

## China NMPA Reform and New Regulations/Guidelines/requirements

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### ABSTRACT

Historically the regulatory environment in China has been highly challenging. However, since 2015 China health authority started reforming the regulatory environment in China to bring China medical products up to international standards in terms of efficacy, safety and quality, so as to better meet the public needs for drugs as well as to improve the process of access to innovative drugs and therapies from global. Reforms are building smoother processes for innovative drug development in terms of adopting global standards and technical requirements, increasing review and approval transparency, accelerating new drugs review and approval. China health authority has refined old regulations to clearly define the requirements to clinical trial operation, multi-regional clinical trial design, biostatistics principles, electronic data capture, data management and statistical analysis reporting and on-site inspection. China health authority has also released guidelines to guide the drug development in terms of communication for drug development and technical evaluation, electronic common technical document implementation, post approval safety surveillance. China health authority has also released regulations including priority review & approval, data protection regime, imported drug registration and new chemical drug classification to encourage the innovative drug development. The reform of China regulatory environment is going on. We have seen more and more IND and NDA has been submitted for innovative drugs developed in local or global than ever since the reform. China regulatory will be further aligned with global standards and requirements. Simultaneous development and approval with the US and Europe can be achieved in the near future.

### INTRODUCTION

The purpose of this paper is to give an overview and summary of the major regulatory changes since 2015 happened in China HA to speed up the new drug development and registration in line with global standards as well as to bring the China medical products to the global level.

### NMPA REFORM

The regulatory environment before reform in China was very challenging and inconsistent with global standard

- Lengthy and unpredictable review timeline
- Additional regulatory requirements
- Unclear technical requirements
- CDE resource issue
- Lack of connection among different authorities bodies
- Local standards
- Local clinical data
- Local quality testing during CTA and NDA
- More CMC data
- Overseas marketing requirements

China State Council approved “Opinions on Reforming the Evaluation and Approval System for Drugs and Medical Devices” and was formally announced to the public on August 9, 2015. It leads to the revision of Drug Administration Law & Drug Registration Regulation in following sections.

- Encourage Innovation
  1. New Chemical Drug Registration Classification
  2. Priority review
  3. Registration technical requirement
  4. MAH Pilot
- Promote Drug Quality
  1. Generic Consistency Evaluation
  2. Chinese Pharmacopeia
- Enhance Supervision
  1. Clinical Study on-site Inspection
  2. GMP Inspection (Domestic & Oversea)
  3. Distribution administration
- Streamline Review & Approval
  1. Filing for BE studies
  2. Work procedure for clinical study on-site inspection
  3. CDE communication meetings
  4. Measures on Advisory Committee
- Transparency
  1. Communication mechanism for CTA & NDA
  2. Disclose drug evaluation information
  3. Re-evaluation procedure in CDE

## NEW GUIDANCE & GUIDELINES

A bunch of new guidance and guidelines has been published since the regulatory reform.

- 2015.01 Multi-Regional Clinical Trial (Pilot)
- 2015.07 Announcement of Self-inspection on the Clinical Trial Data
- 2015.07 Adverse Drug Reaction Reporting and Monitoring
- 2016.02 Priority Review & Approval Procedure
- 2016.03 New Chemical Drug Registration Classification
- 2016.06 Biostatistics Principles for Clinical Trials
- 2016.06 Communications for Drug Development and Technical Evaluation (Trial)
- 2016.07 Electronic Data Capture for Clinical Trials
- 2016.07 Data Management Planning and Reporting of Statistical Analysis
- 2017.01 General Considerations to Clinical Trials for Drug
- 2017.05 Regulatory Data Protection (Draft for Public Comment)

Here are some key points to guidance of Multi-Regional Clinical Trial (Pilot)

