Application and Challenge of Advanced Therapy Medical Products (ATMP)

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Center for Drug Evaluation of NMPA

Biologics CMC Division

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Protect and Promote Public Health

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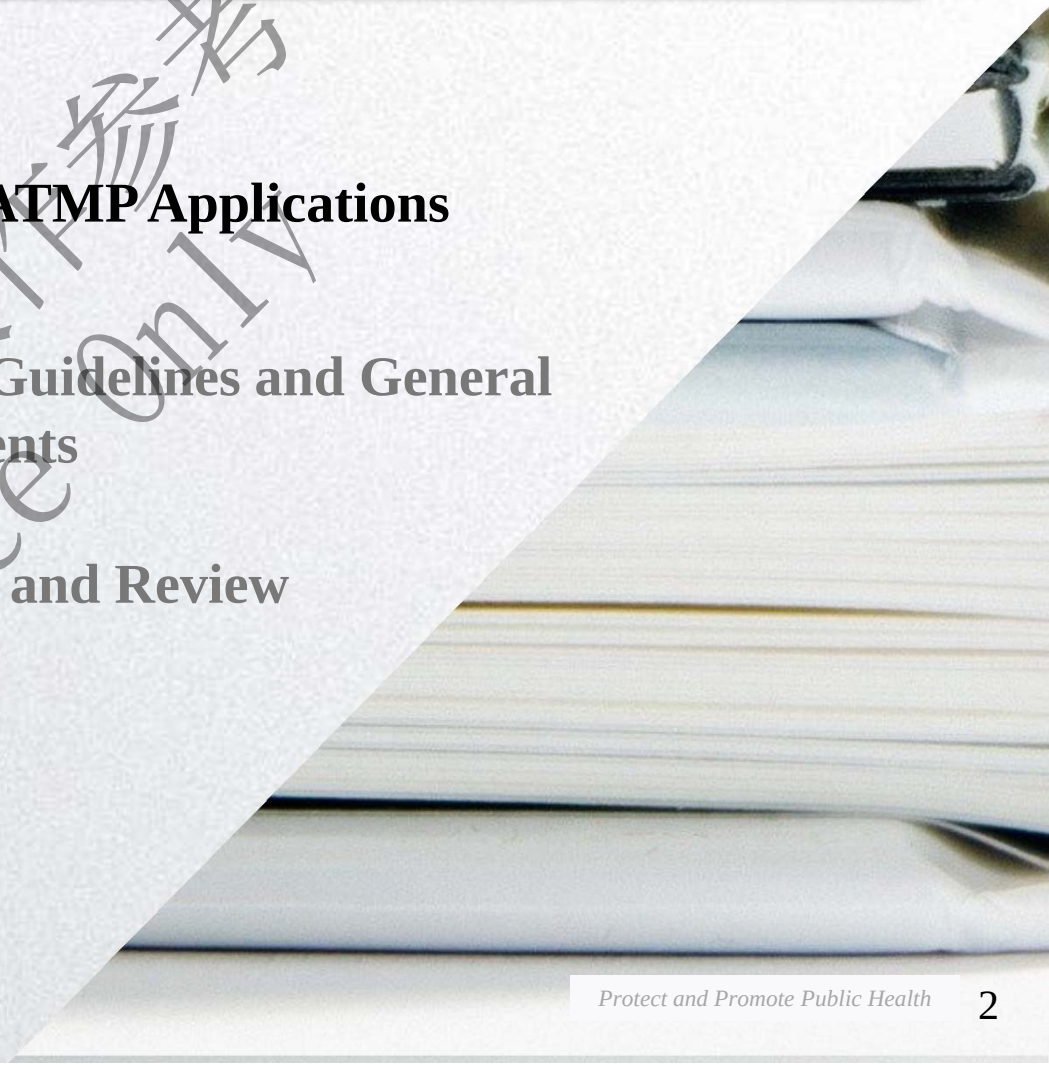

ATMP Applications at INA stage

ATMP Product Development and Application Characteristics					
◆Rich and diverse product types ◆ Quickly updated product types		◆ Mainly immune cell therapy products ◆ Highly concentrated study and repeated development			
IND Phase	Immune cells	Stem cells	Oncolytic virus	In vivo gene therapy	Other types
Number of applications	~115	~51	~62	~18	2
Number of approvals	~79	~39	~38	~10	0
Product type	CAR-T, TCR-T, TIL, universal T cells, DC, CTL, NK cells, PBMC, etc.	Mesenchymal stem cells, megakaryocytes/erythroid progenitors、iPSC, basal cells, etc.	Herpes simplex virus, adenovirus, cowpox virus, vaccinia virus, poxvirus, coxsackievirus, M1 virus, etc.	Adeno-associated virus and plasmid	Organoid products and microcapsulated cells

