MSD
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Bioanalytical Support for Studies in China

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China's Pharmaceutical Market

- Driven in part by Chinese government Initiative that includes ensuring access of new medicines to the Chinese people
  - Healthy China 2030
- Estimated to reach $161.8 billion by 2023*
- 30% share of the global pharmaceutical market*
- As such, it is a huge potential opportunity for companies to grow sales

China has moved from being a secondary market to a primary market for Pharma

*https://www.chinadaily.com.cn/a/201912/20/WS5dfc27a7a310cf3e3557f6da.html

China Clinical Studies

- When China was a secondary market, China specific studies were often conducted after marketing applications were submitted in primary regions.
  - No impact to US/EU marketing applications
- With China moving to a primary market, China studies may be included in initial marketing applications
- There may also be China cohorts in global efficacy trials

Inclusion of China Cohorts in Global Phase 3 Studies Has The Potential to Place an Increased Focus on the Bioanalytical Data from These Studies especially if Multiple BA labs are Utilized Within a Study

The Bioanalytical Challenge

Strategic Shift by Pharma to Include China in Initial Wave of Approvals

- Implementation of that strategy may require **China participation in global clinical trials**.
- Local (**China only Phase I**) studies may also be required early in development in order to support inclusion of Chinese participants in the Global trials.
- **Samples collected during these studies will require Bioanalytical Support**

Chinese government regulations place controls on what laboratories may be used for bioanalytical work

- Due to limitations imposed by the Chinese government, it may not be possible to export samples from China to laboratories used for samples collected ex-China

Regulatory Landscape in China Relevant to Bioanalytical Support

National Medical Products Administration (NMPA)

- Responsible for regulation of drugs and medical devices
- Responsible for Clinical Study Approval (CSA)

Human Genetic Resources Administration of China (HGRAC)

- Under the Ministry of Science and Technology (MOST)
- Responsible for protection of **h**uman **g**enetic **r**esources (HGR) through the regulation of the collection and use of any source of genetic material such as cells, blood specimen, etc., as well as information or data relating to such material.
- **All clinical trials that involve collection and usage of human biospecimens, including uses unrelated to genetics, must be approved by HGRAC.**
  - HGRAC must approve laboratories planned to be used to analyze samples from each study
    - Approval is needed regardless of whether labs are in or outside of China
      - HGRAC must approve export of samples if analysis is planned to be outside of China
- Regulations in effect since 1998, recently updated and strengthened in mid-2019

China Inspection and Quarantine (CIQ)

- Approval needed for export and import of samples/materials
- New regulations require Lead Investigator to apply for export approval and inspection

Study Approval Steps

- Clinical Trial Authorization – NMPA
- HGRAC Approval(s)
  - Initial application
    - Identify laboratories to be used for non-exploratory analyses
      - Provide rationale if sample exportation is requested
  - Supplementary application
    - Identify laboratories to be used for exploratory analyses
      - Intellectual property and data sharing considerations are associated with exploratory analyses
  - HGRAC Shipment export application
    - If exportation is approved in initial application, a separate application must be submitted when each shipment is ready for export
- CIQ application
  - A recent policy change requires this to be submitted by lead investigator to local CIQ office prior to each shipment but after receipt of HGRAC shipment export approval; formerly central lab could file application. Triggers customs inspection at lead investigator site.

Study Objective/Endpoint Considerations

- Primary, Secondary, Tertiary Objectives/Endpoints
  - Require data sharing with clinical investigators in China
  - Included in primary HGRAC application
- Exploratory Objectives/Endpoints
  - Require data and intellectual property sharing with clinical investigators in China
  - Require a supplementary HGRAC application
- Samples for Future Biomedical Research should not be included
- Sample disposal timelines should be defined – 1 to 2 years after analysis complete

Including PK or Immunogenicity Assessment as an Exploratory Endpoint Adds a Layer of Complexity to the China Study Approval Process

