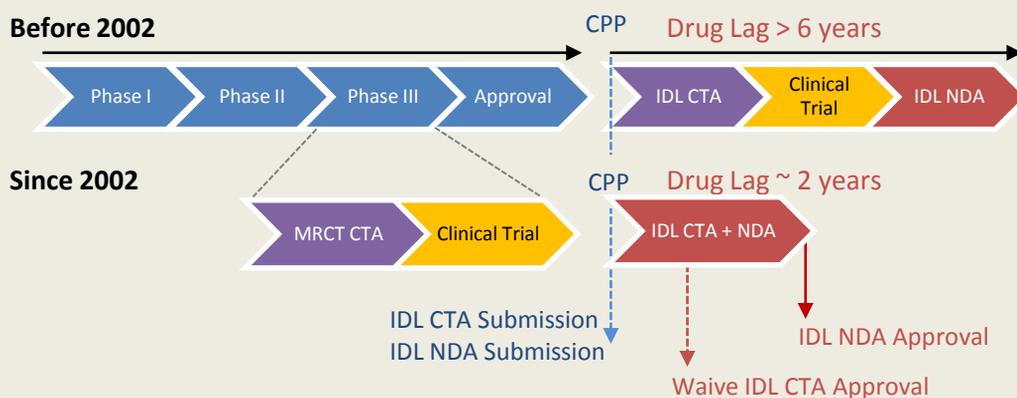


UNDERSTANDING THE DYNAMICS OF CHINA'S MEDICINE REGULATORY ENVIRONMENT

Key milestones of the Chinese regulatory process before and after 2002



Adapted from Scheeren J. 2014 *International Multi-Center Clinical Trial Challenges*. Presented at MRCT and GCP Inspection Workshop, Qingdao, China.

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Changes have occurred in the organisation and procedural activities of the China Food and Drug Administration (CFDA) and the Centre for Drug Evaluation (CDE). Initiatives that were designed to improve the transparency of interactions between the CDE and external stakeholders appear to have slowed and potential challenges to drug registration have emerged. Previously acceptable procedures appear to be changing or implemented in new ways, potentially confusing and adding delays to the regulatory process. Importantly, moves to improve this environment are underway.

The purposes of this briefing are to **assess** recent CFDA decisions for the use of clinical data from multiregional clinical trials (MRCTs) in China to support imported drug registration applications, **describe the challenges** that these changes pose through specific case studies and **identify opportunities** for timely medicines availability based on the experiences of other regulatory agencies that have faced similar challenges.

解析中国药品监管环境动态

- 2014年来, 国家食品药品监督管理局 (CFDA) 和总局药品审评中心 (CDE) 对跨国药企新药注册审批程序的改变, 影响了国际多中心临床试验 (MRCT) 的在中国的开展, 增长了新药获准上市总时间。
- 最近审批流程的变动, 已经造成了跨国企业新药获批的推迟, 以及/或在中国进行国际多中心临床试验(MRCT-CTAs)审批的延迟或失败。
- CDE/CFDA对国际多中心临床试验 (MRCT) 注册的申请, 以及将多中心临床数据用于在中国的临床和新药申请 (MRCT-backed IDL CTA+NDA) 的审批处理都已有所改变。CIRS (药政科学创新中心) 于2014年11月展开的调查表明, 以多中心临床数据用于注册的进口药物申报(MRCT-backed IDL CTA+NDA), 已经确认15例申请受到这次改变不同程度的负面影响, 其他34例申请也面临负面结果的可能。
- 申请国际多中心临床试验的漫长的排队时间 (大于5个月) 以及长时间的审评过程 (约12个月), 造成在外资企业在中国开展国际多中心力创试验的不确定性。监管部门近来实行积极措施, 比如增加注册费来支持人力资源以提高效率, 增加CDE任职人员 (目标为在2020年达到1200名) 等, 以求在未来2-3年间加快处理2013年12月前的积存申请。
- 现阶段国际多中心临床试验(MRCT-CTAs)的审批中值时间为11.5个月(6%的申请在六个月内批准, 4%的申请审批超过18个月)。
- 在接受CIRS调查的21家跨国药企中, 20家企业表示进口药物的验证性临床试验申请与上市申请 (IDL-CTA+NDA)的审评总时间有所增长, 并且大部分企业认为增长时长非常显著 (超过六个月); 在中国的新药上市注册 (NDA)的审评中值时间增长到约600天。
- 国际上曾面临同样问题的国家, 如加拿大 (漫长的申请排队时间), 韩国 (参与国际多中心临床试验的问题与挑战), 日本 (长时间审批时间), 都进行对药物审批程序进行了有效的改革, 成功的将本国病人纳入国际临床试验中, 带动了审批效率。
- 监管部门增加审批中心人力资源的措施, 以及加快处理积存申请的承诺, 都将对未来中国新药审批带来积极的影响。

本报告由以下机构撰写:

CIRS-药政科学创新中心, 是汤森路透旗下的一家位于英国的独立运营分支机构, 隶属于汤森路透知识产权与科技部。CIRS的使命是维护其在业界的权威领导地位, 运用科学方法优化推进药品监管与卫生技术评估 (HTA) 的政策与流程。CIRS 提供了一个国际化的中立的平台, 聚集制药公司, 药品监管部门, HTA 以及其他医疗保健中的利益相关者, 通过药政科学理念的创新运用, 支持多方互动和研讨, 促进药政法规和医保政策。该机构实行自主管理并有独立顾问委员会, 其资金来源于会员的会费, 相关活动费用和其他研发款项。它的运行和经营全部用于支持会员活动。

