Application and Review: Trends in the Past Decade of Chinese Biopharmaceuticals

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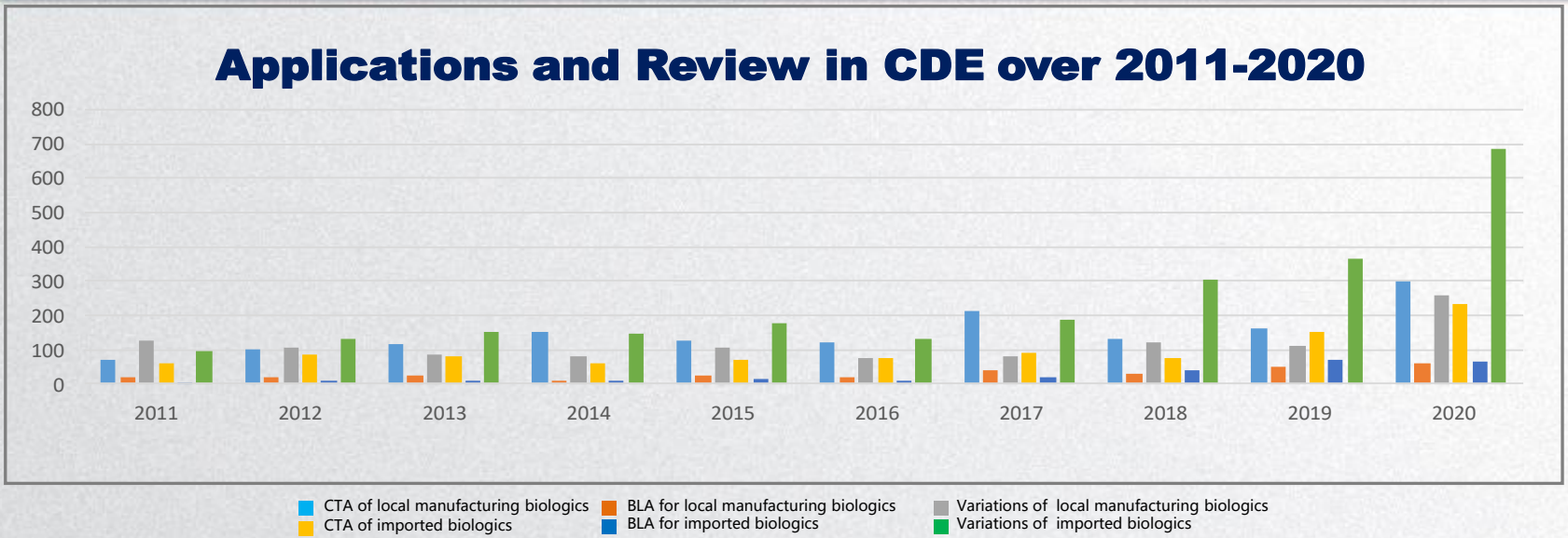
Outline

