e.g. if a product launched in 2013 and missed the NRDL renewal, it may have chance for 2014 PRDL

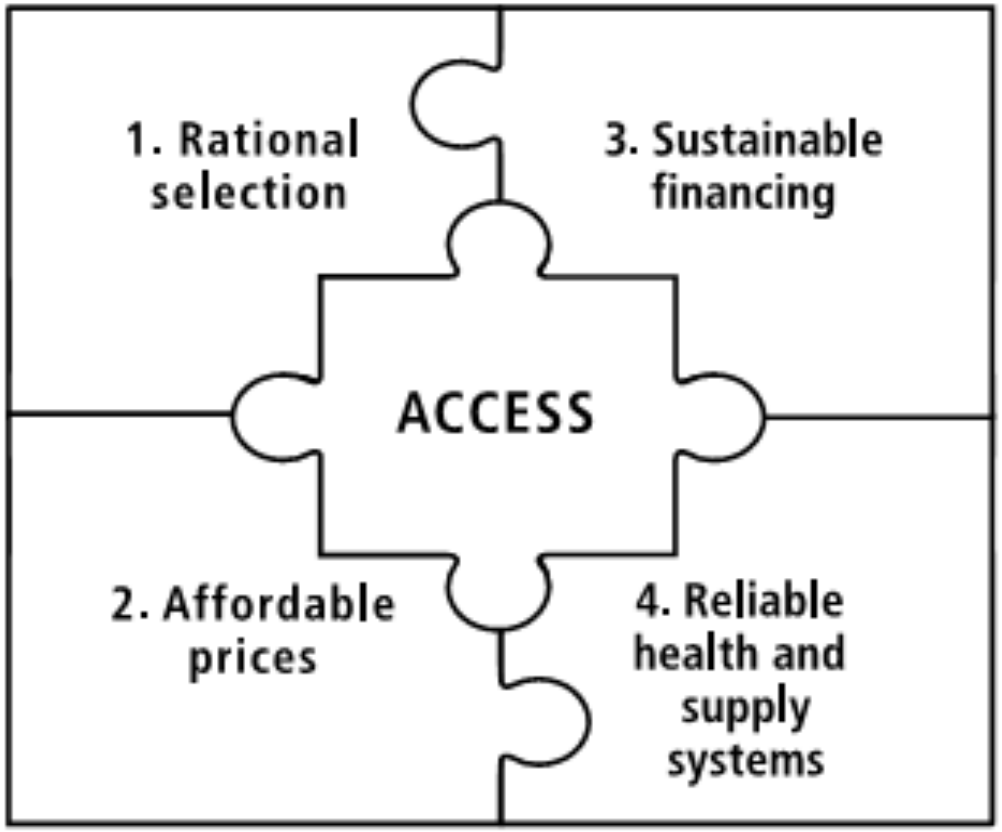


The Essential Drug List (EDL) is a key component under the new healthcare reform plan