Understanding the Dynamics of China's Medicine Regulatory Environment

- Since 2014, changes have occurred in the organisation and procedural activities of the China Food and Drug Administration (CFDA) and the Centre for Drug Evaluation (CDE) impacting participation in multiregional clinical trials (MRCT), and increasing overall regulatory review times.
- Recent interpretation of the guidelines/regulation has resulted in regulatory delays and/or rejections of MRCT-CTAs (Clinical Trial Applications).
- MRCT protocols and clinical data provided as part of a MRCT-backed Import Drug License (IDL) CTA + NDA (New Drug Application) are being addressed differently by the CDE/CFDA. In a survey conducted during November 2014 by CIRS, 15 MRCT-backed IDL CTA + NDA applications were adversely affected by these changes; 34 other applications submitted prior to January 2014 by multinational companies are considered at high risk of being negatively impacted by these interpretive changes.
- The lengthy queue time (> 5 months) before the review of MRCT-CTA applications coupled with a long review time (approximately 12 months) has caused uncertainty about the timely inclusion of China in MRCTs. The agency has recently taken positive steps, for example by increasing resources (through the use of recently implemented increases in registration fees) as well as indicating their intention to increase CDE staff numbers to approximately 1,200 by 2020, in order to accelerate the review of the backlog of older (pre- December 2013) submissions over the next 2-3 years.
- The median time for an MRCT-CTA approval is 11.5 months (6% of applications approved in less than 6 months and 4% more than 18 months).
- 20/21 companies in the CIRS survey perceived that there has been an increase in review time for the IDL-CTA+NDA, with the majority believing that the process in China has become significantly longer (by more than 6 months); China has seen an increase in New Drug Application (NDA) approval times to a median of approximately 600 days.
- Other agencies faced with similar issues [Canada (long queue times), South Korea (MRCT inclusion challenges), Japan (long review times)], have effectively changed their procedures to overcome these challenges, to effectively integrate patients into global clinical trials and bring efficiency to their regulatory processes.
- The CFDA/CDE commitment to increase the internal staff along with their public commitment to reduce backlog have the potential for a positive effect on the dynamic Chinese regulatory environment.

This R&D Briefing was prepared by

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Growing investment in the Chinese pharmaceutical market

China’s fast-growing pharmaceutical market has become a significant growth driver for multinational companies, with spending to hit \$185 billion by 2018 according to *Bloomberg*. If this holds, China will become the second largest pharmaceutical market in the world, followed only by the US. Nevertheless, a number of issues around China’s regulatory procedures need to be addressed in order to decrease the drug lag of 4.5 years that Chinese patients currently face (Figure 1).

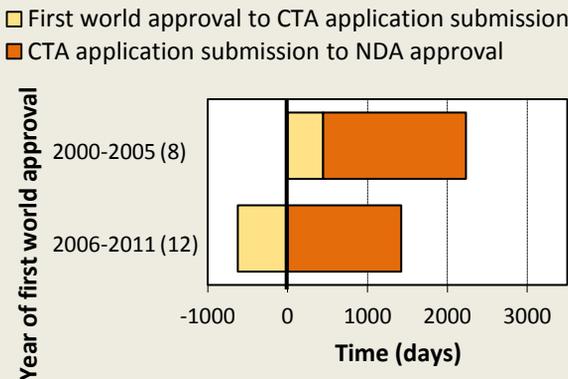
“Between 2007 and 2012, Chinese investments in biomedical R&D grew at a compound annual rate of 33%, compared with an average 7% in the rest of Asia-Pacific” – European Federation of Pharmaceutical Industries and Associations (EFPIA)

Figure 1: Median drug lag for new active substances (NASs) approved 2009-2013 in China (n1 = number of NASs, n2 = number of companies)



Inclusion of China in global clinical trials

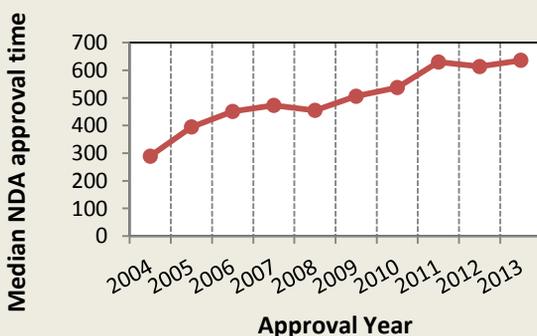
Figure 2: Median roll out times between key milestones from first world approval to drug approval of new active substances (NASs) in China, 2009-2013, by year of first world approval (n = number of NASs)



The time from first world approval to the submission of the Clinical Trial Application (CTA) in China decreased for multinational companies between 2009-2013, with companies starting clinical development in China about two years before their product’s first world approval (Figure 2).

This ability to include China in multi-regional clinical trials (MRCTs) along with the ability, prior to 2014, to obtain a MRCT-backed import drug licence (IDL) with a waiver for a local clinical trial had expedited patients’ access to new medicines.

