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# Clinical Trials In Asia


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The clinical development phase continues to represent the most challenging stage of drug development globally, critical to the successful commercialization of new products but posing multiple and complex considerations in terms of trial design, enrolment and outcomes.

Failure can prove costly and even critical to the survival of smaller companies heavily reliant on relatively few pipeline assets, not to mention the needs of patients awaiting access to ever more effective therapies.

It is thus crucial that companies get things right. Where do we perform trials to optimize speed and outcomes? Who should lead these? How do we ensure timings fit with our strategic plans and investor and patient expectations?

Against this background, this e-book looks at some of the key issues surrounding clinical development in the Asia region, highlighting a number of regulatory and policy changes that are influencing the operating environment. The one common thread that emerges is the pace and breadth of change.

China has made multiple revisions to requirements over the past few years designed largely to smooth and expedite clinical development, with the end objective of speeding up access to needed new therapies. Faster IND approvals and schemes to support orphan and rare disease drugs, along with more acceptance of foreign data are just some of the changes.

Japan meanwhile is looking towards increased cost-effectiveness assessment for selected drugs and how to incorporate real world evidence into the development process, for example by using this as a control to allow simplified single-arm trials.

South Korea's government has drawn up a wide-ranging road map to support and guide clinical development policies, as it looks to stay competitive with other rivals in Asia as a location for trials offering high-quality sites and relevant medical expertise.

In such a dynamic and challenging environment, partnering with organizations that can help ensure success across all aspects of clinical development can pay important dividends.

**Ian Haydock**
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# How To Run Successful Clinical Trials In Japan

There is no longer any excuse not to include Japan as an integral part of any global clinical-development program for either pharmaceuticals or medical devices. With a more receptive climate for both starting and running trials, an improved infrastructure for clinical research, and significant advances in accelerating drug approvals, Japan is now firmly on the global development map.

There have always been strong reasons to secure a foothold in Japan. It is the world's third-largest single pharmaceutical market after the US and China – or second-largest for prescription drugs – with a rapidly aging population (26.6% over 65 years old in 2016) increasing the demand for healthcare and medicines.

Other compelling reasons to always involve Japan in global drug development include: a mature local market; a renewing economy; the regulatory flexibility around Japanese data in global clinical-trial packages; an extensive, nationally-funded healthcare infrastructure with universal health insurance; a large and adherent patient population; and a strong emphasis on quality and precision in clinical research.

Japan's attractiveness for the inward investment proposition for the pharmaceutical sector has further increased in recent years as the Japanese regulatory authorities have made concerted efforts to align drug approval timelines with the US and Europe. The situation in Japan today is a far cry from before, when Japanese patients had access to new medicines five to ten years after their counterparts in the US or Europe.

More specifically, Japanese authorities have created new incentives including, but not limited to, priority- or conditional-approval programs for new medicines in areas of high unmet need such as orphan diseases. Additionally, the regulatory agency has removed some significant regulatory or bureaucratic obstacles for clinical trials, such as past reluctance to consider foreign study data and reliance on bridging studies over full participation in clinical development worldwide.

Nonetheless, the complexities of planning and running clinical trials in Japan can be daunting for

the uninitiated. Tapping into local expertise and resources that help non-nationals to navigate the regulatory hurdles, make the right connections and home in on eligible trial participants can ease the process.

## Regulatory And Operating Environment Changes

In a recent interview with Informa Pharma intelligence, Toru Fujieda, Hiroshi Yamada and Toshitaka Kawaratani, respectively President, Vice President and Head of the Consulting Division at CMIC Co., Ltd, a pioneering Tokyo-based contract research organization, highlighted how the regulatory and operating environment for clinical trials in Japan has markedly improved in the past decade.

Improvements include much shorter review times for new drug applications (NDAs). In 2007-08, for example, the average time taken to assess and approve a NDA in Japan was 1.5 to 3 years. In the US and Europe, the average drug-approval time was about two years. Now drugs are being approved in one year or less in Japan, setting a faster pace than both the FDA and the EMA, Kawaratani notes "The regulatory authority has recognized that in approval timings for product launches, we need to be competitive with other countries such as the US and European markets," he adds.

Along the way, the Japanese government and the Pharmaceutical and Medical Devices Agency (PMDA) have introduced incentives such as a 10-20% 'Japan-first' pricing premium for medicines developed locally in parallel with other major markets, or expedited approvals for rare-disease and other medically significant drugs.

Price premiums are available under the orphan drug designation, launched around three years ago and now applying to 20-25 projects annually. For truly innovative medicines, price premiums can range from 70-120%.

Special provisions were also created for the review and approval of gene and cell therapies in Japan. The Sakigake pathway for breakthrough and regenerative medicines includes substantial regulatory and scientific support for development plans, rolling NDA submissions and an accelerated review period.

