Science For A Better Life

Bayer's experience in sample exportation from China

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September 2014, Berlin

Biosample Management at Bayer

Within Bayer, the department of Clinical Sciences is responsible for pharmacokinetic and biomarker analysis in clinical studies performed world-wide.

To support the study teams, Clinical Sciences has a Biosample Management department, in which the Biosample Operations Managers (BOM) take full responsibility for all operational aspects of pharmacokinetic and biomarker sampling.

This includes the import and export of sampling material and samples in and out all countries in which Bayer performs clinical studies.

Why sample exportation from China?

- To obtain approval for new medication in China, all pharmaceutical companies need to perform studies in Chinese subjects.
- Many methods for both PK as well as biomarker sample analysis for these projects have been established in non-Chinese countries.
- Especially for BM analysis, specialized BM analysis laboratories may not have a subsidiary in China.

What is the background?

Already in 1998 China has adopted a broad set of regulations on the collection and use of its 'human genetic resources' in an attempt to restrict their exploitation by foreign biotechnology and pharmaceutical companies.

Human genetic resources are defined as "any materials of and from human beings that contain human genome, genes or gene products, or parts thereof".

The regulations specify that, if genetic information is generated within collaboration between a Chinese research institution and a foreign organization, the profits from the resultant patents should be shared in proportion to the contribution of the two organizations involved.

The regulations are not supposed to act as a barrier.

What is the background?

Chinese Institutions are allowed to work with international companies but the following requirements need to be met:

- Any application for sharing of genetic data for research and development must include a clear purpose and direction within a scope of work, which defines the duration of the collaboration, its purpose and the source of the genetic material
- The application must also be carried out by groups, that are deemed able to conduct the relevant research, with intellectual property ownership and sharing arrangement clearly defined and deemed reasonable.

Definitions

1. Human Genetic Resource Management Office of the People Republic of China （HGRAC 遗传办）:

   Under the management of The Ministry of Science and Technology, responsible for the Genetic Resource Exportation approval.

   (Shanghai Health Bureau 上海市卫生局, Guangdong Science and Technology Department 广东省科技厅 also involved)

2. Master Approval （大批件）:

   The approval for the sample exportation by STUDY, only one per study.
   Submission for the master approval can only be done 4 times per year (Feb, May, Aug, Nov).

3. Sub Approval （小批件）:

   The approval for the sample exportation by BATCH. Could be several times per Master Approval, no maximum (within the total amount of samples applied).
   Submission for the sub approval can be done every month.

Frequent Asked Question

Is it possible to ship out the samples from a study to Europe/US?

There is no YES or NO

Because sample exportation in China is decided :

- Case by case
- Site by site
- Sample by sample
- PI by PI

But in General

- For PK plasma/serum/urine, the possibility to get approval is very high
- For biomarker plasma/serum and sputum, it's also possible and worth to try
- For biopsy/whole blood, it's very difficult with super high rejection rate
- For feces and BAL, the current experience is very limited