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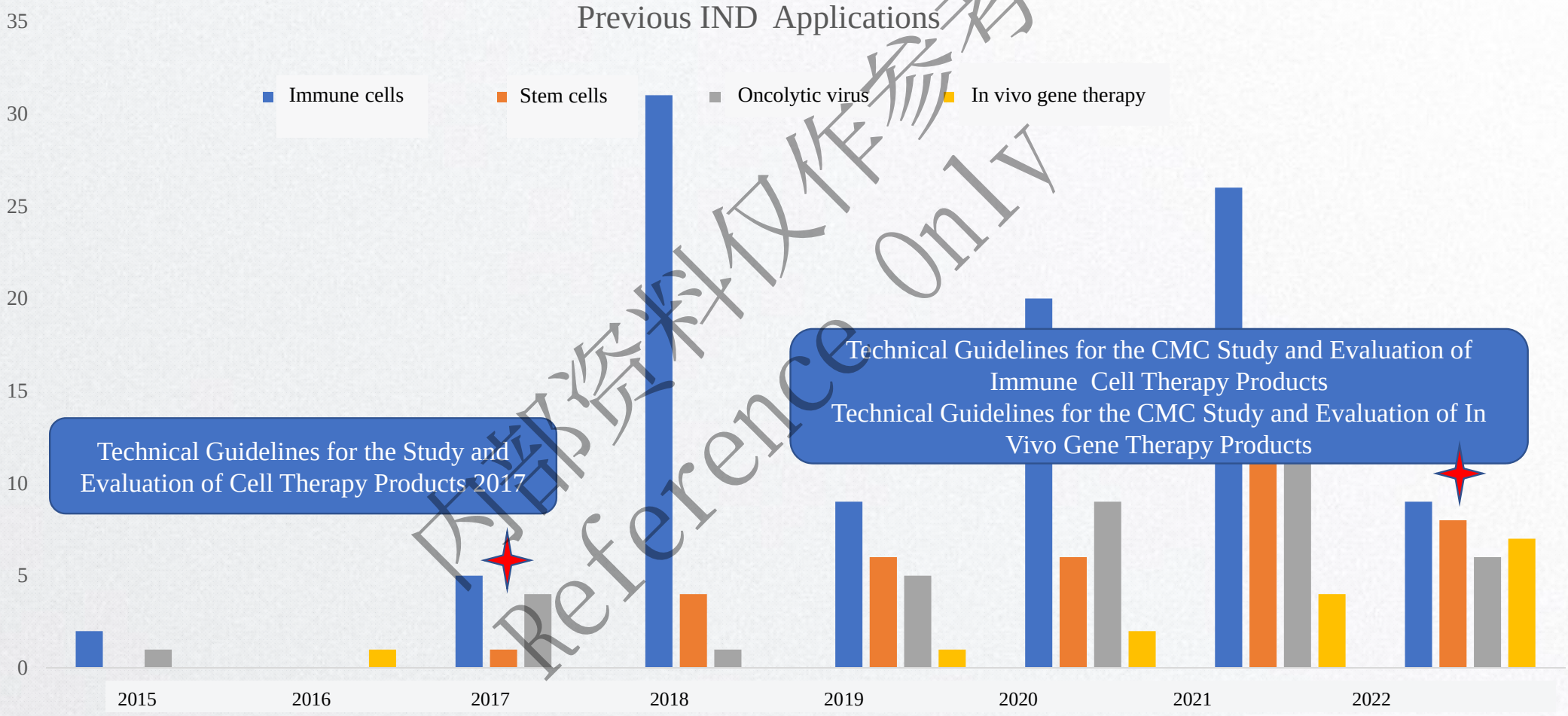
*Data updated as of April 2022