Aggressive recruitment and training strategies were introduced at the PMDA, nearly doubling its review staff. In addition, Kawaratani points out, the agency has adopted a more consultative approach in its relations with the pharmaceutical industry. Both the frequency and quality of communications have improved in both directions, as the PMDA commits determinedly to a strategy of innovation. That includes closer communications with regulatory counterparts overseas, such as the FDA and the EMA, as well as more global alignment through the International Conference on Harmonization (ICH).

## More Flexible Conditions For Clinical Trials

The PMDA's innovative stance has created more flexible conditions for Japanese clinical trials. Rather than asking routinely for large studies in the local population, the PMDA now requires data from only a certain proportion (and sometimes a limited number) of Japanese patients to confirm drug efficacy and safety.

PMDA's increased recourse to term-restricted conditional approvals, supplemented by real-world data post-launch, for innovative medicines in areas of high unmet need is also helping to cut clinical development times.

With the liberalization throughout the drug development and registration process, "many global ventures now want to come into the market to aim for the first launch in Japan", Kawaratani says. That aligns very much with Japan's interest in promoting itself as a viable destination for global clinical trials.

Over the last 10 years there has been a growing trend for programs either to include Japanese sites in their trial protocols or to incorporate bridging studies from Asian countries such as Korea and/or Taiwan. As a result, 50-60% of clinical trials now conducted in Japan are associated with global programs.

## Scheduling Clinical Trials In Japan

In parallel, clinical trial start-up times in Japan have improved significantly. "Around 10 years ago it took around five or six months for site initiation," Yamada mentions. "The current situation in Japan is that it takes three or four months on average."

More efficient study initiation reflects the availability of an extensive infrastructure for clinical trials. "Many public or university hospitals have a very good system in place for clinical trials," Fujieda points out. "It's very easy to conduct trials nowadays." Government efforts to promote a better co-ordinated clinical-trial environment through hubs and networks have further underpinned the infrastructure.

Better resourcing for local trials has also made an impact. Many investigator sites can now call on clinical research coordinators (CRCs) with a full range of capabilities to support trial initiation and implementation.

CMIC launched not only Japan's first CRO but also its first site management organisation (SMO). The group's in-house SMO, Site Support Institute, has partnerships with medical institutes and university hospitals extending from Hokkaido to Okinawa, the northernmost region to the southernmost region of Japan. This extensive geographic coverage enables local CRCs to have an important part in identifying both the right sites and the right patients for specific trials.

With the liberalisation throughout the drug development and registration process, "many global ventures now want to come into the market to aim for the first launch in Japan", Kawaratani says.

Joint ethics-committee reviews for smaller local trial sites are also well established. In the past, one of the hurdles to getting clinical trials up and running in Japan was the need for most sites to have their own institutional review board.

"The time needed for selection and screening [study participants], everything is running more smoothly than 10 years ago," Kawaratani notes.

## GCP Harmonization And SOPs

Touching all bases from first patient in to last patient out, the mechanisms and provisions for running clinical trials in Japan are increasingly harmonized with global standards, Kawaratani emphasizes.

That also goes for Good Clinical Practice (GCP). Despite legislation bringing the country into line with ICH GCP standards in 1997, Japan's rigorous and conservative application had traditionally been a disincentive to clinical-trial notifications. Additionally, other areas of difficulty included the obtainment of informed consent from trial participants who culturally tend to defer to medical professionals and may not welcome a full discussion of their condition with a clinical investigator; and the requirement for chief investigators at each study site to personally supervise financial arrangements and all other aspects of trial conduct. Now, information-

sharing and communications with site heads are more fluid and systematic and so are speeding up clinical research approval and monitoring procedures.

Very often global CROs operating in Japan use their own SOPs when applying GCP to clinical trials. CMIC has no problem conducting trials in accordance with ICH GCP, but CMIC can also use client's SOPs.Clinical research associates (CRAs) working for CMIC are well trained in both the CRO's standard operating procedures and those of its clients.

## Investigator, Patient Commitment To Clinical Trials

While 10-20 years ago hospitals were often reluctant to get involved in clinical trials owing to the perceived administrative and other burdens, with little prestige attached to clinical research among healthcare professionals and academics, and a paucity of financial or other incentives, to act as clinical investigators, that has now changed, according to Fujieda. Today, with a stream of cutting-edge therapies emerging from research and development pipelines in key areas such as oncology, physicians are more motivated to participate as a means to widen patient access to new medicines.

Despite the availability of universal healthcare coverage in Japan, a similar rationale also drives patient interest in clinical trials, particularly with non-responders to existing therapies for cancer or other critical conditions. Transportation-fee support for clinical-trial site visits, and the opportunity for detailed consultations with physicians as well as access to new treatments, may also encourage patient involvement.

Moreover, the cultural deference to healthcare professionals makes these patients more likely than their counterparts in other countries to adhere strictly to study protocols.