Sample Exportation in China

Bayer's timelines

General Procedure for Sample Exportation in China: **12-24 weeks**

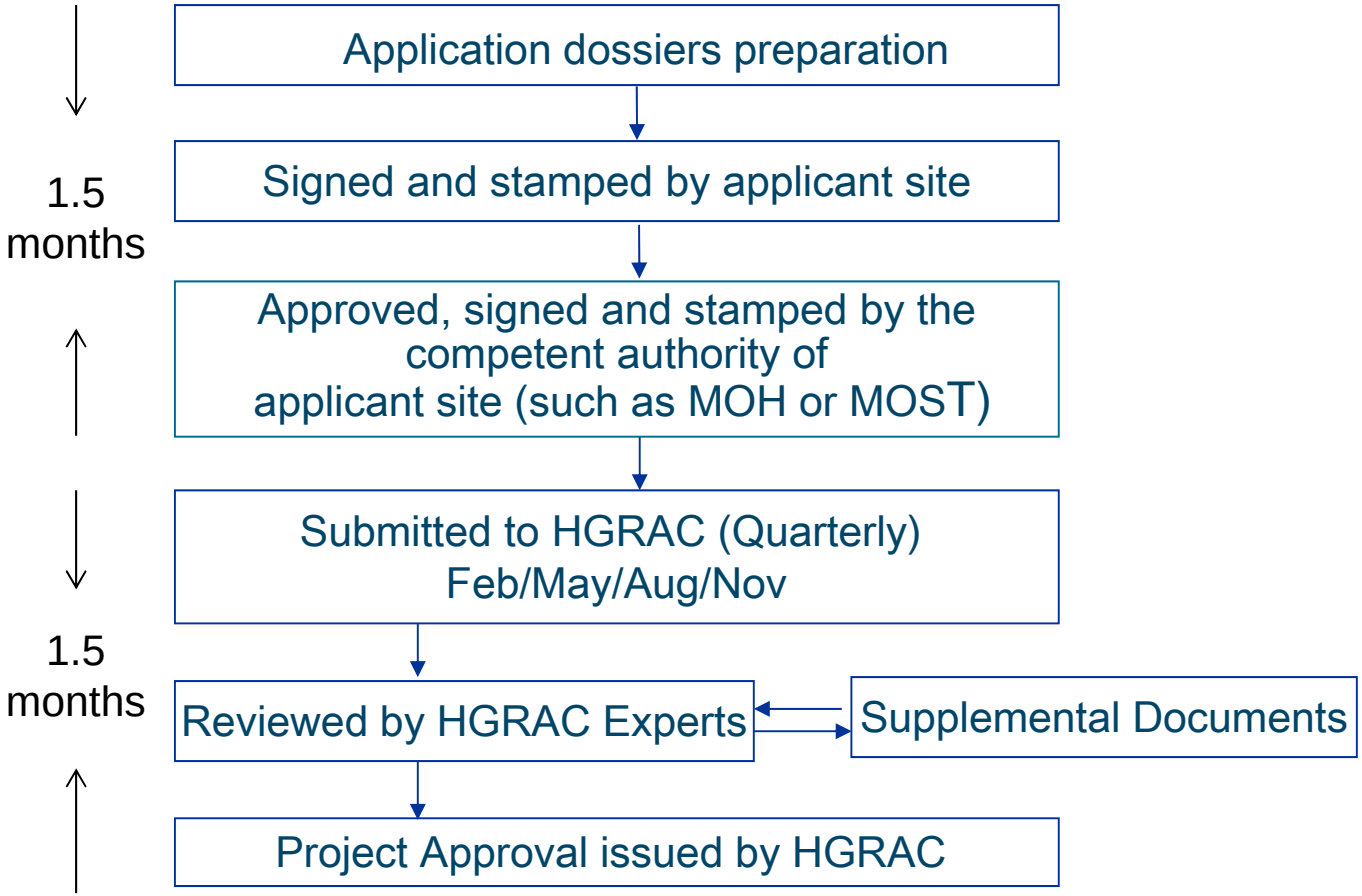
- Master approval can only be applied for 4 times per year (Feb, May, Aug, Nov)
- PK and non-genetic biomarker export application: low risk
- Separate application package for genetic biomarker samples, if possible
- Application package will be reviewed by Bayer China Sample Export Support Group

Current Issues in China

- Sample export regulations constantly changing (orally)
- Numbers of Hospitals or EC reject sample exportation for many reasons
- Application package is very complex with long review and approval timeline
- **No site contracts can be signed before approval of sample exportation.**
- High rejection possibility for genetic BM samples (biopsy, whole blood etc.).