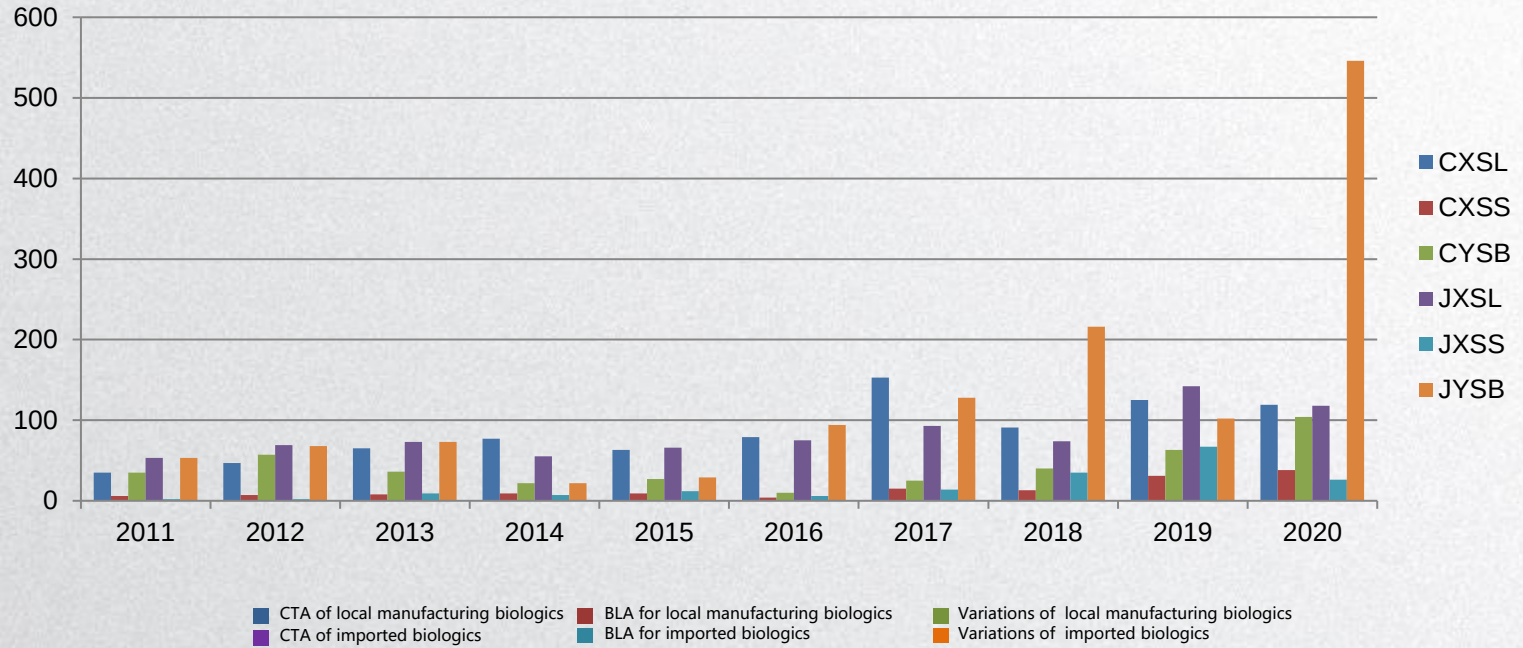
- Biological products applications and review in CDE over the past decade (2011-2020)
- Current CMC technical review strategy of biological products applications in CDE
- Challenges and Opportunities

Applications and Review in CDE over 2011-2020



- All kinds of applications have been increasing for ten years
- Applications of Imported biological products are more than local manufacturing biologics
- The number of variations (especially imported products) has increased sharply, which suggests the demand of life cycle management is strong, how to implement ICH Q12 in China?

Applications and review of recombinant products



How to handle the increasing number of applications of drug products efficiently?

CMC Review Strategy of Applications of Biological Products

Molecular-specific Strategy

Phase-appropriate Strategy

Clinical needs driven Strategy

Molecular-specific Strategy
- Categorization for biological products

- Antibodies: Monoclonal antibodies (mAb), Bi-specific antibodies (BsAb)
- Antibody-Drug Conjugates (ADCs)
- Cytokine and Growth Factors
- Enzymes
- Polypeptide hormones
- Recombinant fusion proteins
- Toxins
- Others (mRNA)

A Comprehensive Scientific Survey of Excipients Used in Currently Marketed, Therapeutic Biological Drug Products
V. Ashutosh Rao
Pharm Res (2020) 37:200 https://doi.org/10.1007/s11095-020-02919-4

The registration classification of biological products

- According to Drug Registration Provisions and Dossiers Requirements

Type 1: innovative biological products, domestically and overseas un-marketed biological products for therapeutic

Type 2: modified biological products, biological products for therapeutic with improved safety, effectiveness and quality controllability and obvious advantages which are obtained by modifying domestically or overseas marketed products.
2.1 Biological products with obvious clinical advantages which are obtained by optimizing the dosage form and administration route on the basis of marketed products.
2.2 Biological products with newly added domestically and overseas unapproved indications and/or changed applicable populations.
2.3 New compound products composed of marketed biological products.
2.4 Biological products with major technical improvements made on the basis of marketed products, such as recombinant technology replaces biological tissue extraction technology; it has obvious clinical advantages after changing amino acid sites or expression systems and host cells compared with products already on the market.