Figure 3: Chinese NDA approval times; 3-year moving average, 2004-2013 (n=46)



However, the China FDA and its review division, CDE, are manpower constrained and the number of generic and new active substance (NAS) applications from domestic and multinational companies has been increasing. Consequently, **China has seen an increase in New Drug Application (NDA) approval times (Figure 3); for multinational company products this was a median of about 600 days (2013).**

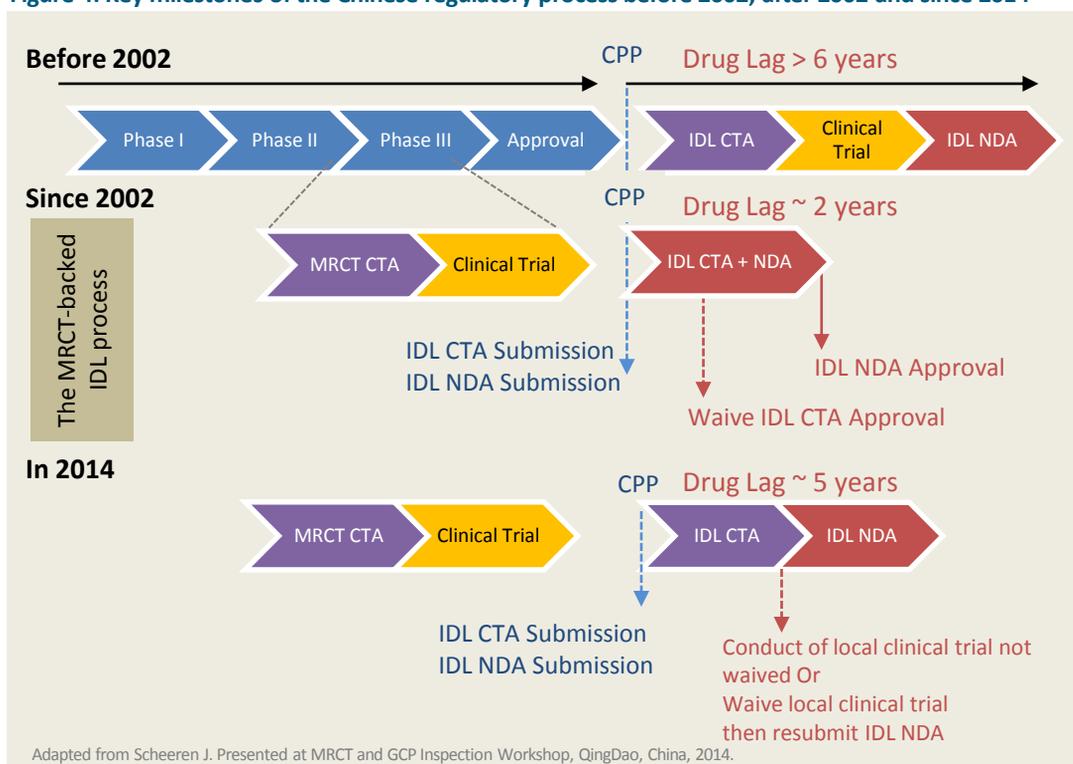
Changing environment in China's regulatory system

MRCTs (also known as international multi-center trials – IMCTs) were formally recognised by CFDA in the 2002 Drug Registration Regulation. Since 2002, the accepted practice was the waiver of a local clinical trial based on MRCT data, after submission of a combined IDL-CTA +NDA, followed by the seamless approval of the IDL-NDA. This practice changed in 2014 as the process was interpreted as deviating from the IDL procedure as set forth in the Drug Registration Regulation.

Consequences of regulatory interpretation changes

- Rejection of the MRCT-CTA and international clinical trial protocol, requiring the applicant to conduct a local registration trial
- Even where a clinical trial waiver has been granted, the applicant is required to resubmit into the IDL-NDA process queue, resulting in an approximate 5-year lag, although recent changes by CFDA have enabled applications made before Dec 2013 to benefit from a more rapid review.

Figure 4: Key milestones of the Chinese regulatory process before 2002, after 2002 and since 2014



CDE Workload

The CDE has been facing an increasing workload, having received 8,868 drug applications in 2014, up from 7,610 in 2013, according to the CDE annual report (*Medical Daily*). According to *Medical Daily*, at the end of 2014, China had more than 18,500 drugs awaiting approval. China has indicated its desire to reduce this backlog over the next 2-3 years. Furthermore, as presented at a recent DIA conference, the CDE have indicated a plan to increase staff to 1,200 by 2020.

Company Commentary: “CFDA is currently revising the Drug Administration Law and the Drug Registration Regulations, two key legislative instruments that govern the regulatory landscape in China. We hope that CFDA will use this opportunity to develop a modern, streamlined, science-based regulatory system that will allow China to be fully integrated into global clinical development, leading to (near-) simultaneous development and approval of new medicines.”

Understanding the impact of changes on multinational development and approval

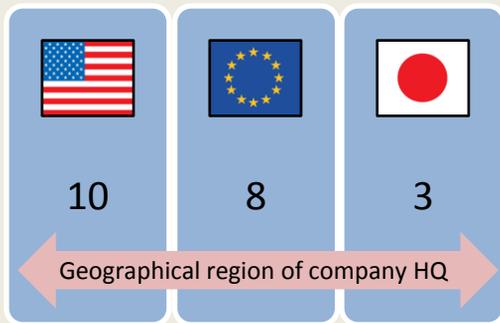
To better understand the real impact of changes in the regulatory environment on multinational companies operating in China, **CIRS conducted a survey in October/November 2014**. The purpose was to assess the implications of the recent CFDA procedural changes regarding the use of clinical data from MRCTs in China to support imported drug registration applications.