## Managing Clinical Trial Costs

One disadvantage to running trials in Japan could be that costs tend to be higher than in other markets, a disparity blamed on various factors such as slow patient recruitment, the necessity for face-to-face communication between the investigators and CRCs, or the complexity of study payment systems.

Site costs can be high, with each trial site employing its own fee system and calculations for different trial components such as principal investigators, clinical research coordinators or indirect costs.

Fee negotiations need to be conducted with site staff, rather than principal investigators as in other markets. While some clinical-trial costs are covered by national health insurance, the sponsor is held responsible for other costs (e.g., laboratory tests, imaging, comparator drugs).

While CMIC tries to keep costs down, they can be complicated by the trend of client requirements such as 100% verification of all source data in Japan. On the upside, this attention to detail pays off in terms of the data quality, given the highly professional attitude of investigators in Japan and their patients' seriousness about following study protocols and reporting requirements to the letter.

Companies bringing clinical trials to Japan can also take advantage of the PMDA's increased openness to data from comparable Asian countries, such as South Korea, Taiwan and Singapore to recommend Asian trials including the Japanese population. They can leverage these other markets to generate an Asia data package that balances the higher costs of running trials in Japan, when US/EU trials are completed in advance.

Usually, these combined packages depend on protocol design and drug indication of interest, Yamada notes. Clinical-trial sites in other Asian

countries must also be 100% GCP-compliant, as the PMDA will directly audit sites abroad where necessary.

At the same time, regulatory conditions still require some level of Phase I, II or III data to account for potential variations in the Japanese population, with pharmacokinetic data depending on the specific compound and indication. This proportion is currently around 15%, depending on the indication and protocol design.

Moreover, the PMDA no longer recommends bridging studies as a means of accessing the Japanese market. It would rather see global clinical trials that take in the Japanese population.

## Overcoming Drug Lag

Most pharmaceutical multinationals start their global trial programs in either the US or Europe and will wait until Phase II studies are started in those markets before initiating Phase I development in Japan. However, some global giants and Japanese companies, developing medicines globally, do start with clinical trials in Japan. As Yamada points out, global clinical trials still tend to be slow at adding Japanese patients to the global program, due to the higher cost of running studies in Japan as well as traditional barriers such as unfamiliarity with Japanese language, culture or clinical-trial processes.

There are exceptions, nonetheless: companies may be encouraged to start global trials in the Japanese population.in indications, such as gastric cancer, which are a high unmet need. Accelerated-approval provisions for oncology therapies may provide further leverage.

Japan's greater reliance on surrogate endpoints as a basis for drug approvals in some conditions is potentially attractive. In diabetes mellitus, for example, the primary endpoint is reduction in glucose levels or HbA1c (glycated haemoglobin) rather than broader outcomes such as death rates.

## Finding The Right Patients

While patients are available and willing to enrol in clinical trials in Japan, it can be difficult making people aware of opportunities to participate and finding exactly the right patient cohort for a particular study.

As Akihisa Mitake, President of CMIC's Site Support Institute Co., Ltd., and Shinichi Keino, President of CMIC Healthcare Co., Ltd., noted in a separate interview with Informa Pharma Intelligence, in the 10 year plus the CMIC group has been involved in patient recruitment,, approaches to enrolling patients have evolved in line with the shift in the marketplace and companies' research and development pipelines from chronic diseases towards more complex conditions such as rare diseases, difficult-to-treat cancers or central nervous-system (CNS) disorders.

This shift has boosted demand for specialist patient recruitment organisations (PROs) and more targeted recruitment strategies away from traditional reliance on print media or the internet. These strategies may be hampered by the difficulty of obtaining detailed information on relevant trials from public websites such as ClinicalTrials.gov.

"Even if they find the right information, they cannot directly access the clinical-trial sites for more information," Keino comments. Moreover, participating study sites may be reluctant to disclose details such as the names of hospitals involved in a trial.

Against this backdrop, CMIC is developing new initiatives tailored to patient recruitment in the fast-growing oncology market. These include setting up an online portal for cancer trials that would act as a go-between by screening eligible patients and referring them to trial sites.

CMIC is also working with ReasonWhy Inc., an internet-based company offering second opinions on medical diagnoses through a system called Findme, on disseminating oncology-trial information to patients.

Another initiative involves partnering with life assurance companies enabling CMIC to provide information on available clinical trials to newly diagnosed cancer patients. Emphasis is on having a flexible approach to patient recruitment and a customized alternative to one-size-fits-all strategies, where the primary focus is on trial registration panels, Keino explains.

Recruitment techniques can be modified according to age, gender and target disease. For example, an analog approach may still be suitable and effective for older people unfamiliar with, or little interested in, digital media.

In the absence of a Japanese subsidiary able to conduct clinical trials under local GCP requirements, such companies must appoint an in-country clinical caretaker (ICCC) that can jointly assume their legal, regulatory and operational obligations.