Type 3: Domestically or overseas marketed biological products:
3.1 Overseas marketed manufacturing in oversea, domestically un-marketed biological products register for marketing.
3.2 Overseas marketed and domestically un-marketed biological products register for domestic production and marketing.
3.3 Biosimilars.
3.4 Other biological products

Phase-appropriate Strategy：

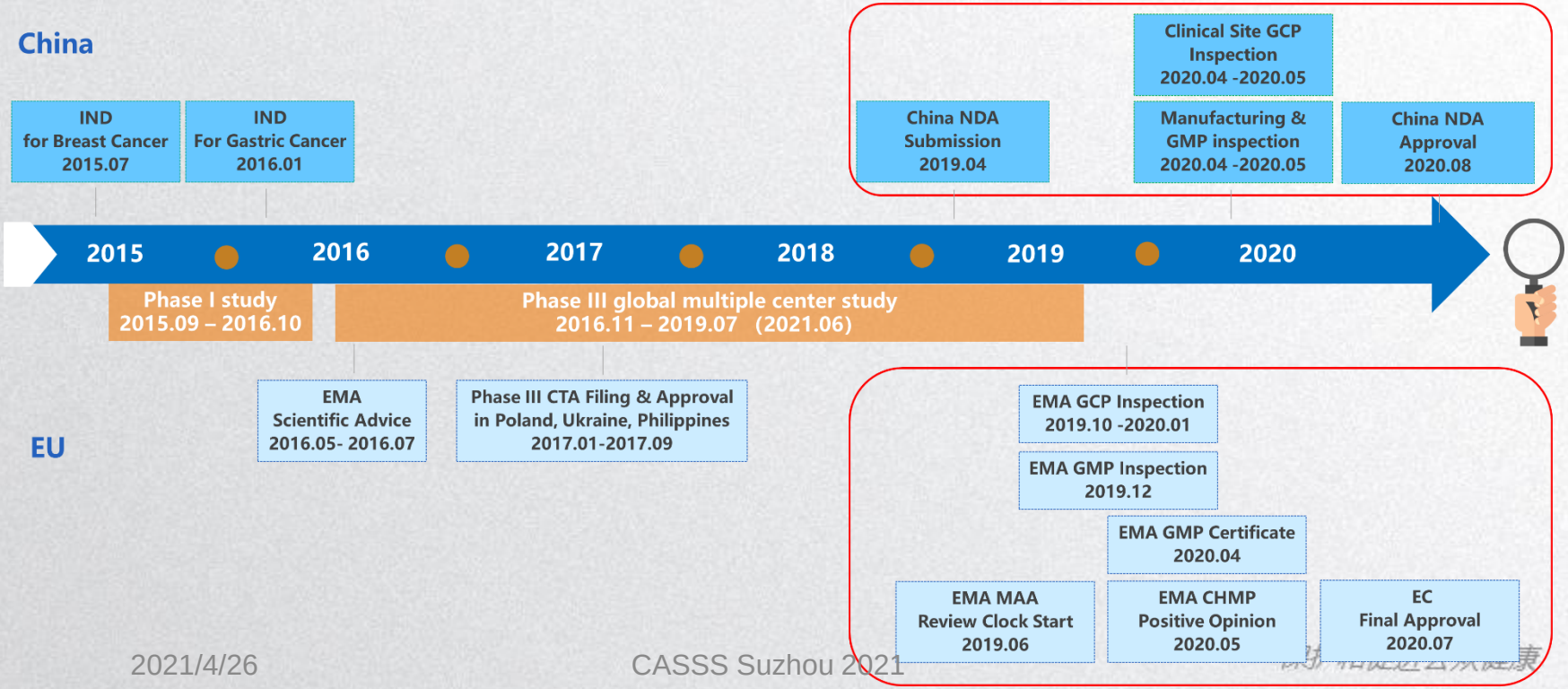
- **IND , NDA or Post-approval**
- **Early stage or late stage**
- **Major concern:**