The survey was divided into three parts:

1. An assessment of the impact of recent procedural changes associated with the acceptance of MRCT data to support IDL registration (MRCT-backed IDL)
2. An evaluation of the impact of the review and approval of MRCT applications (MRCT-CTA)
3. Interviews with companies on their overall recent regulatory experiences in China

This briefing provides the key results from the survey and interviews

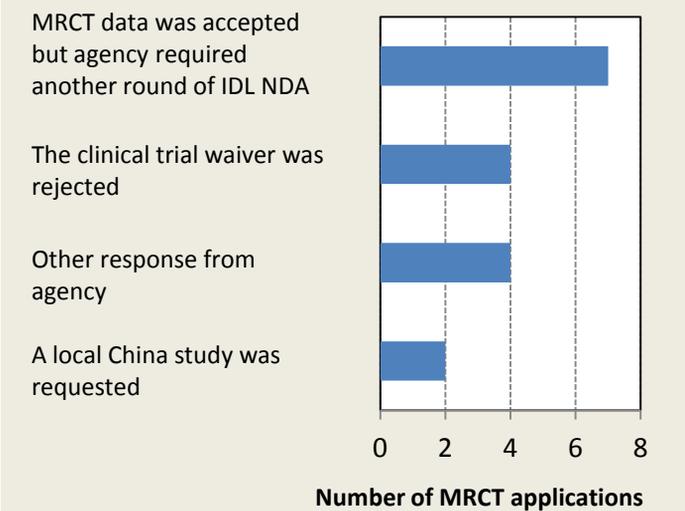
Figure 5: Survey response distribution by location of company headquarters (HQ)



- The survey was sent to the International Regulatory Affairs department of 33 multinational companies
- 21 had relevant activities in China and completed the questionnaire
- **20 of these companies were aware of recent procedural changes in the way that data from MRCTs that have been provided as part of a MRCT-backed IDL are being evaluated by the CDE/CFDA**

MRCTs provided as part of a MRCT-backed IDL are being evaluated differently by the CDE/CFDA.

Figure 6: Nature of CFDA responses for 15 applications affected by interpretive changes (through Nov 2014)



The acceptance of data derived from MRCTs appears to have changed from 2002; by 2014 the change in practice was reflected in the nature of responses to submissions provided by CDE.

15 MRCT-backed IDL applications from 8 companies were affected by Nov 2014. (Figure 6)

14 companies identified a further 34 applications submitted prior to January 2014 which are at high risk of being affected by recent interpretive changes.

The following case study is based on consolidated insights from interviews conducted with multinational companies

The IDL-CTA/IDL NDA coupled process: How the addition of an extra step to the process has amplified the queue burden and the drug lag in China.

Company experiences: The IDL-CTA/IDL-NDA process

- **Change in practice:** Prior to 2014, most companies received an opinion within 2 years, during which time they received a clinical trial waiver followed by the NDA approval without the need to resubmit the NDA. Recently, however, one multinational company submitted an IDL-CTA+NDA with MRCT data to support a request for waiver of a local clinical trial. The application was delayed in the queue and review process for approximately 2 years and although the company was granted the clinical trial waiver, the agency asked them to resubmit for the IDL-NDA, the dossier for which was returned to the start of the review queue.
- **Long queue and approval times:** Several companies have experienced a delay of 14 months or more in IDL-CTA review times.
- **This new approach to MRCT-CTA assessments has affected many companies in 2014:** Over the past year, 7 product approvals have been delayed by the addition of an extra submission and review step – the resubmission of the IDL-NDA following the granting of the clinical trial waiver upon the successful review of the IDL-CTA. Companies have indicated to CIRS that this new step (third step) will add approximately 2 years to the approval process.
- **Clinical trial waiver may be denied:** Following the IDL-CTA/IDL-NDA submission route provides no assurance or predictability that the results of data from a robust MRCT study will be acceptable to the agency and consequently, the request for a local clinical trial waiver may be denied. In this survey, 3 applicants had their waiver for a clinical trial turned down.
- **Returning dossiers to the start of the queue:** This new third step at the final IDL-NDA review is likely contributing to the review backlog, now estimated at 18,500 applications according to *Medical Daily*.

Implications

- There is an increasing backlog of applications with progressively longer queue times.
- The requirement to return an IDL-NDA submission to the start of the review queue following its review to support a waiver for a local clinical trial increases the backlog of applications and can add an additional 2 years to the approval process.
- Recent interpretation of the regulations has effectively turned the regulatory review into a 3-submission, 3-review-step process when including China as part of an MRCT (submission and approval of MRCT-CTA; submission and approval of IDL-CTA with waiver; returning into start of queue for the submission and approval of IDL-NDA), whereas prior to the changes it had been a 2-submission, 2-review-step process (submission and approval of MRCT-CTA; submission and approval of IDL-CTA+NDA with waiver). Furthermore, as presented at a recent DIA conference, China has recently addressed this challenge recommending that dossiers submitted before Dec 23, 2013 will not queue for the NDA review after having obtained an approval for the CTA; this will accelerate the overall review process.
- There is an increasing drug lag of new product availability in China.