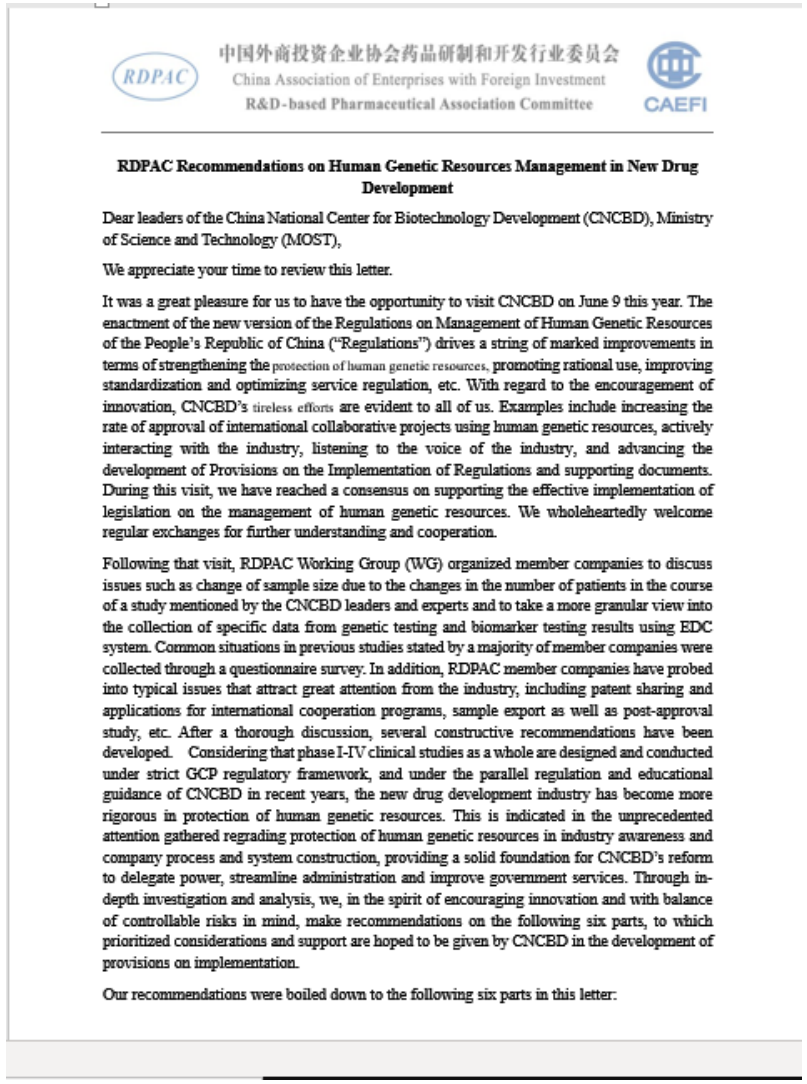
Current State of Bioanalytical Support for China Studies

- Prior to 2019, in many cases, justification for sample exportation was accepted
- New HGRAC regulations implemented in 2019 have led to an increased rate of rejections for requests to export samples for bioanalysis
- In response to the COVID pandemic, to our knowledge very few sample export requests have been approved since early 2020
- Changes in CIQ regulations that require primary investigator to apply for export and undergo inspection have added to export challenges
- As a result, at least for the present, the majority of PK and ADA samples collected in China need to be analyzed in China

Working to Drive Change
Pharma - China Regulatory Interactions

- RDPAC
  - Under the China Association of Enterprises with Foreign Investment (CAEFI), the R&D-based Pharmaceutical Association Committee (RDPAC) is a non-profit organization made up of 45 member companies with pharmaceutical R&D capability.
  - Partners with PhRMA and EFPIA

Recent HGRAC/RDPAC Interaction



中国外商投资企业协会药品研制和开发行业委员会
China Association of Enterprises with Foreign Investment
R&D-based Pharmaceutical Association Committee

RDPAC Recommendations on Human Genetic Resources Management in New Drug Development

Dear leaders of the China National Center for Biotechnology Development (CNCBD), Ministry of Science and Technology (MOST),

We appreciate your time to review this letter.

It was a great pleasure for us to have the opportunity to visit CNCBD on June 9 this year. The enactment of the new version of the Regulations on Management of Human Genetic Resources of the People's Republic of China ("Regulations") drives a string of marked improvements in terms of strengthening the protection of human genetic resources, promoting rational use, improving standardization and optimizing service regulation, etc. With regard to the encouragement of innovation, CNCBD's tireless efforts are evident to all of us. Examples include increasing the rate of approval of international collaborative projects using human genetic resources, actively interacting with the industry, listening to the voice of the industry, and advancing the development of Provisions on the Implementation of Regulations and supporting documents. During this visit, we have reached a consensus on supporting the effective implementation of legislation on the management of human genetic resources. We wholeheartedly welcome regular exchanges for further understanding and cooperation.