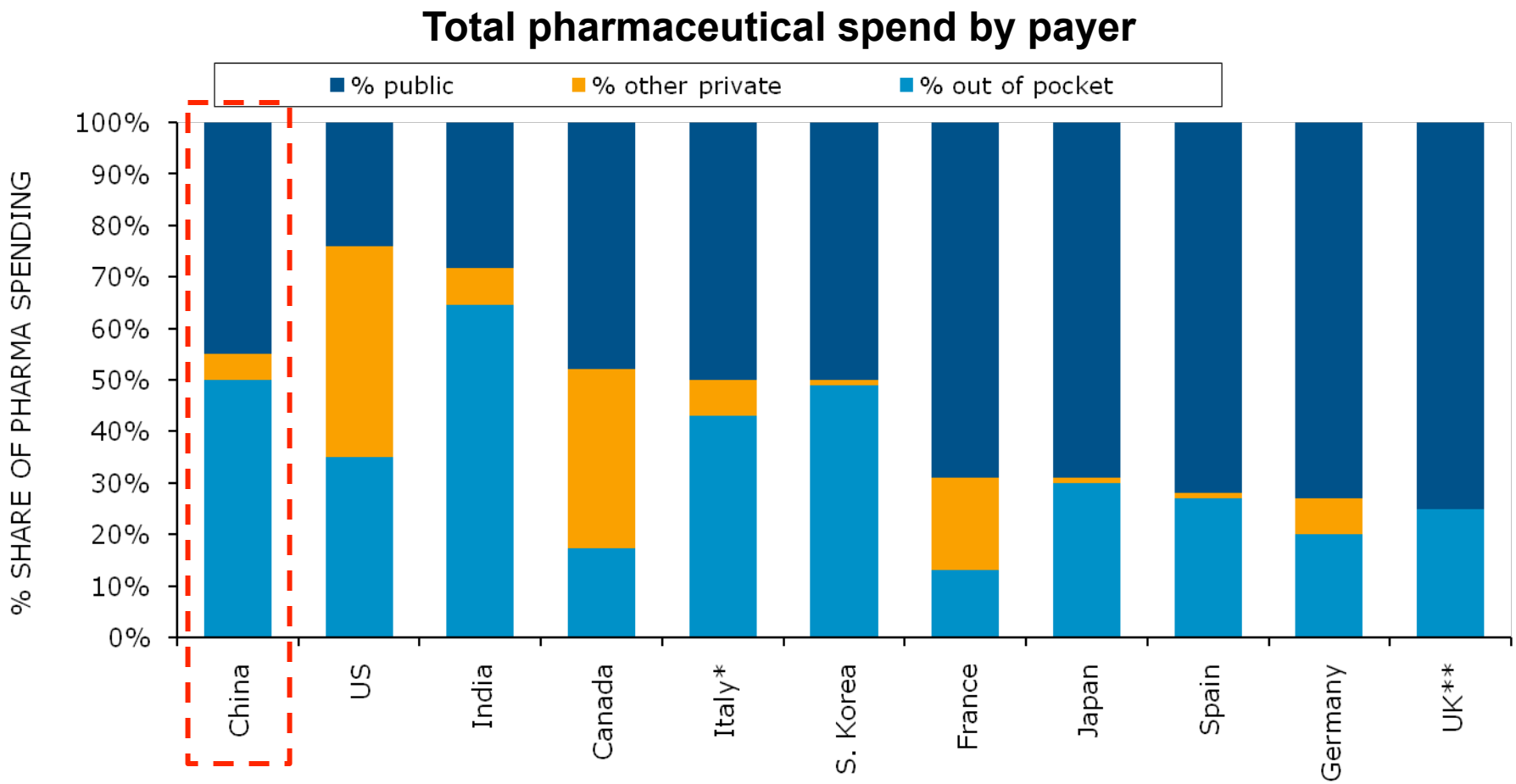
- Started as a recommendation to rational drug prescription/use
- More recently has become a way to control price for the very basic drugs
- EDL overlaps well with the medicines On RDL List A

EDL system is under going fast changes and the new EDL is already in the work



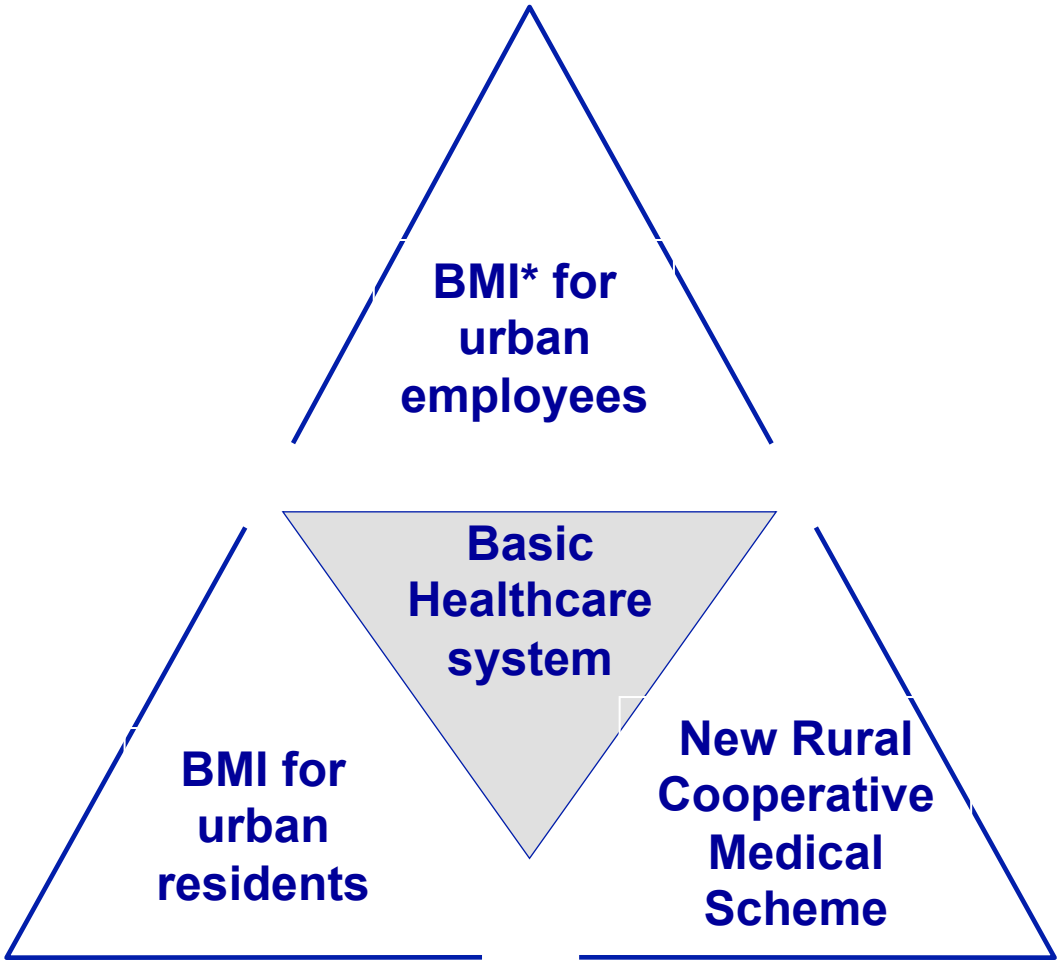
- Price set by NDRC
- Bidding and distribution managed at Provincial level
- 100% reimbursed for all drugs all patients
- Compulsory 100% usage in community hospitals and rural medical facilities
- NDRC is considering national level central bidding process
- 2012 EDL likely to include some innovative drugs
    - Would pose greater pricing pressure