Opportunities for the future

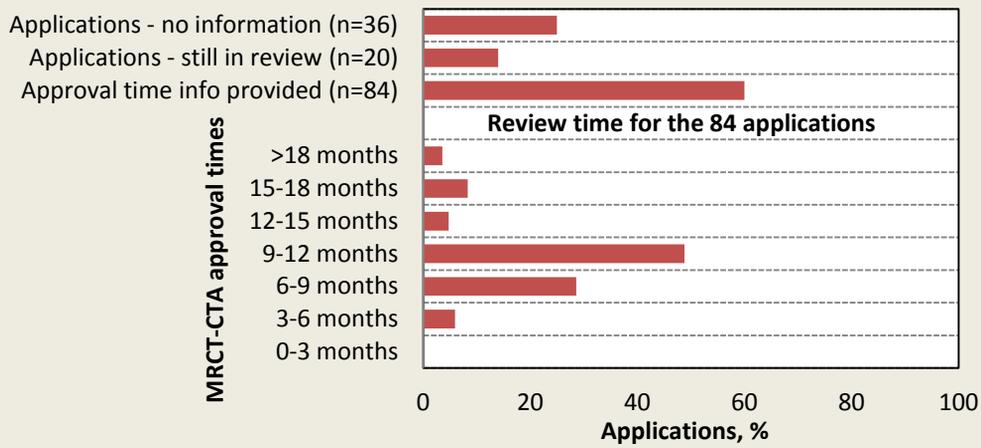
- Build clarity around the procedures by which MRCT data can be used to support a more streamlined regulatory process.
- Agencies have in the past undertaken proactive measures such as risk-based review strategies (Mexico), internal business transformation initiatives (Canada; see page 11) or overhaul of their approval process (Japan; see page 12) to reduce backlog of applications and ensure a timely approval processes and availability of new medicines.
- The Agency's commitment to increase the internal staff along with their public commitment to reduce backlog have the potential for a positive effect on the dynamic Chinese regulatory environment. Other agencies that have undertaken similar business transformation initiatives have also observed a positive effect on application backlog and approval time, although there is a time lag between implementation and observing the expected outcomes.

Changes in time taken to review MRCT-CTA applications

Survey respondents' experiences with regard to questions on MRCT-CTA applications:

- Within the past 24 months, 19 of the respondent companies have submitted an application to CFDA/CDE to seek permission to include China in a MRCT study (MRCT-CTA).
- In this survey, 140 MRCT-CTA applications were submitted, of which 84 (60%) had been approved.
- For these 84 MRCT-CTA applications, companies identified how long has the application had been under review .

Figure 7: MRCT-CTA applications from multinational companies and time taken in the review (n= number of MRCT-CTA applications)



The median time for an MRCT-CTA approval was 11.5 months (range: 6% of applications approved in less than 6 months and 4% more than 18 months).

Rejections and non-approvals of MRCT-CTAs

Within the past 12 months, 6 companies have received rejections/non-approvals for 12 MRCT-CTAs in China. The reasons for these rejection/non approvals were:

- The product's development was not at the phase II stage at the time the MRCT-CTA submission was made (n = 5)
- Lack of preclinical study data from juvenile animals (n = 2)
- Insufficient data (n = 2)
- Application - MRCT is not recommended for imported biosimilar (n = 1)
- Other – Paediatric indication, no information provided (n=2)

Impact on company strategy

Recent interpretation of the guidelines/regulation has resulted in the rejection of MRCT-CTAs. This change in practice coupled with the long CTA review time has consequences for companies that would like to include China in a global MRCT.

Company commentary: "Generally speaking, it's challenging registering products in China – a long and complex process of review, obstacles in obtaining a clinical trial waiver, inconsistencies in documentation requirements, inflexibility/ lack of understanding of administrative details that cause delay in submission and review of the IDL-NDA, and managing the changing of policies by CFDA."

The following case study is based on consolidated insights from interviews conducted with multinational companies.

Including China in global clinical trials: How the changes in interpretation of MRCT guidelines is resulting in inefficient integration of Chinese clinical experience in MRCTs.

Company experiences: The MRCT-CTA process

- **Change in practice:** A multinational company submitted the MRCT-CTA for a product for which the global phase II studies had not yet been initiated; however, the company expected the MRCT to be started by the time the MRCT-CTA was to be reviewed by CDE. The MRCT-CTA was rejected. Previously, the agency applied a broader interpretation of existing statutes, which, as long as the MRCT had been started in at least one jurisdiction, the MRCT-CTA review could proceed.
- **Delays in approval process.** In another case, the inclusion of China in the MRCT development programme for a novel oncology product has been jeopardised because the MRCT-CTA has been in queue with the agency for almost a year with no indication of whether the protocol is considered suitable by the agency.

Implications

- The lengthy queue time (> 5 months) before the review of MRCT-CTA application coupled with a long review time (approximately 12 months) causes uncertainty about the timely inclusion of China in MRCTs.
- If the MRCT-CTA protocol is not accepted, multinationals need to undertake local Chinese registration trials in their development programme, a step that introduces potential duplication in scientific research, increases time to submission of the IDL-NDA, and may contribute to the growing drug lag in China.
- Recent procedural changes to the interpretation of Chinese regulations have altered practices at CDE/CFDA giving the perception that the agency is becoming more conservative with regard to accepting data from MRCTs as part of the IDL-CTA, thereby limiting the opportunity to waive the need for a local clinical study. Because the agency appears to be applying stricter criteria in approving MRCT-CTAs, companies will likely have less opportunity to use this route as part of their development plans in China.