ATMP Development Trend



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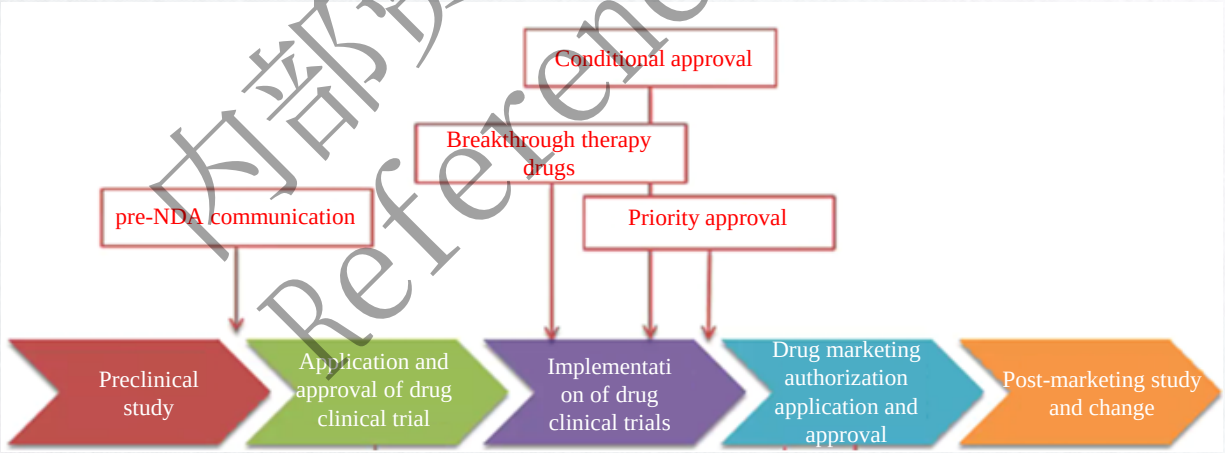
Marketing authorization application of ATMP

- ATMP marketing authorization application
  - 2 CAR-T cells marketed: Yescarta and Relma-cel
  - 1 cell therapy product is under review for marketing authorization
  - Multiple varieties are under pre-NDA communication stage
- Expedited marketing and registration system of drugs
  - Breakthrough therapy drugs: ~22.7% (biological products)
  - Priority approval: 100%
  - Pre-NDA communication: 100% (with priority)



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ATMP technical guide and general requirements (CMC)

Technical guide (CMC)

Technical Guidelines for Study and Evaluation of Cell Therapy Products (2017)

Technical Guidelines for CMC Study and Evaluation of In Vivo Gene Therapy Products (interim) (2022)

Technical Guidelines for CMC Study and Evaluation of Immune Cell Therapy Products (interim) (2022)

Technical Guidelines for CMC Study and Evaluation of In Vitro Gene Modification Systems (interim) (2022)

Other relevant supporting guidelines…

Technical considerations (CMC)

Main Considerations on the Application of Cell Therapy Products for CMC Study of Clinical Trials and Application DOSSIER (2018)

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Q&A documentation (CMC)

Q&A on Application for CMC Study of Clinical Trials for Cell Therapy Products (Issue 1) (2019)

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General requirements of technical review at IND phase

- **Risk analysis and control of raw materials:**
  - Donor pathogen screening; Preparation and verification of working cell bank/seed lot;
  - Raw materials of human and animal origin; General raw materials... .
- **Validation of production process of clinical samples:**
  - Stable production of samples for clinical study
  - Necessary production process control items
- **Product quality study and quality control:**
  - Study on product structure and physical and chemical properties, and the preliminary establishment of quality specifications and analytical methods
  - Batches for non-clinical study support the safety of samples for clinical study
- **Stability study:**
  - Study on product storage and use stability characteristics of products
  - Product stability study data should support the clinical study of the product

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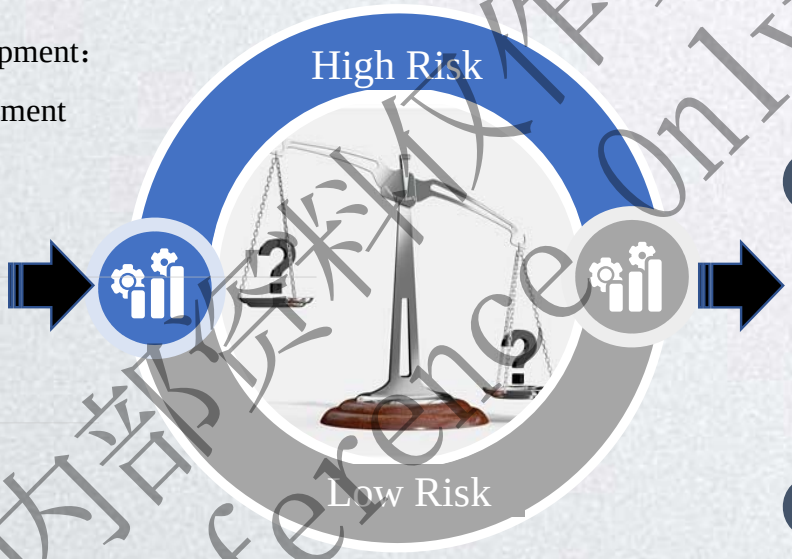
Risk-based comparability study strategies

Risk assessment

1. Development phase.
   - Early stage of process development；
   - Late stage of process development
2. Change process unit
   - Upstream process
   - Downstream process
   - Preparation process
3. Types of change
   - Cell batch update, process adjustment
   - Expanded scale and supplier change
   - Increase or change of production sites…



Comparability study protocol

1. Range of study
   Process, process control, release test, extended study, clinical/non-clinical
2. Study batch
   Change type, quality variation, quality control strategy, methodology, and development phase
3. Comparability standards
   Progressively strict standards of comparability.
4. Methodology: Methodology development and bridging
   Application of statistical tools.