## Partnerships For Patient Recruitment

CMIC's strength in having patient recruitment as a group function lies in its broad range of partnerships, which also includes pharmacies, companies that process prescription receipts, organizations providing regular medical check-ups, and nursing-care specialists. All of these are potential channels of communication with patients who may wish to take part in clinical trials.

Medical- and prescription-claims databases provide another means of identifying eligible patient pools through recorded prescriptions and diagnoses, or of assessing site feasibility for clinical studies.

In-market specialists such as CMIC can also help a study run smoothly by taking a meticulous approach to patient awareness and informed consent, or ensuring that any devices used in a trial, such as electronic patient diaries, are user-friendly and fully connected.

As Mitake observes, Japanese people expect their devices to work, and something as simple as using foreign batteries with the wrong voltage for Japan can undermine confidence and trust if it interferes with device functionality.

## Continuing Challenges

Despite the many improvements in the Japanese clinical-trial environment, challenges, such as slow progress with access to electronic medical records, patient consent for secondary data use and integration of Japanese clinical-trial data into global databases, remain.

Such challenges can be particularly taxing for small- to medium-sized pharmaceutical companies and bioventures without experienced international staff. In the absence of a Japanese subsidiary able to conduct clinical trials under local GCP requirements, such companies must appoint an in-country clinical caretaker (ICCC) that can jointly assume their legal, regulatory and operational obligations.

Indeed, an ICCC-licensed service provider is the crucial bridge between an overseas company and the PMDA as well as clinical-trial sites. Third parties can open doors in contract negotiations with study sites, as well as reconcile different contract formats for individual sites.

It can also act as a go-between with the PMDA, which welcomes early consultation – whether formally or informally – on clinical-trial designs and data specifications. Japan has very specific requirements for post-marketing surveillance (PMS), with a particular focus on risk management during the first six months after launch, and strict monitoring requirements in specialist areas such as rare diseases.

All interactions with the PMDA need to be in Japanese, as do most interactions will clinical researchers. Indeed, a strong, traditionally insular national culture pervades all aspects of the business and regulatory environment in Japan, which to outsiders can sometimes appear opaque. Consequently, a local partner can make a huge difference in breaking down any communication barriers.

## Disconnecting Development

Companies looking to conduct clinical trials in Japan should be thinking about disconnecting drug development from commercial activities, such as business partnering, so that their development program runs simultaneously in Japan and other key markets such as the US and Europe.

That way, they can take full and early advantage of the new wave of regulatory liberalization in Japan and a growing pharmaceutical and healthcare market geared to innovation. Teaming up with the right partner will go a long way towards ensuring this experience is a positive one.

CMIC is Japan's largest CRO, with more than 25 years' experience, 1,200 clinical research associates, over 140 consultants and medical writers, and services ranging from contract-development-and-manufacturing (CDMO), preclinical, and clinical-trial support through to regulatory consultation, PMS and pricing consultation for negotiations with the Ministry of Health, Labour and Welfare (MHLW).

## Pharmaceutical Value Creator

This broad range of services underpins CMIC's unique 'Pharmaceutical Value Creator' business model. With so many varied inputs from different areas of the business, the group has prompt access to large volumes of valuable information on pharmaceutical-market trends. This enables CMIC not only to expand the scope of its business but to provide considerable added value to its industry clients.

Given the growing encouragement for Asia data packages to support global clinical trial programs and product approvals in Japan, CMIC is also well placed as the leading pharmaceutical-services provider across Asia, with headquarters in Japan and operations in China, Korea, Taiwan, Hong Kong, Singapore, Malaysia, Thailand, Vietnam and other countries in the region.

With expertise in key therapeutic areas such as oncology, cardiovascular disease, CNS disorders and regenerative medicine, as well as medical devices and gene or cell therapies, CMIC can be an invaluable partner for companies ready to give a more outward-facing Japan the parity of recognition it now deserves in global drug development.

# Japan Firms Up Cost-Effectiveness Plans As Industry Concerns Linger

IAN HAYDOCK

Japan is taking new steps to expand what has so far been a pilot-scale cost-effectiveness assessment (CEA) scheme for drugs and medical devices, a move that may lead to price adjustments for selected products, potentially including some already marketed drugs.

The expansion, being taken as part of the country's national health insurance reimbursement system, has been widely anticipated given first indications from regulatory authorities several years ago that they were looking to roll out a formal CEA process.

It now seems that this will indeed be adopted on a broader basis by the end of the current fiscal year (on March 31), according to recent government policy proposals.

Such economic evaluations have been running on a limited trial basis in Japan since April 2016 and have already led to price readjustments for a small number of marketed products.

But the plans continue to concern the research-based pharma industry, which sees a number of issues both with the basic idea and specific planned methodology, and is worried that the process will add another hurdle that could delay launches and patient access to new drugs.

On the positive side, the new proposals incorporate limits to the size of price cuts calculated under the CEA process, and would apply to only one component (premiums) of a product's overall price, rather than the total price. Potentially, though adjustments could still run into the double digits.