Healthcare in China is paid for by a combination of government funding and self-pay



Sources: WHO Model List of Essential Medicines, 2009, OECD, China MOH, etc.

The government funding comprises BMI for urban employees, BMI for urban residents, and NRCMS



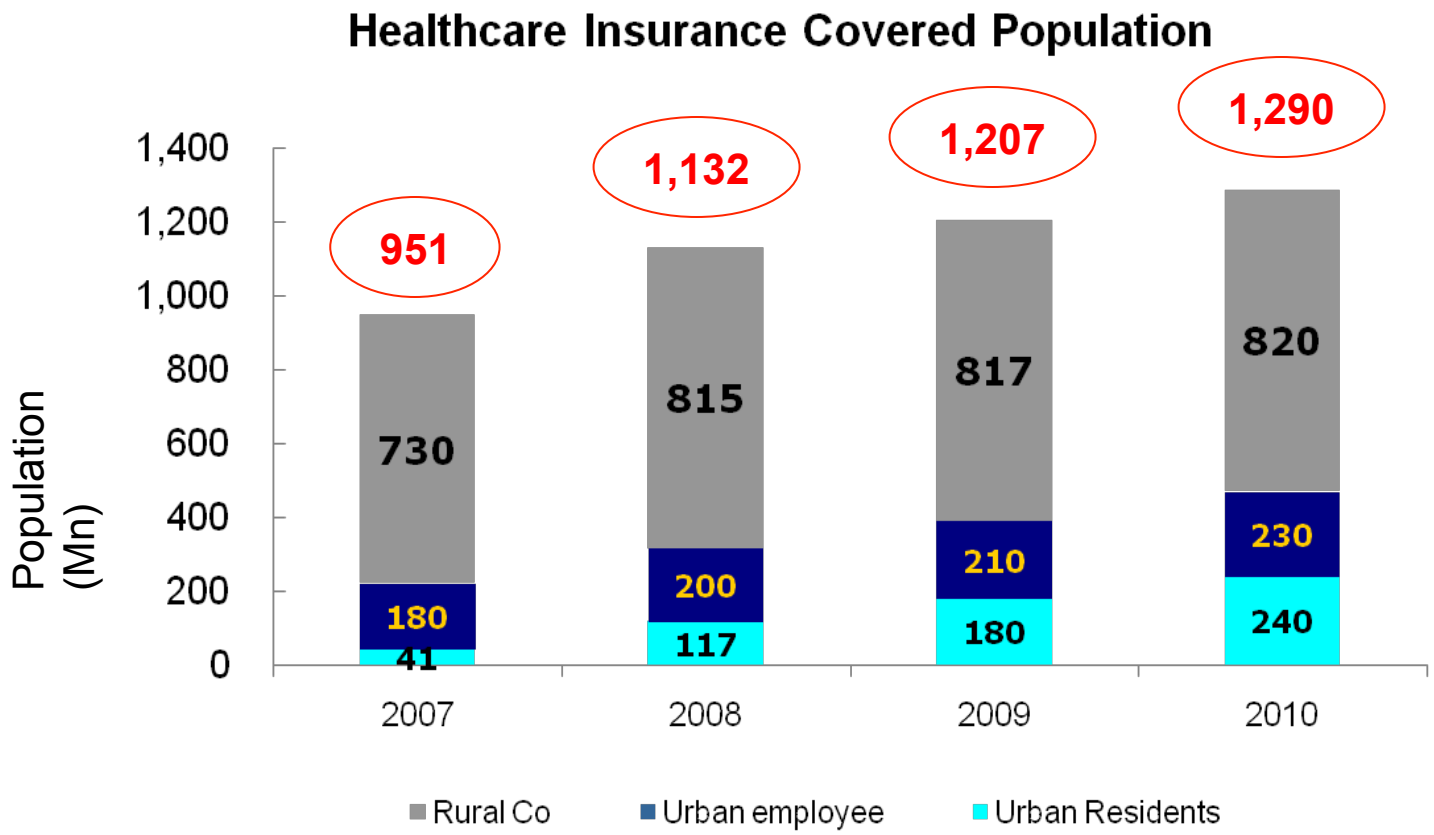
*: BMI: Basic Medical Insurance; funded by the government