- Two types of clinical trials
  1. The trials performed simultaneously at multiple centers in different regions according to the same clinical trial protocol
  2. The regional trials simultaneously at multiple centers in different countries within a region for scientific and safety considerations according to the same clinical trial protocol
  3. If the data is used for drug registration in China, it should be derived from at least two countries (China plus 1 country at least)
- Trend consistency of subgroup
  1. It is required to first develop the statistical methods to evaluate if there is trend consistency between the subgroup results and the overall results
  2. With regards to the use of data for drug registration application in China, first, the overall evaluation of the global clinical trial data and then further trend analysis of the clinical trial data generated in Asia and China are required
- Sample Size Considerations
  1. Sample size should be reasonably distributed among different countries and centers, and corresponding scientific and legal basis for determination of such distribution should be provided
  2. When conducting the clinical trials, in addition to satisfaction of the statistics requirements, it is also required to satisfy the needs for subgroup evaluation and fully consider the epidemiological characteristics of disease, the representativeness of sample selection and other relevant factors
  3. Attention is to be paid to whether the sample size of Chinese subjects is big enough to evaluate and demonstrate the safety and efficacy of the investigational drug for patients in China

Here are the critical changes to the Decisions on the Adjustment of Imported Drug Registration

- Synchronized phase I clinical trials for MRCT are permitted
- Removal of restriction that product or indication is globally already in phase II/III
- Removal of certain import drugs' overseas marketing requirements
- MRCT data can be used for registration directly; CTA waiver is not required

According to the guideline of Technical Guide for Acceptance of Overseas Clinical Trial Data for Drugs which has been newly announced. The acceptance depends on

- Authenticity/Integrity/Accuracy/Traceability
  - Applicable to innovative drugs as well as generic drugs
  - Compliant with ICH GCP in the lifecycle of data generation
  - Entire overseas clinical trial data must be provided for China registration
- Technical Requirements
  - Domestic/overseas clinical trial data should be fully summarized and organized in a package following Drug Registration Regulation
  - Data of Biopharmaceutics, Pharmacology, Safety and Efficacy are inclusive
  - CTD format is recommended

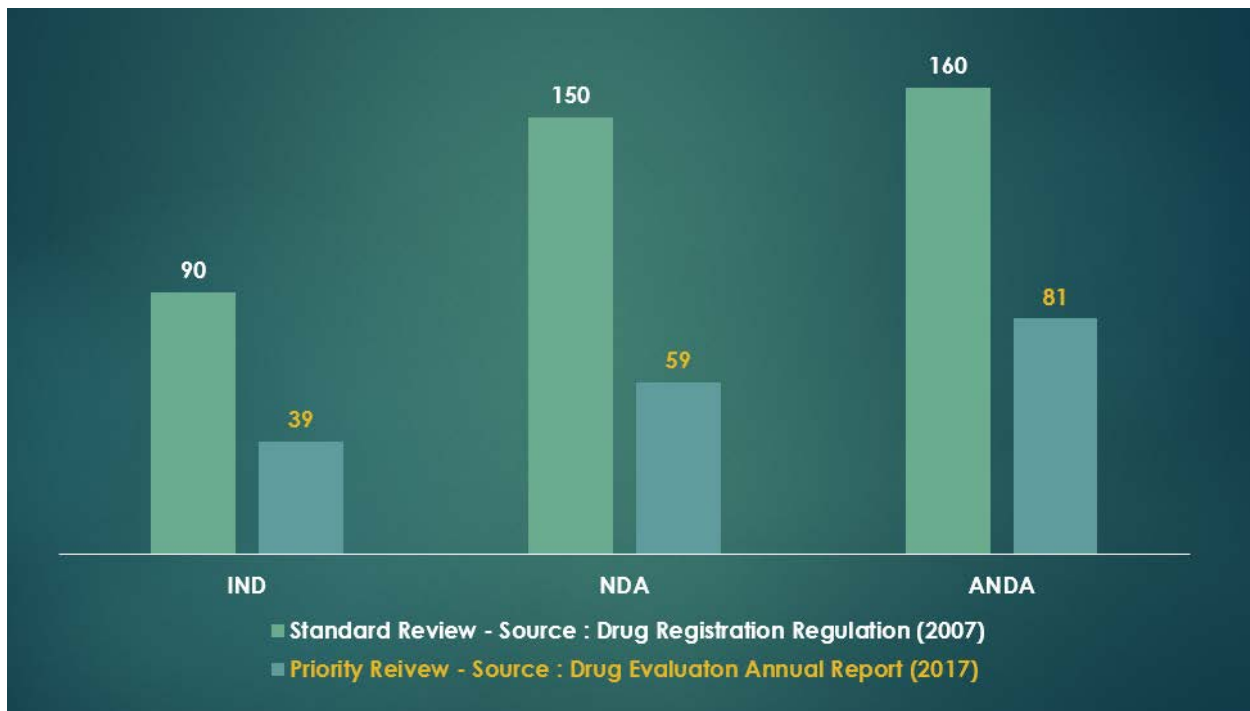
- Acceptance Subject to Data Quality
  - Data is authentic and reliable; compliant with DRR; sufficient to support evaluation of safety and efficacy; with no impact on safety and efficacy due to ethnical sensitivity is fully acceptable
  - Data with uncertainty in extrapolation of safety and efficacy on China population or data with impact on safety and efficacy due to ethnical sensitivity is partially acceptable
  - Data insufficient to support evaluation of safety and efficacy or data with significant issues is unacceptable
  - Data for drug registration for life-threatening disease, rare disease or pediatric with no effective treatment is conditionally acceptable even if it was partially acceptable