## Pilot Scheme Progress

The trial CEA scheme has so far led to 13 products (including seven devices) being designated for cost-effectiveness assessment, resulting in the repricing of two products in April 2018 as part of the wider regular biennial drug price revision in Japan at that time.

In a late January 2019 meeting, a committee of the Central Social Insurance Medical Council (Chuikyo), a policy and pricing advisory body to the ministry of health, labour and welfare, laid out plans for the full adoption of CEA this April.

Under the criteria and five main product groupings newly outlined by Chuikyo, the key concepts are QALY (quality-adjusted life years) – an internationally recognized measure that considers length and quality of life – and incremental cost-effectiveness ratio (ICER), which measures the broad economic value of a product versus a comparator.

ICER, which considers proportional benefit, forms a core part of the proposed stratification of products in the Japanese scheme, the concept being to consider the total added cost of a product in relation to the expected beneficial effect over a comparator.

The ratio is calculated by the difference in cost between two interventions, divided by the difference in their effect, meaning that a product with a higher cost per QALY will be seen as less cost-effective.

The indications coming out from Chuikyo are that around 10 products are expected to undergo formal CEA annually, with the council anticipating that the process would take place as part of the price-setting process. Newly approved products are normally priced (which allows commercial launch) within 60 days in Japan.

The categories cover products launched both before and after the planned start of the scheme, based on government forecasts of peak annual reimbursement level sales and, importantly, there would be caps on the scale of CEA-calculated price revisions, of 10-15%.

## Product Groupings

The main groupings proposed by Chuikyo are as follows, although there is ongoing assessment and discussion of these:

1. Products with an official peak sales forecast of more than JPY10bn ($92m) that are awarded premiums for innovation, usefulness or utility (as available under the current price calculation scheme), and/or a product with no comparator priced using the cost-plus based method, with less than 50% certainty over what actual manufacturing costs would be;

2. These same criteria but with peak predicted sales of JPY5-10bn;

3. Products with a "high" price that Chuikyo decides should be evaluated under CEA;

4. Products already reimbursed prior to the start of the expanded CEA scheme and with the same criteria as group 1, and peak annual forecast sales of JPY100bn or more, or with a high price that Chuikyo decides should be evaluated;

5. Products used as comparators in the price-setting of products in categories 1-4.

Other allowances provide for case-by-case CEA decisions based on annual sales or changing available data, although there would be exemptions for orphan, serious disorder, HIV and hemophilia products, and pediatric-specific drugs, unless the annual reimbursement-level sales of these exceed JPY35bn.

Along with these categories to determine the initial triggering of a CEA process, other methodology would be used to recalculate the adjustment in any awarded price premiums.

If there is less than a JPY5m per QALY value, there would be no adjustment, with a sliding scale above this, Chuikyo proposes: and ICER per QALY of JPY5-7.5m would entail a 30% cut in premium; ICER of JPY7.5-10m a 60% cut; and ICER of over JPY10m a 90% reduction.

For cost-based product pricing (where no comparator is available), there would be an adjustment in both premiums and allowable operating profit on a sliding scale of 17%, 33% and 50% respectively across the same bands.

If orphan or rare disease drugs are targeted for CEA, these bands would be upped by 1.5x, taking the ranges from less than JPY7.5m/QALY to more than JPY15m or more.

Resulting price reductions are proposed to be capped at 10-15% of a product's total price, and products would not be put under the JPY5m threshold so that they are not opened up to further possible reductions.

## Industry Worries

True to Japan's current reimbursement price calculation methodology, the proposals are complex, but the main concern of the research-based industry is that the scheme will focus too much on reducing costs, rather than taking a more holistic view of the broader economic benefits of drug treatment, such as reduced work absences and savings elsewhere in the health system.

The innovative industry in Japan has long expressed concern about the CEA plans, which recently were in the spotlight in a rare joint statement from the main local, US, and European associations in the country.

US association PhRMA said last year for instance that the country should learn from experiences in other countries. The key consideration should be to ensure transparency and that any scheme promotes innovation and patient access to new drugs, something that it sees as lacking in similar programs elsewhere.

The pilot process "lacked clarity in company requirements and timelines [and] provided inadequate consultation with industry, patients and providers," the group said at an event in Tokyo last year.

Of particular concern to PhRMA at that time (before the new proposals) were the "narrow focus" of the pilot on the cost-per-QALY thresholds, which was seen as undervaluing innovation and life, and the effective targeting of the most innovative medicines for price cuts.

It also has worries about the availability of expert reviewers within Japan's regulatory bodies, and the likely necessary outsourcing of CEA work to external reviewers.

For its part, the European industry, through the Japanese arm of regional federation EFPIA, has long maintained that health technology assessment should consider not just simple drug costs but also wider outcomes, and that all stakeholders, including patients, be given a chance to comment. (Chuikyo has been holding sessions for the industry to comment as part of its policy-making process in the field.)

