



Early Drug Development



While pivotal clinical trials remain critical to securing the approvals required for the launch of new drugs, it is interesting and also encouraging to observe a common thread running through some recent regulatory and policy discussions.

That theme is ever closer cooperation between industry sponsors and regulatory authorities, particularly in relation to new forms of therapy.

This e-book takes a look at some of the considerations when planning and conducting early stage trials, highlighting several major issues in the space and lessons from changes to regulatory guidance. It also examines the current industry trends for early drug development and market access, especially in Japan where increased incentives and recent reforms have provided new opportunities for pharma in the region.

With the steady rise of innovative forms of treatment such as cell and gene therapies, regulatory systems are having to adapt to new modalities. In the US for instance, the FDA emphasizes in its guidance on chemistry, manufacturing and control information for investigational gene therapies, finalized in January 2020, that IND sponsors are expected to continually improve manufacturing processes during development, updating INDs as they go. Viral vectors are a specific focus, reflecting the issues around gene therapy production.

The FDA is also working closely with industry more generally to solicit sponsor suggestions on effective development policy, holding a meeting last November where, among other things, it heard ideas on promoting innovative trial design. This was described by industry as nothing less than a “life or death” issue.

Elsewhere, Japan’s main cancer center has expressed willingness to work closely with regulators and companies to share its clinical assets and expertise, to help speed new drugs to patients. The EU meanwhile has made revisions to its draft Clinical Trials Regulation to better clarify and consolidate information requests to sponsors relating to clinical trial applications.

These and other moves all point to increased flexibility and collaboration, with the ultimate aim of speeding up early access to novel therapies, while also helping to reduce development costs.

Continued close industry/regulator dialog will be essential.

Ian Haydock
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Opportunities In Japan: Supporting Early Drug Development And Market Access

Scrip spoke to Toshitaka Kawaratani, EVP Head of Consulting Division, and Kazuhiro Fukuta, Head of Regenerative Medicine Group from CMIC's Strategy & Regulatory Affairs Consulting department about the increasing opportunities for pharma in Japan, and how they are utilizing their extensive understanding of the market to support businesses in taking advantage of these.



As the first and largest clinical CRO in Japan, can you tell us more about CMIC's regulatory consulting and medical writing services?

TOSHITAKA KAWARATANI (TK): Our consulting team has an excellent relationship with and understanding of the Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Labor and Welfare (MHLW). PMDA consultations take place on a daily basis and we have an in-depth knowledge of the discussion points, from strategy to protocols.

For example, PMDA consultations on cell and gene therapies require three types: product quality (CMC), non-clinical (efficacy and especially safety) and clinical protocols and strategies for filing. The team also actively participates in PMDA-sponsored symposiums, so they keep updated with changes in various guidelines, PMDA guidance and the introduction of new regulations.

In addition, our subsidiary company can offer non-clinical strategic RA consulting and medical writing.

CMIC Pharma Science Co. Ltd. has consultants who are specialized in non-clinical areas, and work with the clinical RA team together in the same venue, so we can offer strategic consulting utilizing in-depth knowledge and experiences.

What trends are you observing for early drug development in the industry?

TK: There is increasing collaboration between academic and industry sponsors. Many cell and gene therapy products are developed by academia, so it is important to work together with them. The role of the contract research organization (CRO) has become particularly significant because of this trend.

In addition, regulatory agencies are working with the industry to continue to streamline the application process. In the development of cell and gene therapies, the role of regulatory affairs consulting is significant because many pharmaceutical companies do not already have the necessary know-how. We can therefore even be asked to provide due diligence support to evaluate data sets created by overseas companies for their in-license purposes.

The rise in fast track and incentives for key treatment areas – such as oncology, rare disease and cell and gene therapies – is also notable. For cell and gene therapy products in particular, there is the potential to get conditional and time-limited approval with just the results of early clinical trials, which is attractive for companies looking for quick market entry. This is followed by a formal new drug application (NDA), usually 7 years later when enough evidence is compiled for their experience.

In Japan in particular, companies are taking advantage of the Sakigake Designation System. Sakigake aims to provide the most advanced treatments and medical devices in Japan ahead of the rest of the world, and provides incentives for

consultation and examination of innovative new drugs that meet certain requirements as follows:

1. Innovation of the drug
2. Seriousness/severity of the target disease
3. Extremely high efficacy
4. Willingness to develop and apply in Japan ahead of the rest of the world, or in parallel with first launch countries

If a company receives Sakigake approval, a PMDA concierge will provide the company with detailed and agile support for the NDA to make global top speed development and its review possible. The target review period is six months after the application and rapid approval is usually expected.