China HA also rolled out the Self-Inspection & On-site Inspection

- Regulatory Background
  1. Self-inspection and on-site inspection is required for all NDA approval as of now
  2. Sponsors can voluntarily choose to withdraw the NDA if the data reliability and integrity cannot be guaranteed
  3. All domestic and foreign research centers participating in the MRCT should accept the on-site inspections organized by NMPA
- Data Fraud Consequence
  1. If data integrity is questioned, this would result in rejection of the NDA
  2. Data fraud is treated as a criminal felony and will result in penalties including
    - a. Ban of submission of the same application within 3 years
    - b. Any other submission by the same sponsor within 1 year
    - c. No other NDA approval would be granted to the sponsor during this time

Priority Review & Approval brings huge benefit to the medications meeting the criteria.

**Figure 1. Working Days of Evaluation for Priority Review & Approval**



Here are the criteria for Priority Review & Approval.

- Drugs with significant clinical value
  1. Innovative drugs not yet marketed anywhere
  2. Innovation drugs transferred to China for local manufacture
  3. Drugs with advanced formulation technologies, or innovative therapies, or substantial clinical advantage
  4. CTA submission within 3 years before patent expiry and NDA within one year before patent expiry
  5. Simultaneous IND (approved in US/EU); NDA for local manufacture (under review in EU or US and passing GMP/GCP inspection)
  6. Traditional Chinese Medicine with clear clinical therapeutic purpose in prevention and treatment for major diseases
  7. New drug listed in the Specific National Program
- Drugs with significant clinical advantage
  1. AIDS, TB, Viral hepatitis, Rare disease, Cancer, Pediatric, Geriatric
- Others
  1. Drugs in urgent clinical demand & shortage of market supply (list finally determined by CDE)

New Chemical Drug Registration Classification has also been updated.

- New Drugs
  - Classification 1 - Innovative drugs not marketed at home and abroad
  - Classification 2 - New improved drugs that are not marketed at home and abroad
- Generics

Classification 3 - Imitation of original drugs that are marketed overseas but unavailable domestically

Classification 4 - Imitation of original drugs that are marketed domestically

- Imported Drugs

Classification 5.1 - Application for the domestic marketing authorization of original drugs marketed overseas

Classification 5.2 - Application for the domestic marketing authorization of non-original drugs marketed overseas

A guidance for having Formal Consultation Meetings with CDE has also been rolled out for trial operation.

- Type I
  1. A meeting that is necessary for solving an critical issue in clinical trials of an innovative drug or to address an important safety issue
- Type II
  1. Meeting at a critical development stages Pre-Phase I, End of Phase II, Pre-Phase III and Pre-NDA
  2. Risk Evaluation and Management Meeting pre-NDA approval
- Type III
  1. Any meeting other than Type I or Type II of new drug, and critical issues in the development of improved new drugs and generic drugs

According to the guidelines to Data Management Planning and Reporting of Statistical Analysis, DMP should cover

- Study Overview
- Roles & Responsibilities
- Type, format, source and flow of study data
- Systems employed in data collection, management and integration
- Data management documentation, activities and operation procedures
- Quality assurance quality control systems
- Blind Review

And SAP should cover

- Type of design and comparison
- Randomization and blinding method
- Definition and measurement of primary and secondary indicators
- Test hypothesis
- Definition of analysis set
- Plan for efficacy and safety evaluation and statistical analysis

- Principles for the analysis of primary indicators and expected method of analysis for confirmatory trials
- Generalized principles and methods for explanatory trials

China Specific document - Data Management Report. It should be written in Chinese.