A long ago as 2015, EFPIA pointed to potential delays in product launches, limited appropriate data for new products, and the fact that Japan's regular price revisions already effectively control overall national healthcare costs, given that drug spending (around 20% of the total) is flat.

In a recent interview, the president of Janssen Pharmaceutical KK in Japan, Christopher Hourigan, echoed these concerns, telling the *Pink Sheet* that the new proposals are positive in that they focus on adjustment of premiums rather than total price.

"But they focus only on costs, not on wider value such as productivity and employment. We are concerned about potential delays in access to new drugs," he noted, adding that industry has provided modelling of different systems and can bring experience from other countries.

"While the government has been open and we have had constructive discussions, we feel that innovation must be rewarded. It is still not completely clear what the interpretation of the proposals will be" given the ongoing policy discussions, Hourigan noted.

# Korea's Clinical Trial Road Map Eyes Faster Development, Patient Safety, Rare Diseases

JUNG WON SHIN

South Korean regulators see the more systemic management of clinical trials and safety becoming more crucial, as subjects from the country increasingly participate in such studies and new drug development activities focus more on rare and intractable diseases.

Although clinical trial activity is increasing globally, particularly in markets like China, Australia and Europe, growth in South Korea has slowed recently, largely because of a rise in relative costs and despite abundant medical expertise and an outstanding trial infrastructure in the country.

On top of this, regional and global competition to attract clinical work is becoming ever fiercer because of the potential positive economic impact on job creation and the growth of related industries.

Against this background and to improve its global competitiveness and accelerate activity in the sector, South Korea has now unveiled a five-year road map to support and advance clinical trials, focusing on expansion of treatment opportunities for rare and intractable disease patients, protection of the rights of subjects and enhancement of new drug development capabilities.

The blueprint, drawn up by the Ministry of Food and Drug Safety, focuses on establishing an effective safety management system, stepping up global competitiveness, expanding

treatment opportunities and forming efficient communication systems.

Earlier this year, Syneos Health's chief scientific officer Nicholas Kenny told *Scrip* that South Korea could improve its attractiveness if it could keep abreast of requirements in new areas such as cell/gene therapies and rare diseases. It should also be able to deal with the evolving global clinical market environment and accept harmonized data, both preclinical and clinical, from multiple regions, he said.

## Review Process For Early Trials

To improve the global competitiveness of trials conducted in South Korea, the government said it aims to improve the study approval system in a more rational way.

With the introduction of the International Conference on Harmonisation's E17 guideline on multi-regional clinical trials, it has become crucial to participate in early-stage exploratory studies. A separate review process is needed to focus on the evaluation of safety during early trials. the ministry said.

The MFDS will set up a system to approve early trials to support new drug development, and will form an "innovation review team" for Phase I work with such products. The aim is to "reinvigorate" the preliminary and prior review systems for data submissions, and after reviewing drug safety through prior reviews, the IND approval period is expected to fall to just seven days on average from 30 days previously.

## No Separate Approval Needed For Changes

The road map will also rationalize data required for IND approval review by analyzing and comparing the scope of data to be submitted versus other countries, and adjusting requirements if necessary.

At present, if there is a change in approved clinical trial plans, a new regulatory approval of the change is required, which can cause delays because trials are suspended during the review. In countries like the US, changes to trial plans can be made without a separate regulatory approval of the modifications, just by reporting the changes and with the approval of the institutional review board.

As a result, the MFDS plans to allow such changes - as long as they don't involve the quality of the drug - by reporting and submitting IRB approval alone, on condition they meet safety requirements.

## Rules Eased For Investigator-Initiated Trials

Investigator-initiated clinical trials are seen as having public value in terms of addressing unmet medical needs and improving patient treatment technologies. Under current rules for the approval of such trials involving already marketed anticancer therapies, academic papers or data that can prove scientific validity must be submitted.

However, this can cause difficulties in research because of problems with the availability or submission of such data or because it takes a long time to review this information.

The ministry now plans to accept research and approval reviews on the scientific and ethical validity of clinical trial plans submitted by expert groups, which will be limited to organizations formally acknowledged by the drug ministry.

## Differential Approval System

The ministry will also introduce a differential system for the approval of clinical trials. At present, South Korea takes 30 days to process such requests and issues a final approval after reviewing related issues.

However, countries like the US, Australia and China operate a reporting system for trial plan reviews, and amid competition between countries to gain a competitive edge in attracting and conducting trials, social demand has been rising to expand treatment

opportunities for South Korean patients through the early start of studies, the MFDS notes.

Based on experience and a trial subject protection system, the ministry will introduce in stages a differential approval system for trials that have assured safety and if essential information on the trials is submitted.

Initially low-risk studies will be eligible for the differential approval system. These would include for marketed drugs that compare pharmacokinetics and pharmacodynamics, multinational trials already approved by the US, Japan, UK, Germany, France, Italy, Switzerland or Canada for the purpose of gaining conclusive therapeutic evidence, or investigator-initiated studies for marketed anticancer drugs.