Raw materials　Impurities　Virus safety　Lots

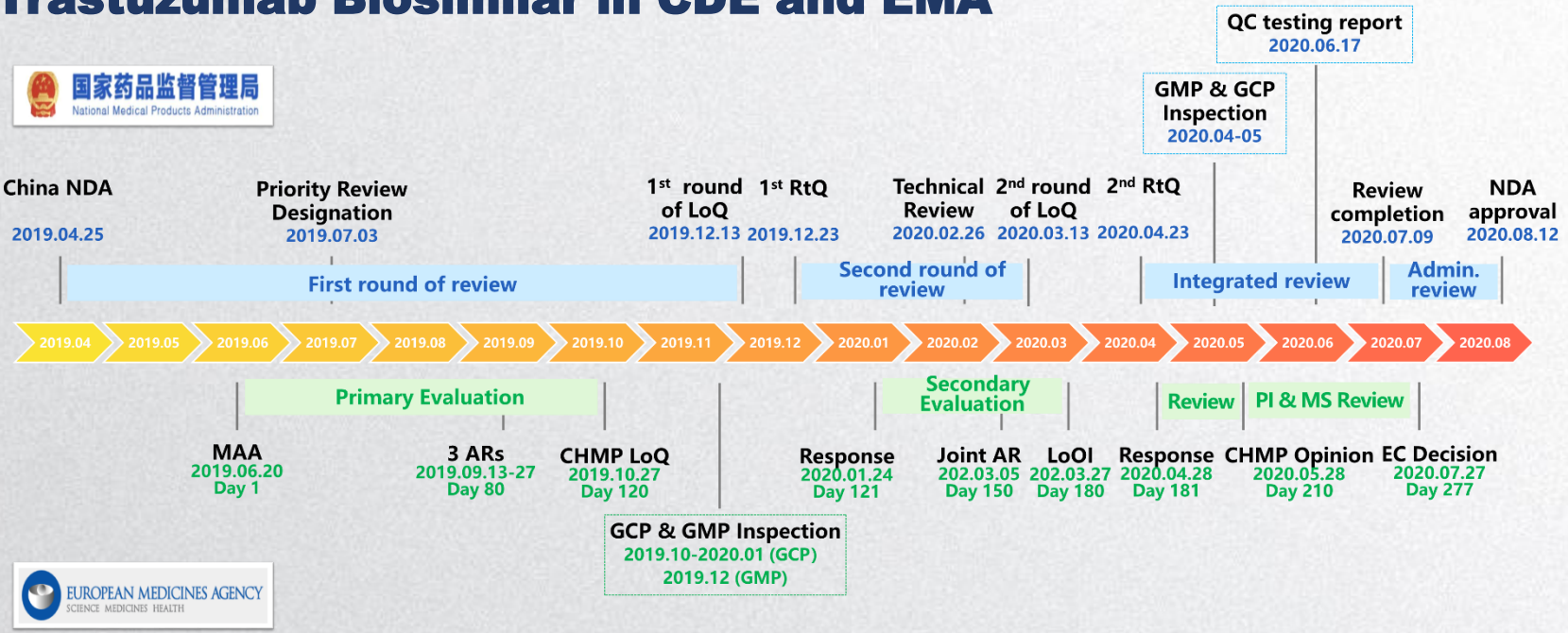
Clinical-needs Drive Strategy :

- No available therapy for a serious condition
- Available therapy but not good enough (efficacy/safety)
- Biosimilar and so on

Development and Registration Milestones of Trastuzumab Biosimilar in China & EU



Comparison of the Review Process for Trastuzumab Biosimilar in CDE and EMA



AR: Assessment Report from Co-/Rapporteur; LoOI: List of Outstanding Issues
PI: Product Information MS Review: Member State Review; EC: European Commission;
RtQ: Response to Questions

Comparison of Technical Review Query by CDE & EMA on Trastuzumab Biosimilar

Note: More details please refer to the following slides

CMC key questions summary of Trastuzumab Biosimilar (1/2)