Following that visit, RDPAC Working Group (WG) organized member companies to discuss issues such as change of sample size due to the changes in the number of patients in the course of a study mentioned by the CNCBD leaders and experts and to take a more granular view into the collection of specific data from genetic testing and biomarker testing results using EDC system. Common situations in previous studies stated by a majority of member companies were collected through a questionnaire survey. In addition, RDPAC member companies have probed into typical issues that attract great attention from the industry, including patent sharing and applications for international cooperation programs, sample export as well as post-approval study, etc. After a thorough discussion, several constructive recommendations have been developed. Considering that phase I-IV clinical studies as a whole are designed and conducted under strict GCP regulatory framework, and under the parallel regulation and educational guidance of CNCBD in recent years, the new drug development industry has become more rigorous in protection of human genetic resources. This is indicated in the unprecedented attention gathered regrading protection of human genetic resources in industry awareness and company process and system construction, providing a solid foundation for CNCBD's reform to delegate power, streamline administration and improve government services. Through in-depth investigation and analysis, we, in the spirit of encouraging innovation and with balance of controllable risks in mind, make recommendations on the following six parts, to which prioritized considerations and support are hoped to be given by CNCBD in the development of provisions on implementation.

Our recommendations were boiled down to the following six parts in this letter:

中国外商投资企业协会药品研制和开发行业委员会
China Association of Enterprises with Foreign Investment
R&D-based Pharmaceutical Association Committee

Part V: Recommendations on sample export applications

- **Recommendation 1**: Under the existing regulatory policies, the application for studies that require exportation of biological samples are subject to stringent review and approval process, which may lead to delays or rejection of approval affecting China's participation in global simultaneous R&D. Specifically, the early stage studies on these new products are conducted for the purpose of research methodology, during which the uncertainties affecting method transfer are rather complicated compared with that in late-stage clinical trials, and the judgment of test results may lead to negative impact on the treatment effects in patients due to methodological bias among different laboratories. Therefore, it is suggested that CNCBD relax the requirements for review and approval of outbound samples in early stage studies, thus to speed up China's participation in global simultaneous early stage studies and deliver tangible results to Chinese patients.
- **Recommendation 2**: The application for outbound biological samples usually takes longer time due to the cumbersome and complicated review and approval processes currently in effect. As a result, the data generated from Chinese patients may fail to be included in the final data analysis report, and it may ultimately be a drag on the final registration results. CNCBD is recommended to complete submission and review of all sample batches and specifics of the study that require exportation in the initial exportation application, and the subsequent outbound batches, if falling within this scope, will only be required to submit a note for record-filing upon exportation application, which is expected to streamline and expedite the exportation review and approval process.

Recent Industry Experiences

- American Assoc. for Pharmaceutical Sciences (AAPS) has established a discussion group to share experiences regarding bioanalytical support for China studies
  - Monthly Webex meetings
  - Representatives from over 20 organizations participate
    - Primarily US Pharma and CROs
- Over the last few months two companies have shared that they have been able to obtain HGRAC export approval for samples from clinical studies conducted in China
  - Genentech
  - Sanofi – indicated that these were samples for immunogenicity assay and basis for export request was difficultly associated with cross validation of ADA assays and the generally accepted position that all ADA assays from a study should be conducted in the same lab
    - Willingness of PI to work with sponsor for CIQ application/inspection

Options for Support of Global Studies with a China Cohort

- Attempt to get HGRAC to approve export of samples
  - Pro: Eliminates need for cross validation and ensures consistent results
  - Con: Low probability of success
- Analyze all samples in China
  - Pro: Eliminates need for cross validation
  - Con: Import challenges for ex-China samples – example: COVID testing
  - Con: May be challenging or impossible to get ex-China samples out of China once analyzed
- Utilize separate labs for China and ex-China cohorts
  - Pro: Highest probability for HGRAC approval
  - Con: Cross validation of assays required

The Bioanalytical Laboratory Landscape in China

- Prior to 2015, a large percentage of BA work in China was conducted by academic institutions
  - Bioanalytical support bundled by investigators with clinical study conduct
- In 2015, China instituted a self-assessment program that mandated that sponsors assess studies that they submitted for compliance to regulatory expectations
  - Implemented prior to an enhanced inspection program
    - Serious issues identified during regulatory inspection would disqualify sponsor from future submissions for multiple years
- Led to shift in bioanalytical landscape toward “commercial” BA labs
  - Some of these are part of multinational organizations