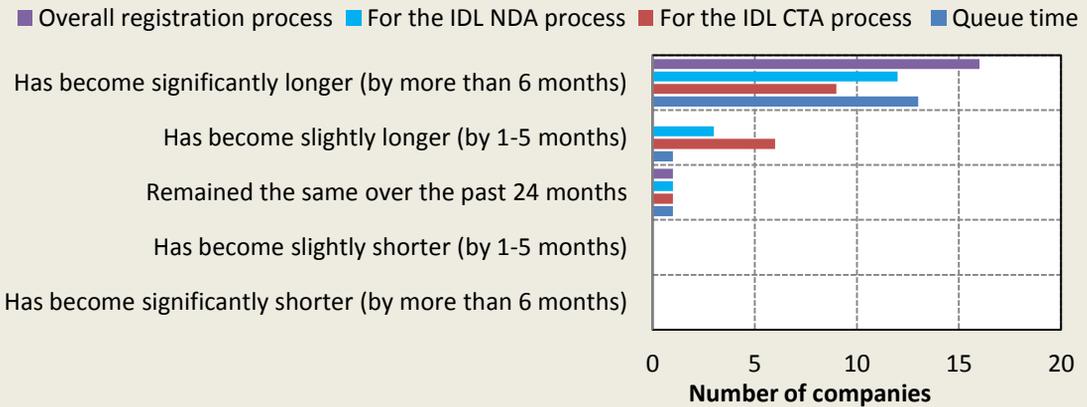
Opportunities for the future

- Under the new Guidelines for Multicentre Clinical Trials, sponsors are encouraged to include China in MRCTs to expedite development of new medicines. The utilisation of these guidelines can enable opportunities for China's timely participation in MRCTs.
- Better company-agency dialogue could encourage a more complete appreciation of the available clinical data from MRCTs.
- Therefore, to reduce uncertainty, two areas of focus are needed: an institutional drive to encourage participation in MRCTs and timely approvals of MRCT-CTAs.

Changing regulatory timelines

Multinational companies were asked for their opinion regarding their experiences with the Chinese regulatory agency over the past 24 months, in terms of how they would rate the time taken to have a new molecular entity progress through the IDL-CTA+NDA registration process (post-Certificate of Pharmaceutical product, provided sufficient clinical data in Chinese patients are available). Companies were also asked to comment on what they perceived as the main reason for changes in time taken.

Figure 8: Company responses on increasing IDL CTA+NDA timelines



20/21 companies perceived that there has been an increase in time, with the majority believing that the process in China has become significantly longer (by more than 6 months)

Figure 9: Rate limiters for regulatory approval in China

Rate limiter Key area	No. of responses
Queue time	9
Long CTA \NDA review timelines	9
New policy on IDL-CTA process	7
CPP requirements	4
Other:	
Quality testing	2
Agency queries	2
CDE resources	2

Company Commentary: “China’s drug lag has been described as 3-5 years over the last 10 years, and the recent MRCT policy shift extends it by 2 years, thus creating a drug lag of up to 7 years. Insufficient resources within CDE has been one root cause.”

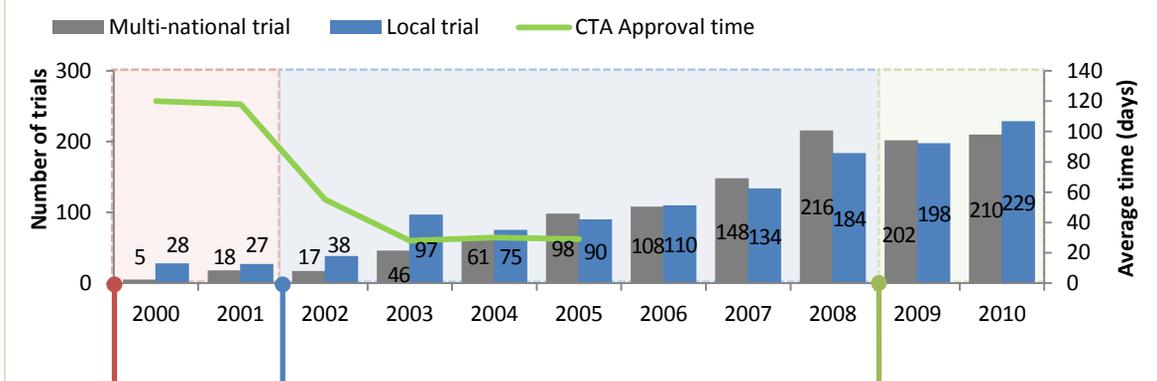
Figure 10: Regulatory challenges identified by companies in developing medicines for the Chinese market

Regulatory challenge	No. of responses
Lengthy queue/review times	12
Process requirement uncertainties including	5
Acceptability of global clinical trial data for registration	
Increased number of steps in the process - 3 submissions 3 approvals	
Lack of consistency, transparency and predictability within the process	4
Other	4
• Inefficient regulatory system for clinical trial applications that does not meet the needs of industry or academic applicants (domestic and non-domestic), is out of step with international norms	
• Differentiated local vs. imported drug category rather than new drug vs. generic drug development	
• Difficulty in inclusion of China in global phase II/III studies (global simultaneous development)	

Agencies can improve timelines by proactive internal action, as exemplified by South Korea

In order to facilitate early clinical development in South Korea, the government and the Korean FDA (KFDA; Ministry of Food and Drug Safety - MFDS) have facilitated legislative changes, notably the separation of CTA/NDA regulations and the reduction of CTA approval time, as well as changes to clinical trial coordination, which expanded the infrastructure for local and MRCTs and established South Korea as a global clinical trial hub.