- Execution process & major time points
- Operation practice and quality of data management
- Participating entities and responsibilities
- CRF, database design & external data management
- Data quality assurance & data validation and cleaning
- Medical coding
- Data transmission record of major time points
- Version change record of critical documents
- Deviations from DMP

China Specific document - Statistical Analysis Report. It should be written in Chinese.

- Key information from CSR
- Raw and analysis database and variable description
- Flow chart of subject distribution
- Randomization scheme
- Blind Review Resolution
- Statistical charts and tables supplementary to the main text
- SAS codes for non-standard statistical methodologies
- Published literature of statistical methods for non-standard statistical methodologies

Here is an overview of the Schedule of eCTD implementation in CDE.

- 2018.06 Invitation for bidding
- 2018.07 Bidding Closed
- 2018.08 Contract Signed
- 2018.12 System pre-check
- 2019.03 eCTD technical conformance guidelines released for public comments

A draft guideline of Regulatory Data Protection has been published for public comments for Innovative Drugs, Innovative Treatment of Rare Diseases, Innovative Treatment of Pediatric Uses and Innovative Therapeutic Biologics. The protection ranges from 6 to 10 years.

ICH Guidelines Implementation is undergoing.

- 2018.02.01 - Registration Application
  1. M4 The Common Technical Document
- 2018.05.01 - Clinical Development Adverse Events Monitoring
  1. M1 MedDRA Terminology
  2. E2A & E2B(R3) Clinical Safety Data Management
- 2018.07.01 - Post Approval Adverse Events Monitoring
  1. E2D Post-Approval Safety Data Management
- 2019.07.01 (Optional) & 2022.07.01 (Mandatory) - Post Approval Adverse Events Monitoring
  1. M1 MedDRA Terminology
  2. E2B(R3) Clinical Safety Data Management

China HA is also launching Post Approval Safety Surveillance activity for the Adverse Drug Reaction Reporting & Monitoring

- Regulatory Background
  1. All companies must implement an intensive monitoring procedure
  2. Publication and Implementation of final guidance in 2015
- Technical Requirement
  1. Requires non-interventional study protocol submitted within 60 working days of receiving approval certificate
  2. Data on at least 3000 patients within 5 year license period; For rare diseases, 80% of patients administered with study drug
  3. Real world setting including hospital, community medical service institution, drugstore, family planning station, drug rehabilitation center, and other drug using units
- Summary Report
  1. Submit CSR to Adverse Drug Reaction group within 5 year and before license renewal
  2. Failure to comply leads to rejection of license renewal or withdrawal

Sponsor needs to think more about Pros/Cons of Clinical Trial Strategies in China

	<b>Advantages</b>	<b>Disadvantages</b>
<b>China in Global</b>	<ul style="list-style-type: none"> <li>➤ Budget and timeline optimal</li> <li>➤ Quickest access to new drug</li> <li>➤ Mitigate lack of power in China subset if clinical need plus consistent positive trend in data</li> </ul>	<ul style="list-style-type: none"> <li>➤ China subset typically not statistically powered</li> <li>➤ Limited by timeline of China CTA &amp; global phase III recruitment</li> <li>➤ FDA may not accept global studies dominated by China subjects</li> </ul>
<b>China Regional</b>	<ul style="list-style-type: none"> <li>➤ Acceptable approach if insufficient China subjects in the global program</li> </ul>	<ul style="list-style-type: none"> <li>➤ Enough China subjects to ensure adequate power</li> <li>➤ Larger sample size</li> </ul>



		<ul style="list-style-type: none"> <li>➤ Considerable loss in time to market</li> <li>➤ Additional cost</li> </ul>
<b>China Alone</b>	<ul style="list-style-type: none"> <li>➤ Traditional approach</li> <li>➤ Acceptable to NMPA</li> </ul>	<ul style="list-style-type: none"> <li>➤ Slowest approach – start when drug is approved in US/Europe</li> <li>➤ Usually requires Active comparator</li> </ul>