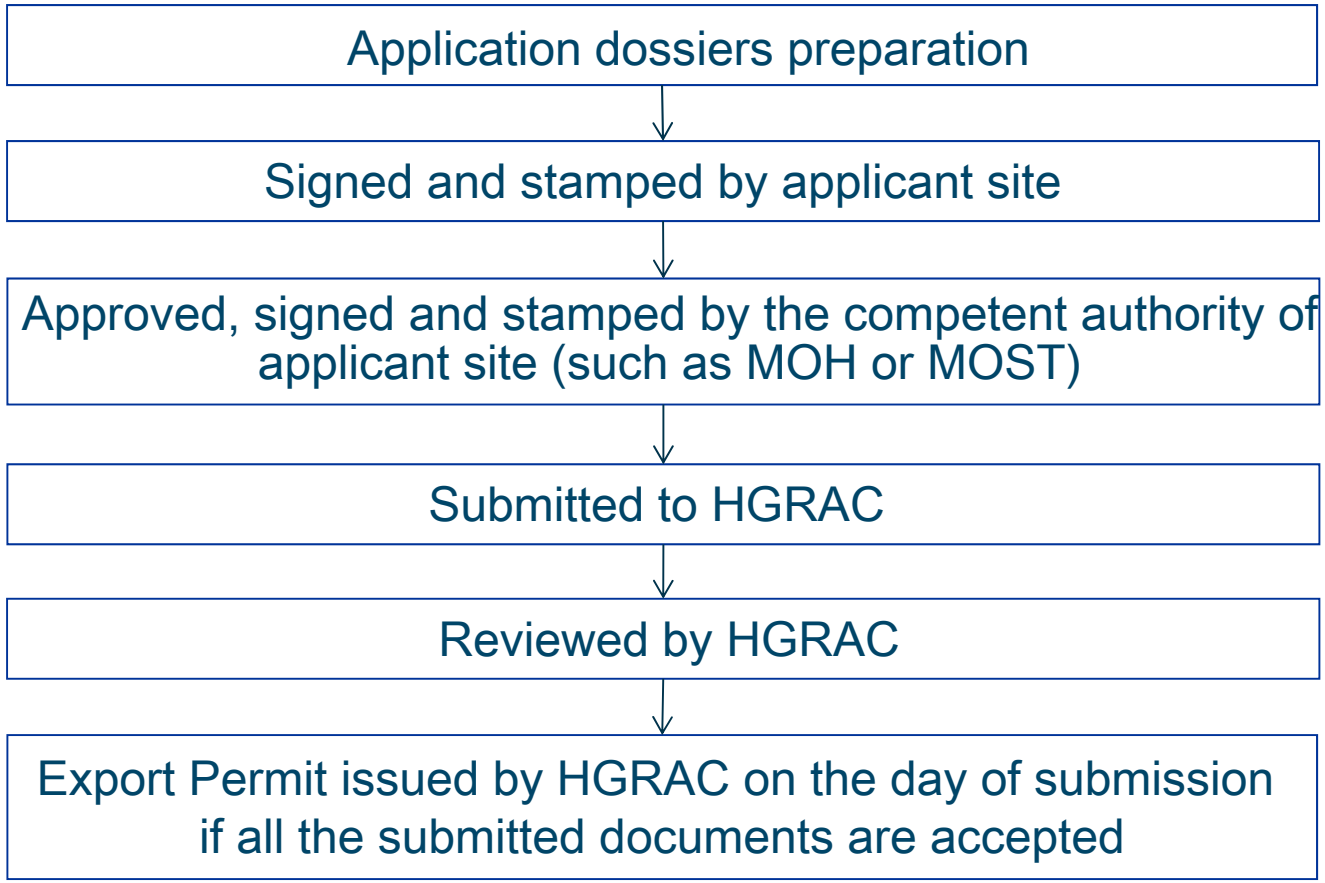
HGRAC Export Application Process

Master approval letter Application (best case)



HGRAC Export Application Process

Batch approval letter application for Export Permit



Master application document request list

1. **Application form**
   should be signed and stamped by applicant site & its competent authority
2. **Copy of signed Investigator Agreement between sponsor and applicant site** (Chinese & English version Investigator Agreement)
3. **Copy of signed Agreement between sponsor and foreign test lab**
   Chinese & English version
4. **Current version of Clinical Study Protocol**
5. **Clinical Trial Approval** issued by CFDA
6. **Copies of Ethics Committee approval letter** of all involved sites
7. **ICF Template** (explanation of sample export and copies of signature page for export application must be included)

New requirements since July this year

New requirements for dossiers preparation:

1. Contract (draft version) with sites is required in submission (previously signed version was required by HGRAC)
2. Contracts with all involved sites should be signed after HGRAC main project approval and need to be submitted to HGRAC when fetching the original approval letters.
   (Contract dates should be later than main project approval dates).
3. This requirement is for all new submission studies.
4. Other documents requirements are as the same as before.