Figure 11: The number of trials approved by the KFDA has rapidly grown due to various government strategies



Key issues

- Coupling of the CTA-NDA resulted in barriers to participation in MRCTs and exclusion of South Korea from many global development strategies.
- These procedural barriers were aggravated by deficiencies in the coordination of trials and training of study professionals.

Levers for change

- Adoption of the Bridging Study concept in line with the ICH E5 Guideline in 2001
- Revision of the Korean Good Clinical Practice (GCP) in 2002 in line with ICH GCP
- Regulatory changes that reduced target review time for CTAs to 30 days (formal law in 2009)
- Coordination of clinical trials through government initiatives such as the Korea National Enterprise for Clinical Trials (KoNECT) to promote creation of Regional study centres (15 by 2009), education of study professionals, and research into new facilitating technologies (e.g., IT, biomarkers)

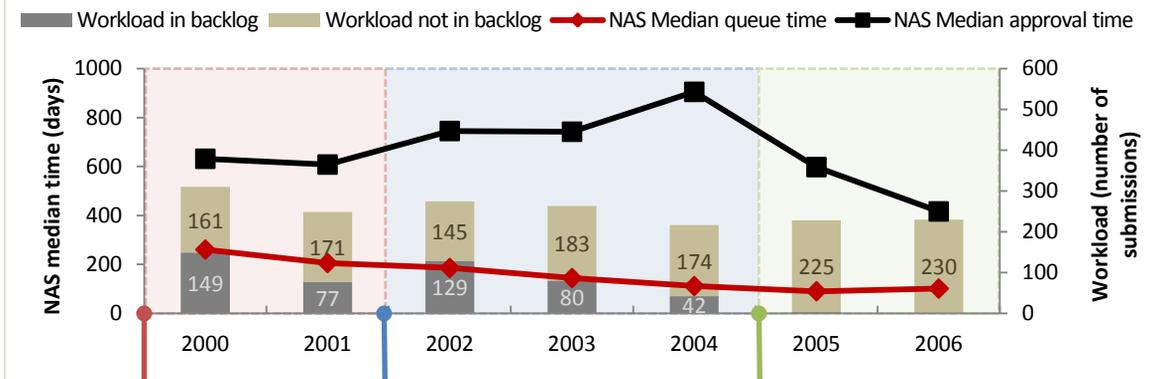
Outcomes

- Uncoupling of CTA-NDA and changes in the regulations of the CTA process have permitted Korean institutions to become more competitive in the clinical trial arena by participating in MRCTs during new drug development
- Government initiatives have enabled multinational pharmaceutical companies to include Korea in global development strategies
- The total number of studies conducted in Korea increased by over 10-fold in the past 10 years

Agencies can improve timelines by proactive internal action, as exemplified by Canada

Since the early 2000s, the Therapeutic Products Directorate under Health Canada undertook business transformations to decrease the backlog of applications that were exceeding the target approval time. These changes have enabled a more timely and predictable review process that meets industry and patient needs and meets statutory target times.

Figure 12: Introduction of a project management system lead to a reduction of backlog and queue time



Key issues

- Long approval times due to a backlog of applications held in a queue for 200 days after validation in order to wait for internal review resources to become available for assessment
- The agency wished to proactively address the anticipated increase in the number and complexity of filings starting in 2005

Levers for change

- Cooperation with agencies (EMA, FDA) to identify best practices and build trust in mutual recognition
- Participation in comparative agency benchmarking studies (Hirako et al, 2007) to identify process limitations
- Funding from the government and commitment to update the fee structure to address increasing resource needs
- Improvement of project and workload management approach (modelled on FDA and EMA)
 - Increased staff (project managers)
 - Proactive, team-based management of review process, submissions and pre-submission tasks
 - Emphasis on planning, internal and external communication and early interactions