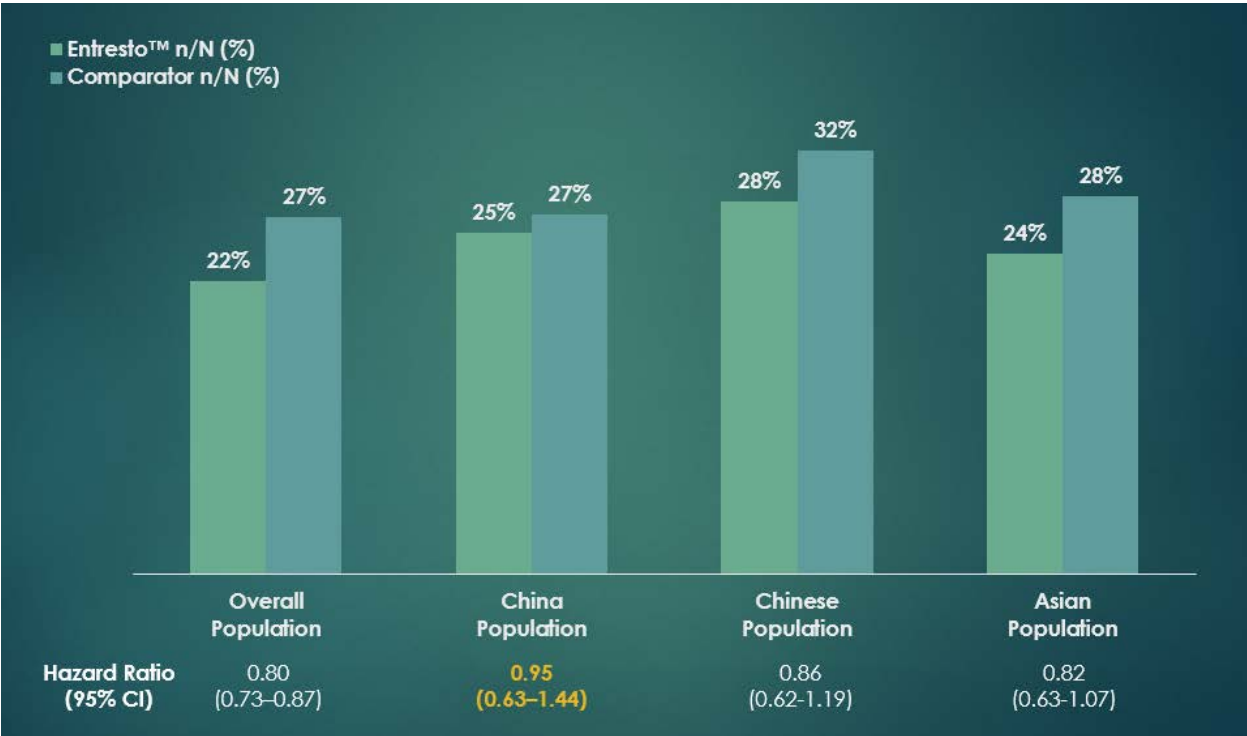
**NMPA SUBMISSION CASE STUDY**

Sacubitril/valsartan offers superior outcomes versus ACE inhibitors

- 20% reduction in CV mortality
- 21% reduction in HF hospitalization

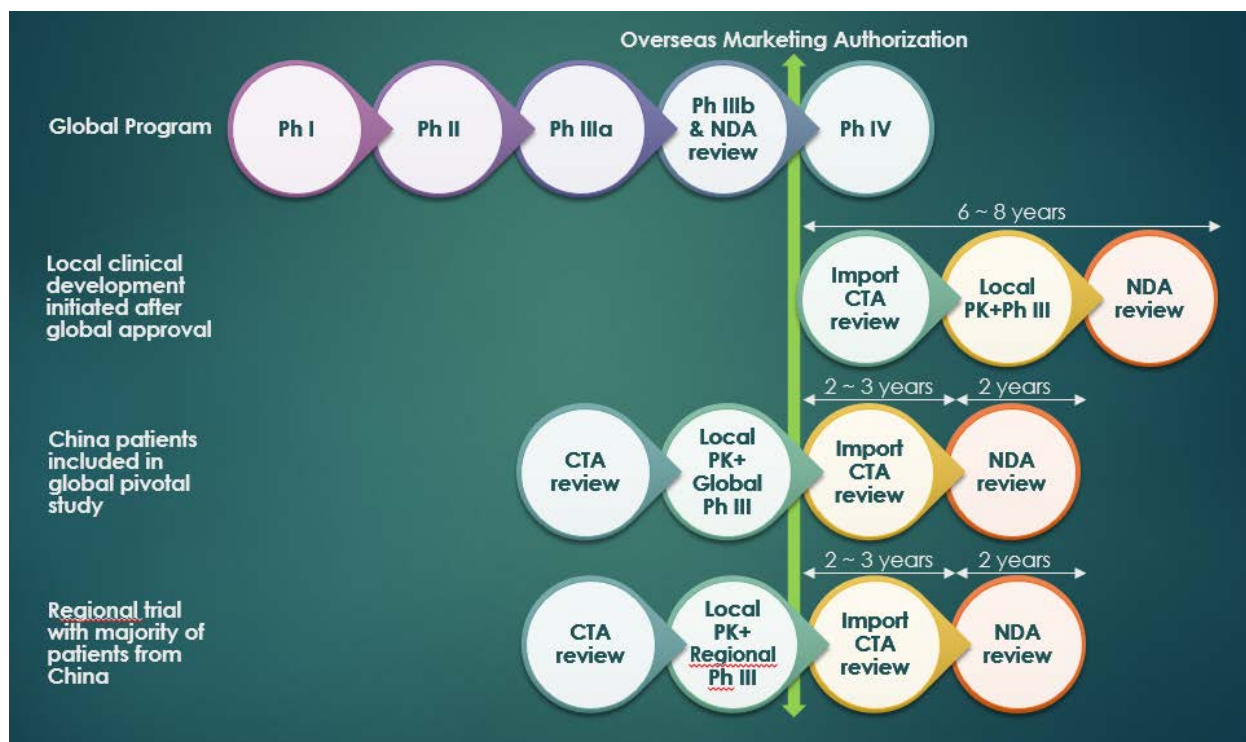
Sacubitril/valsartan is the new foundation of care that symptomatic HFrEF patients should not be without. That offers superior outcomes versus ACE inhibitors because of its novel mechanism of action. Sacubitril/valsartan helps keep HFrEF patients living longer, out of the hospital, and feeling better

**Figure 2. Primary Efficacy Evaluation (Endpoint - CV mortality or HF Hospitalization)**



The overall safety and tolerability profile of Sacubitril/valsartan in the China population, the Chinese population and the Asian population was similar to that of LCZ696 in global population.

**Figure 3. Development Strategies Pursued in China**



Usually the new drug approval in China is 4-5 years or even longer behind of the US and EU

Sacubitril/valsartan won the NMPA approval merely two years after its launch in the US and EU. The product should appreciate the NMPA for the grant of priority review. Because of this, the product got a set timelines for review, testing, inspection and final disposition.

- 2015
  - Mar 29 Pre-NDA meeting with CDE
  - Jul 8 FDA approval of Entresto™
  - Oct 21 Submission of post-CPP CTA
- 2016