Provinces and large cities design and specify their own policies

	Insured	Funding	Coverage
BMI for urban employees	Urban employees	• Both employee and employer contribute • Premium is based on individual salary and payroll of employer	• Annual max: >US $47,000 in 2011 among the coastal developed areas
BMI for urban residents	Urban residents	• Central government • local government • individual	• Annual max: >US $24,000 in 2011 among the coastal developed areas
NRCMIS	Rural population	• Central government • local government • individual	• Annual max: >US $10,000 in 2011 among the coastal developed areas

Sources: MOH, National and Local Health Statistics

The government's goal was to provide basic insurance to essentially everyone by 2011



Sources: MOH, National and Local Health Statistics

Overall medical insurance in China becomes more comprehensive and rational

Before 2008

- Development and beginning of policy implementation
- Alignment of financial resources

2008-2011

- Alignment of financial resources
- Coverage of rural population
- Coverage ceiling raised substantially
- Introduction of supplementary programs
  - Supplementary for significant events
- Private insurance as supplement

>2012

- More comprehensive and rational programs
  - DRG-based policy
  - Clinical pathway
- Future medical insurance will likely be a mix of
  - BMI (government)
  - Supplementary insurance (government)
  - Private insurance

Pricing and reimbursement dynamics - summary

- RDL is “Product” specific, not “Brand” specific
- RDL List B: mainly innovative drugs; partially reimbursed
  - The reimbursement ratio (reimbursed/co-pay) can be as low as 10% for some very expensive drugs
  - Certain premium drugs (such as oncologicals) may be better off as cash-pay compared to be on the RDL
  - A new segment - RDL List C has been in discussion for a couple of years
  - Retail prices of RDL drugs are determined by NDRC and local PB
  - Retail prices of non-RDL drugs are set by drug companies but approved by provincial divisions
  - The success of cash-pay drugs requires support of other commercial tactics
  - The National RDL is updated every 4-5 years
  - Regional differences of RDL and reimbursement ratio can be significant
  - Strong push for “zero” mark-up
  - Price/volume trade-off

Agenda

- Pharmaceutical Operating Environment
  - Market Overview
  - Drug Approval
  - Pricing and Reimbursement
  - Tendering and Bidding
  - Hospital Listing

The bidding process was first established in 2001; its efficiency & transparency are improving over the time

Manufacturer

Local bureau of health & hired agency/bidding platform

- Tendering committee consists of (local) government officials, pharmacists and one representative from Local NDRC
- Price (wholesale) is one of the key factors in the decision-making process
- Local distributors are the agents to help manufacturers in the bidding process
- Tendering is generally conducted once or a few times a year at provincial level
- NDRC is considering to centralize bidding for EDL drugs at national level

Hospital Listing (of a brand) is the pre-requisite step for prescribing by physicians in the hospital

Hospital Management/ Administration

- Hospital Pharmacy Director leads the process within the hospital
- It is consensus-based with Department Chiefs recommending drugs needed for their departments/ specialties
- Each hospital reviews and updates its Drug List once or twice a year
- Each review cycle takes approx. 3-5 months

Specialties/Departments

- The process is consensus-based with Department Chiefs recommending drugs needed for their specialties
- Awareness and acceptance among physicians before P&T meetings is critical

Thank you for your consideration!

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