## Improving Efficiency, Accepting Wider Preclinical Data

The new road map also lays out moves to improve the predictability of reviews. There has been some criticism that trials are being delayed in South Korea because of issues with the consistency and expertise in this area.

The ministry says it will come up with a process to improve predictability, and will step up the transparency of reviews by analyzing and sharing information on similar cases and being more transparent on reviews.

At present to gain an IND approval, information on the drug development and trial plan and non-clinical data are required. Data receipt and process work and reviews are handled by the MFDS and Health Insurance Review And Assessment Service.

The ministry says it will reorganize the system to step up management of trial reviewers and efficiency, helped by a task force that will look at reviews, expansion of reviewer numbers and the creation of a new division for trial reviews.

At present, non-clinical data in compliance with good laboratory practice (GLP) standards are accepted when IND approvals are filed, and non-clinical data from OECD member states and from six GLP-compliant non-OECD countries are mutually accepted. The MFDS will change the rules to allow submission of non-clinical data from non-OECD, non-GLP compliant countries, significantly including China.

Multinational trials are increasingly based on non-clinical studies conducted in countries like China, and the US and Europe are accepting China's non-clinical data, the road map observes.

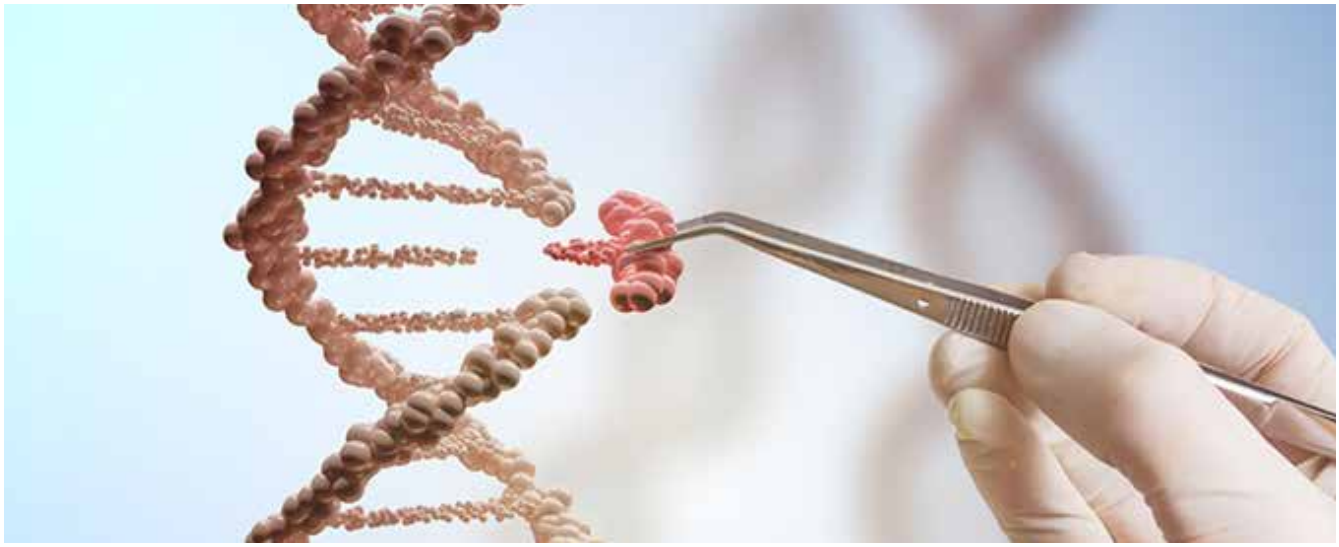
## Global Standards, Expansion Of Treatment

The MFDS says it will proactively prepare trial guidelines that reflect global standards, amid the need to flexibly deal with regulatory changes in line with the advancement of cutting-edge technologies and to promptly deal with the fast-evolving international situation.

The ministry will come up with guidelines for innovative drugs and support trials of regenerative medicines and "new concept" drugs.

To expand treatment opportunities for patients, it aims to grant approvals for the use of investigative drugs in emergency cases in just one day, versus the current seven days. Investigational drugs used in clinical trials can also exceptionally be used for the treatment of patients in critical condition.

In cases of life-threatening rare diseases that have no alternative treatments, investigational drugs already being used in overseas clinical trials will be allowed in a humanitarian gesture, with use strictly managed to ensure safety.



# China Tightens Clinical Trial Oversight Post Gene-Edited Babies Scandal

BRIAN YANG

One of the first tasks after the Lunar New Year for China's National Health Commission (NHC) was to release a draft guideline on Feb. 26 to rein in a seemingly wild area of development in the country – cell and gene therapy.