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Comparability study of ATMP Products

- Strategy of comparability study of autologous cell therapy
  - Head-to-head comparative study: Cell bisection method
  - Comparison of historical study data: Reasonable range of historical batches
  - Statistical analysis method

- Strategy of comparability study of in vivo gene therapy products
  - Head-to-head comparative study: Reduce the impact of differences in analytical methods
  - Comparison of historical study data: Consider the impact of analytical methods, instruments, raw materials and personnel
  - Statistical analysis method

- Setting criteria for comparability study
  - Establish acceptable criteria based on risk and product quality attributes
  - Reasonable standards are not limited to meeting quality specifications
  - Study phase and number of batches

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Development and Review Challenges of Autologous TCR-T Cell

Product and process characteristics

- Individualization and heterogeneity
- Diverse cell composition
- Differences in cell culture differentiation
- Integration and insertion of viral vectors
- Complex functional activity
- …

Development and Review Challenges

- Mutations caused by random insertion of modifying genes
- Impact of cell components and subtypes on product safety and efficacy
- Impact of modification of nontarget cells on activity and safety
- Complex mechanism of action and poor indicative significance of bioactivity test item
- Complex change comparability studies

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Development and Review Challenges

- Mutations caused by random insertion of modifying genes
- Impact of cell components and subtypes on product safety and efficacy
- Impact of modification of nontarget cells on activity and safety
- Complex mechanism of action and poor indicative significance of bioactivity test item
- TCR receptor chain in mismatch and risk control
- Complex change comparability studies
- …

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Development and Review Challenges of Autologous TIL Cell

Product and process characteristics

- Individualization and tumor heterogeneity
- Various indications
- Diverse cell composition
- Differences in cell culture differentiation
- Complex functional activity
- …

Development and Review Challenges

- Impact of cell components and subtypes on product safety and efficacy
- Complex mechanism of action and poor indicative significance of bioactivity test item
- Complex change comparability studies
- Residual tumor cells:
  - Sensitivity and limit of detection of the detection methods
  - Rationality of tumor marker selection
- …

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Development and Review Challenges of Universal Cell Therapy Products

Product and process characteristics

- Complex and diverse origin of cells
- Diverse cell composition
- Differences in cell culture differentiation
- Complex functional activity
- Gene editing operation

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Development and Review Challenges

- Impact of cell origin and individual differences on quality between batches
- Impact of cell components and subtypes on product safety and efficacy
- Complex mechanism of action and poor indicative significance of bioactivity test item
- Complex change comparability studies
- Impact of gene editing on mutation and genome stability
- Impact of incomplete gene editing on GVHD and immunogenicity

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Development and Review Challenges of iPS cell therapy products

Product and process characteristics

- Complex and diverse origin of cells
- Diverse combination of expression factors
- Differences in cell culture differentiation
- Complex functional activity
- …

Development and Review Challenges

- Impact of cell origin and individual differences on quality between batches
- Expression pattern of initiating cells and induction factors, and impact of induction conditions
- Cell induction efficiency and heterogeneity of induced cells
- Limited evaluation indexes of stemness and differentiation potential of cells
- Control of tumorigenesis risk of cells
- Complex mechanism of action
- Complex change comparability studies
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Development and Review Challenges of AAV-Mediated In Vivo Gene Therapy Product

□ Product and process characteristics

- Diverse serotypes
- High proportion of basic infection in the population
- Various packaging systems
- Various forms of transformation …

□Development and Review Challenges

- The vector showed a certain affinity to cells/tissues, but its specificity was not high enough
- Immunogenicity of empty viral vectors and competition for receptor binding
- Impact of different packaging systems on particle and gene heterogeneity
- Risk of genome integration
- Impact of mispackaging genes on safety

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Summary

- There are Rich product types, increasing number year by year, and problem of repeated research and development
- Limited product recognition and relevant technical guidelines in urgent need for improvement
- Quality study needs to be deepened, and risk control needs to be strengthened
- Limited study and analytical methods, and new methods and platforms need to be established

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Thanks for Listening

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