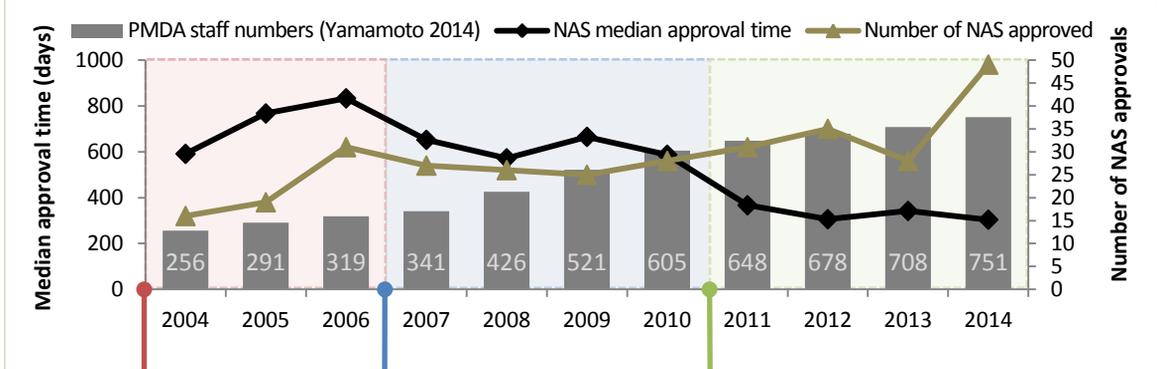
Outcomes

- A successful business transformation rendered the review process more predictable and sustainable.
- From April 2003 to March 2005, an 89% reduction in review backlog had been achieved for pharmaceutical submissions, and 99% of the backlog had been eliminated as of September 2005.
- There was a halving of queue time and overall NAS approval time from 2000 to 2006.

Agencies can improve timelines by proactive internal action, as exemplified by Japan

In 2004, the Japanese government proactively set up the PMDA to ensure the timely introduction of safe and effective NASs to improve therapy and contribute to a better quality of life. Subsequent changes to the PMDA organisation and learnings from external interactions have enabled it to decrease its drug lag and become a world-class agency with approval times on par with US FDA.

Figure 13: Increase in staff led to a decrease in NAS approval time whilst addressing rising approval numbers



Key issues

- An important agency with a small number of reviewers was facing an increasing workload.
- There was a drug lag between Japan and US/EU of approximately 2.5 years, due to long development times and long approval times for medicines including NASs

Levers for change

- Increased company dialogue and scientific advice during the pre-submission period
- Enhanced global cooperation and harmonisation with US FDA, EMA and Asian agencies to identify best practices
- Collaborations with academia and Japanese government
- Legislative changes through Revision of Pharmaceutical Affairs Law
- Organisational changes resulting in an increased number of reviewers with comprehensive training programme

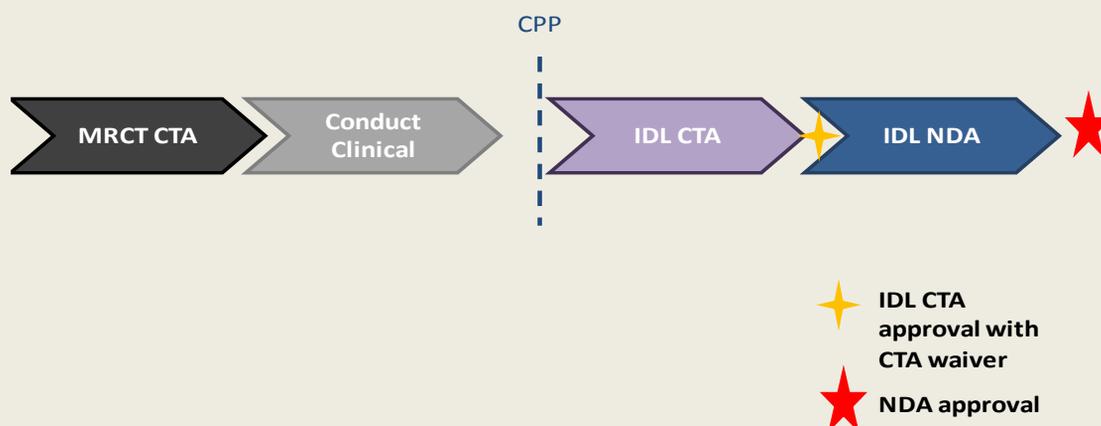
Outcomes

- There was a strengthening of the agency organisation in both size and quality (staff numbers tripled in 10 years).
- The approval times for NASs halved from 2010 to 2014, reducing the drug lag by about 1 year.
- The number of approved NASs increased by approximately 30% in the past decade.

NOTE: The gap between hiring of new staff in 2009 and the drop in approval times in 2011 was due to the fact that many new graduates with little experience were hired ("Joint Graduate School Program") requiring about 2 years of training.

- **Certificate of Pharmaceutical Product (CPP):** A certificate issued in the format recommended by the World Health Organization (WHO), which establishes the status of the pharmaceutical product
- **Import drugs licence (IDL):** drug marketing permit which is issued by State Food and Drug Administration (SFDA) or SDA of China. All the pharmaceuticals exported to China must obtain an IDL before being marketed in China
- **Multi-regional clinical trial (MRCT)** is a clinical trial simultaneously conducted for multiple geographical regions under the same trial protocol. It may also be referred to as international multi-center trial (IMCT).
- **New drug application (NDA):** vehicle through which drug sponsors formally propose to SFDA to approve a new pharmaceutical for sale and marketing
- **New molecular entity (NME):** A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans in China. The term also includes: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available; a biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation; a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product.
- **Clinical trial application (CTA):** dossier that includes all documentation pertaining to the conduct of clinical trial in China according to the regulation.

The following summarises the key milestones of the Chinese regulatory process.



- **First submission:** Sponsor submits for clinical trial waiver through the IDL CTA application
- **First approval:** CFDA can approve a waiver for a clinical trial (and investigational drug importation) based on existing legislations
- **Second submission:** IDL-NDA submission occurs in parallel
- **Second approval:** IDL-NDA approved

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