The move was prompted by a string of clinical trials in which Chinese researchers stunned the world with gene-editing technology. In addition to conducting the first ever human study using CRISPR gene-editing technology to treat lung cancer patients, China last year also saw the highly controversial birth of the world's first gene-edited babies.

Shenzhen-based researcher Jiankui He from the China Southern University of Technology in December announced he had used embryo-stage gene engineering tools to enable the birth of twin baby girls genetically engineered to be resistant to HIV, through removal of the CCR5 gene that usually allows HIV infection at the cellular level.

Long considered as an ethical red line for scientists around the world, He's work sparked immediate shock waves and global criticism.

In the wake of these events, the NHC has now issued a draft regulation to rein in the relatively unregulated development area, after the scandal was widely considered to be a blot on China's ambition to take a leadership position in the global gene and cell therapy race.

## Risk-Based Oversight

The new guideline covers a broad range of new technologies that are not limited to cell and gene therapies.

"The new biomedical technology defined in this regulation refers to medical professional means and

measures for the purpose of completing preclinical studies intended to act on cell and molecular levels to treat or prevent diseases, eliminate or alleviate the disease, reduce pain, improve function, prolong life, help restore health, etc." noted the draft.

It will apply to clinical trials using technology that: (i) is directly used in the human body; (ii) involves in vitro tissues, organs, cells etc. after implantation or input into the human body; or (iii) involves human germ cells, zygotes or embryos after implantation.

Second, it addresses risk-based oversight, classifying the following as technologies with high risks:

- those involving genetic material changes or regulation of the expression of genetic materials, which include gene transfer, gene editing, gene regulating, stem cells, somatic cells, mitochondrial replacement, etc;
- those involving heterogeneous cells, tissues, organs, including the use of biological materials;
- those for use in the human body including synthetic organisms, and genetically engineered or modified bacterial transplantation technology;
- assisted reproductive technology;
- other research projects with high risks and difficulties that may have a "significant impact."

The classification and oversight of the high-risk technologies will be conducted by the state-level health regulatory agency, which suggests the National Health Commission, rather than the National Medical Products Administration (NMPA, formerly the China FDA) will take the lead in overseeing cell and gene therapy research.

## Three-Level Review

The third aspect involves the tightening of requirements for ethics review and clinical approvals. Applicants will have to go through several layers of regulatory agencies, starting from clinical sites, which are required by the draft to be located within Class AAA (top level) hospitals.

A hospital's academic review and ethics review committees will conduct a first-round review of the necessity, legality, scientific, feasibility, safety and ethical aspects of the research, and upon the approval, the application will be sent to city or provincial regulators for review.

If the products are deemed to carry low to middle risk, the local regulators will make a decision within 60 days. For products with high risks, applications - upon obtaining the approval from the local authority - must be submitted to the state-level regulators for review and approval.

## Hefty Penalties

The draft also outlines penalties for those who conduct clinical trials without the requisite approvals. Hospitals could face fines of CNY50,000-100,000 (roughly $7,500-15,000) and potential revocation of licenses, while investigators in charge of studies could face revocation of their license to practice medicine.

Medical institutions conducting clinical research without following a previously approved study plan could face CNY30,000-50,000 in fines.

If physicians conduct clinical research without obtaining the required approvals, they will be ordered to halt activities for six months to one year, and could face a lifetime ban from conducting any clinical studies of new biomedical technologies.

Public comments on the draft regulation are being gathered until March 27, and can be submitted via email to ylglc@nhc.gov.cn.

# Merck Scores A First With Keytruda Under Australia's Provisional Pathway

VIBHA SHARMA

Merck Sharp & Dohme's anticancer medicine, Keytruda (pembrolizumab), has become the first drug to have additional indications registered on the Australian Register of Therapeutic Goods via the provisional approval pathway.

This means Keytruda can now also be used to treat patients with metastatic colorectal carcinoma and other solid tumours with certain types of mutations (deficient mismatch repair). The product is already approved in Australia for a variety of indications, including melanoma in adults and non-small cell lung cancer in adults.

The new indications were provisionally approved by the Therapeutic Goods Administration based on early clinical data in these specific types of mutations. The continued approval of Keytruda for these new indications "will depend on further evidence of clinical benefit from clinical trials being provided by the product sponsor," the TGA explained.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The TGA's provisional approval pathway was launched last year and it is available for new prescription medicines or new uses for already registered prescription medicines. The pathway allows sponsors to apply for time-limited provisional registration of their products on the ARTG, where there is potential for substantial benefit to patients.

Eli Lilly's oncology drug, Lartruvo (olaratumab), was the first medicine to be granted a provisional approval determination under the pathway. The determination process allows the TGA to make a decision about whether a medicine is eligible for the provisional approval pathway, but does not necessarily mean that the medicine will be provisionally registered after evaluation.

Under the provisional approval pathway, companies must agree to continue clinical trials and submit comprehensive evidence for review. If they do not follow this plan or submit this evidence, the TGA can cancel the approval.

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