  - Jan 26 NMPA approval of CTA with conclusion of clinical trial waiver
  - Mar 2 Submission of NDA
  - Mar 17 Submission of priority review application
  - Sep 21 Submission of self-inspection results
  - Dec 12 NMPA approval of priority review
  - Dec 19 Submission of on-site inspection acceleration request
- 2017
  - Apr 26 Completion of on-site inspection
  - May 14 On-site inspection report transfer to CDE
  - Jul 24 Highest level NMPA approval meeting
  - Jul 28 NMPA approval of Sacubitril/valsartan

Here are the Key Factors to Submission Success

- Proactive response to the HA queries
- Timely and active communication with the HA
- Efficient NDA strategy
- Flawless inspection with no major findings
- Well-organized NDA package
- Actively participation into MRCT
- High quality clinical trial operation
- Consistent trend with global results

## CONCLUSION

Significant Improvement of Regulatory Environment is coming.

- CTA timelines shortened from average of 2 years to 4-5 months; In the future, 60 wds under the filing mechanism announced Jul 27, 2018
- Shorter and predictable approval timelines
- More flexible with regards to local clinical data
- Simultaneous development and approval with US/EU
- ICH aligned technical requirements to promote clinical trial quality and be consistent with global standards

## CONTACT INFORMATION

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