Assay Validation and Study Audit Considerations

- Methods (PK/Immunogenicity) to support China studies should be validated in accordance with global BMV guidances
  - China specific guidances are largely in line with EMA/FDA guidances
    - ICH M10, once implemented, will result in completely consistent guidance for PK type assays
- Audits
  - Audit of China Studies by NMPA is common, and should be anticipated
  - Audit is typically end to end
    - Clinical site/sample collection
    - Bioanalytical lab – usually a focus on chain of custody of samples
    - PK calculations
      - Unique to China audits – need to reproduce PK calculations in the presence of the auditor
        - Report modeling efforts separately from the CSR
  - Consider audit experience when selecting a China BA lab

Regulatory Guidance Regarding PK Assay Cross-Validation

- US FDA 2018 Guidance
  - Cross validation is a comparison of validation parameters of two or more bioanalytical methods or techniques that are used to generate data within the same study or across different studies. Also, **cross validation is necessary when sample analyses within a single study are conducted at more than one site or more than one laboratory.**
- 2011 EMA Guidance
  - Where data are obtained from different methods within and across studies or when data are obtained **within a study from different laboratories, applying the same method, comparison of those data is needed and a cross validation of the applied analytical methods should be carried out.**

Cross-Validation for Immunogenicity Assays

- US FDA Immunogenicity Guidance
  - Reproducibility is an important consideration if an assay will be run by two or more independent laboratories during a study, and a sponsor should establish the comparability of the data produced by each laboratory.
- NMPA Immunogenicity Guidance
  - If samples will be tested by two or more independent laboratories during the study, reproducibility is an important consideration, and the comparability of data generated by different laboratories should be ensured. Comparable method performance should be established between laboratories, including cut-off value, sensitivity, drug tolerance, and precision.

Cross-Validation Considerations

- Scenario 1: The only subjects in the study are from China
  - If assay used outside of China can be established within China, a cross-validation may not be required
    - Recommended that China lab conduct and document full assay validation
    - Need for cross-validation issue driven and assessed by sponsor
  - If assay used in China is different from that used to support ex-China studies, cross-validation is required
- Scenario 2: Global study with separate labs supporting China and ex-China work
  - Cross-validation required

If Cross Validation Fails or is not Possible, the Ability to Aggregate China Data with Ex-China Data from Global Studies may be Limited

PK Cross-Validation

- May be conducted with spiked and/or post-dose samples
  - Importing post-dose samples into China may be challenging due to COVID testing requirements
- Develop a priori data analysis plan/acceptance criteria
- Data analysis should include assessment of bias
  - Applying ISR criteria alone does not satisfy this requirement
    - Differentiate within lab from between lab variability by conducting replicate analyses over several days

Cross Validation for Immunogenicity Assays

- Cross-validation of Immunogenicity assays is not explicitly covered in regulatory guidance
  - Immunogenicity assays typically use a “surrogate” as positive control
    - Testing samples spiked with surrogate may or may not yield results representative of patients’ samples
    - Ideally previously tested patient samples should be used to compare immunogenicity results between labs
      - Importation of patient samples into China may be logistically challenging especially in the COVID era
  - Immunogenicity assays utilize a cut-point to differentiate between positive and negative
    - Cut points are typically determined on a lab by lab basis and are set based on control matrix available at the lab
      - Cut points for the same assay may differ significantly between labs, hence impacting the immunogenicity rate generated at the different labs

Demonstration of Consistent Immunogenicity Results Between Labs May Be Challenging

What if Cross-Validation Fails

- Reports that HGRAC have been willing to re-consider export requests if cross-validation efforts fail
  - Data from cross-validation attempt needed to be provided

Closing Thoughts

- Support of bioanalytical work in China requires the navigation of a complex set of regulatory requirements.
- The current restrictions on sample export may require assay establishment in China to support analysis of samples collected from China subjects
- Global studies with China cohorts may require the use of multiple labs to support bioanalysis
  - triggering the need for assay cross-validation
- The bottom line, however, is that successful navigation of the process results in a win-win situation for China (new therapeutics become available) and Pharma (new markets).

Acknowledgements

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