Content	EU EMA	NMPA CDE
Cell bank	➢ Explain the strategy developed to ensure clonality of the OCB ➢ Perform southern blot analysis to confirm the clonality of the MCB ➢ Confirm the number and/or days of passages for EOPC at the End of Production Cell Bank (EOPC)	➢ Determine the maximum number of Passages for the Cell bank by the studies which were simulate actual production conditions
Manufacture Process Process Controls Process Validation	➢ Provide the FMEA analysis for each step including the risk score for each parameter ➢ Justify the batch size range for the Drug Substance. Minimum and maximum batch size should be challenged in DS process validation ➢ Define holding times with a proper justification and validation for this acceptable range ➢ Clarify which filtration steps are referred to and under which conditions such refiltration would be deemed acceptable, a validation protocol should be provided to support re-filtration.	➢ Studies of antibody recovery Rate and the yield of the antibody were required, Cell culture cascade amplification process parameters should be provided, ➢ Have the rate of antibody recovery and the yield of the antibody studies ➢ Life time of the intermediates should be justified based on the CQA (E.g Glycan, post-translational modifications) and safety criteria (Microbial Limit). ➢ Justify the process parameters of low pH process ➢ Exogenous virus should be controlled in the DS produce process and exogenous virus testing for UPB should be done regularly
Raw material & Container Closure System	➢ Provide more details on the proprietary medium. ➢ Changes in the concentration of particular medium components may have an impact on the DS/DP quality, any changes in the concentration of medium components should be properly qualified and implemented via a variation procedure. ➢ Safety evaluation of antifoaming agent, poloxamer 188, puromycin, and benzyl alcohol was carried out based on the impurity safety factor (ISF),taking into account that LD50 is used in the calculations of the ISF and justify the LD50 values associated with each impurity. ➢ Provide the information related to the storage conditions and maximum number of uses for the different columns used during the Drug Substance purification ➢ Provide validation data for the sanitation/regeneration for all reusable columns.	➢ Provide more details on the proprietary medium (E.g ingredients and sources). ➢ Integrity tests were required after the filter were used. ➢ Resin life time supportive studies were required, cleaning validation of columns and filter were required as well as the life time studied of the filter ➢ Use the DS & DP by the final commercial manufacturing process to do the Extractable/Leachable studies

CMC key questions summary of Trastuzumab Biosimilar (2/2)

Content	EU MAA	NMPA CDE
Reference Materials	➢ Appearance, pH, identity, glycan profile and HER2 binding should be analyzed ➢ Provide testing programme for qualification of future reference standards	➢ Provide sufficient Characterisation , impurities and Biological activity data of reference materials ➢ Critical glycan profile should be analyzed ➢ Determine shelf life of reference material based on stability studies
Specification & Batch Analyses	➢ Provide batch analysis results for all DS batches manufactured ➢ The tests for mycoplasma and in vitro adventitious agents on unprocessed bulk are critical tests. Proper acceptance criteria should be set ➢ Any bulks contaminated with mycoplasma or viral contaminants should not be further processed. And the result of these tests (although performed on an upstream intermediate) should be included in the DS release specifications and/or release certificate. ➢ Specification of DS/DP should be determined based on all of the batch analysis results and product characteristics	➢ Clarification should be provided when the Analysis procedure were changed and provide the bridge studies. ➢ Specification of DS/DP should be determined based on all of the batch analysis results and stability studies.
Similarity study	➢ Provide justification to support the use of quality data obtained from expired reference product batches that were frozen before the expiry date. ➢ Perform ADCC assay using natural NK cells or PBMCs for the bio-similarity analysis.	➢ Accumulate more data of Sialylation Glycan and binding to FcRn and pay attention to effect to the safety and PK/PD at clinical practice.
Comparability study	➢ The impact of the observed differences of quality attributes such as intact mass, post-translational modifications, charge heterogeneity and forced degradation should be discussed on comparability and clinical safety and efficacy.	➢ Pay attention to post-translational modifications.
Stability/Shelf-life	➢ The shelf life granted for DS/DP based on supportive data from at least 3 representative batches for the time points available at time of approval.	➢ DP shelf life is preferred to be granted through stability studies using DS close to the expiry date, and the DS/DP should be produced from the final commercial manufacturing process.

Challenges and Opportunities

- **Simultaneous global development and registration (One drug application goes to different Agencies at the same time)**
- **First-in-class drug applications reviewed by CDE first**
- **Science goes faster than we learn**

Thank you !