Type of samples successfully approved

- Whole blood sample
- Serum
- Plasma
- Tissue
- Data (Fluorescence in situ hybridization [FISH] results)
- Deoxyribonucleic acid (DNA)
- Slides – Pleural fluid
- Blood cell pellets
- Urine

Unsuccessful case: example

中国人类遗传资源国际合作项目审批书

复旦大学附属肿瘤医院:

按照《人类遗传资源管理暂行办法》的有关规定，根据专家评审意见，经我办审核，不同意你单位申报的“服用　　的亚洲转移性结直肠癌患者的生物标志物分析”项目开展国际合作，原因如下:

1. 全血和肿瘤组织切片样品出境的理由不充分，相关检测和分析工作可在国内开展;

2. 拟出境样品数量的科学性和依据不明确;

3. 中方单位在该合作项目中的责任和权利不清楚;

4. 知识产权归属和分享的安排不合理。

Translation of rejection letter

1. The reason to export whole blood samples and tumor tissue out of China is insufficient, the testing and analysis can be conducted in China .
2. The theoretical and scientific basis of the quantity of exported samples is unclear
3. The work content, distribution and responsibilities of China collaborative institutes (site) are not clear .
4. Ownership and share of the intellectual property rights is not reasonable.

Bayer's strategy how to handle export applications

- China Sample Export Support Group (CSES)
  - The group will advise study teams on the China Sample Export Application Process and provide support. The export permit application process will continue to be led by the Monitoring group in China.
  - The group will meet at least 4 times per year ahead of the master Application Submission Deadline, to review applications to be submitted and provide comments. Teams should, in future, build this review timeline into their Sample Application Planning timelines.
  - The group will be responsible for ensuring any updates to the Export Application Process regulations are made available to study teams. This will take place through. the group SharePoint and via updates to the process by presentations.
  - The support process will be continuously reviewed and process updates will be made as applicable.
- The Biosample Operations Managers will keep a close contact with the CSES group concerning studies which are planned to have study sites in China.

SharePoint for Sample Exportation

Welcome to China Sample Export Support Team SharePoint

Exporting biomarker and pharmacokinetic samples from clinical studies out of China has been quite a challenge in the past years. This is further confounded by frequently changing sample export regulations which are difficult to adapt to.

It remains important for us to export these samples. As for instance, the comparability of bioanalytical results within a multinational clinical study is extremely important and the establishment of the bioanalytical methods in a Chinese CRO is expensive and time consuming.

Therefore, the China Sample Export Support (CSES) group has been established. The CSES group is China based and consists of:

- Cheng (Andy) Wang, Biosample Operations Manager (cheng.wang2@bayer.com)
- William Liu, Study Manager (william.liu@bayer.com)
- Julia Jiao, Clinical Trial support manager (julia.jiao@bayer.com)
- Shuang Zhou, Clinical Trial Administrator (shuang.zhou@bayer.com)
- Group Coordinator: Johanna Beekman, Head Biosample Management (johanna.beekman@bayer.com)

The CSES group will advise study teams on the China Sample Export Application Process and provide support. The export permit application process will continue to be led by the Site Management group in China.

The CSES group will meet at least 4 times per year ahead of the master Application Submission Deadline, to review applications to be submitted and provide comments. Teams should, in future, build this review timeline into their Sample Application Planning timelines.

The CSES group will be responsible for ensuring any updates to the Export Application Process regulations are made available to study teams. This will take place through the group SharePoint and via updates to the process by presentations.

The support process will be continuously reviewed and process updates will be made as applicable.

Tips for ICF

In order to protect patients personal information as much as we can, please kindly make sure the sentences below should be included in ICF

Chinese version: **然而，如果您决定参加**该项生物标记物研究，本患者须知**/知情同意的副本（有您的姓名而不是您的随机号）将会被提供**给药政部门来获取生**物**标记物样本出口的批件。

English version: However, if you decide to take part in the Biomarker Analysis, he/she will need to provide a copy of this form to the Authorities to obtain permission to send your samples abroad to be analysed. This form does not contain your randomization number.

Further tips

- CSES uses a sharepoint to inform all involved people on procedural changes
- The sharepoint contains template application forms, which contain pre-formulated text modules
- The sharepoint contains a frequently asked question section

Bayer Success Cases (since 2011)

Study number	Sample Type	Number of samples
Study 1	PK serum	1440
Study 2	PK plasma & PK serum	2100 and 1200
Study 3	PK serum	2800
Study 4	BM plasma & PK plasma	600 and 400
Study 5	PK plasma	130
Study 6	PK plasma	1920
Study 7	PK plasma	1000
Study 8	PK plasma	616
Study 9	PK plasma	500
Study 10	PK plasma	2880
Study 11	BM plasma & BM slide	2160 and 2160

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Thank you!