Following regulatory reform in Japan, what changes have you noticed in the Japanese pharma market?

TK: There has been a change of focus in the industry. Development of cell and gene therapy products has been active to achieve innovative treatments for intractable diseases. The Enforcement of the Pharmaceuticals and Medical Devices Act (PMD Act) in 2014 was the major turning point to boost the development of these therapies.

The PMDA has also had an attitude change, having established various consultation systems and created guidelines to support development, including cell and gene therapy products. This is positive because in the past in Japan this has not always progressed rapidly. In many cases, it would take considerable effort before clinical trials were started, with the lack of resources with practical experience in the area acting as a bottleneck.

An organization called the Forum for Innovative Regenerative Medicine (FIRM) has also been created which is led by the industry, and proposes various policies for industrialization of cell and gene therapy products from processing, manufacturing, distribution, development to commercialization.

How are industry sponsors and regulatory authorities working together in the launch of new drugs in Japan? How does CMIC's Consulting Team contribute?

KAZUHIRO FUKUTA (KF): In general, PMDA consultations made the industry secure a set of dossiers necessary for NDA, and often receive advice to speed up development considerably in Japan compared to 10 years ago. Regarding cell and gene therapies, a new consultation system for Cartagena applications was established in 2019. An organization called the Forum for Innovative Regenerative Medicine (FIRM) has also been created which is led by the industry, and proposes various policies for industrialization of cell and gene therapy products from processing,

manufacturing, distribution, development to commercialization. FIRM has many working groups that CMIC works together with, and monitors industry trends and participates in the formation of policies.

What opportunities are there for pharma companies looking to undertake early drug development in Asia?

KF: Treatment needs for cancer, neurological disorders, motor organ disorders and orphan diseases are still expected to increase. In these areas, new treatment can be provided by innovative methodologies, including cell and gene therapy technology, which are advancing daily.

Are any new changes or guidance expected from the PMDA relating to cell and gene therapies, orphan drugs or real-world data usage?

KF: In June 2019, a guideline was issued on the detection of undifferentiated pluripotent stem cells and transformed cells in human cell processing products, tumorigenicity tests and evaluation of genetic stability.

With regards to clinical trials of gene therapy using genome editing, these have not yet started in Japan and no relevant guidelines have been developed. However, given the high possibility that it will happen here, the Scientific Committee – an advisory committee of PMDA – published its “Report on quality and safety considerations of cell and gene therapy products using genome editing technology” in February 2020. 🍀

Japan Cancer Center Looks To Leverage Expertise As It Builds Pharma Ties

IAN HAYDOCK



As the operator of the largest cancer hospital in Japan, the Tokyo-based National Cancer Center (NCC) is looking to parlay its experience, expertise and clinical resources into increased activity as a hub for Asian clinical trials in oncology.

"We have been focusing mainly on Phase I trials over the 2014-19 period and the number of these [at NCC] is increasing," says Dr Noboru Yamamoto, deputy director of NCC Hospital, who leads its Department of Experimental Therapeutics and the NCC Hospital's Clinical Research Support Office.

But he is aware of the challenges in this process and pharma's concerns in early development, as

the NCC looks to build its position. "Most global pharma companies have their headquarters outside Japan, so tend to launch clinical programs in their home country. Japan also presents a language barrier and time difference, while body size is different so sometimes there is the perception that dosing may need to be adjusted," he told *Scrip* in an exclusive interview at the NCC Hospital in Tokyo's Tsukiji district.

But some of these concerns may be overstated, he believes. "There are some data on comparative tolerability in Japanese patients which show this is actually very similar to patients in the west. Otherwise the trial selection process is done just as carefully."

Promoting Capabilities

US and European companies have already been increasing the number of trials they conduct in Japan, either as part of parallel multinational studies or as stand-alone work. Members of the industry associations EFPIA and PhRMA together are currently conducting more than 800 trials across around 18,000 sites in the country.

Even so, Yamamoto believes that “we [NCC] could explain our capabilities better. While the number of patients available in Japan is lower than in China, we have an excellent and detailed collection of trial [tissue] samples.”

The NCC sees this as a particularly strong point of its expertise and a valuable resource for pharma companies wanting to conduct translational research on specific gene types or clinical trials. “Tumor sampling in Japan is usually done endoscopically. Lung biopsies are normally difficult to do but we have very good sampling in this case, and our multipoint biopsy success rate is close to 90%.”

“The samples are stored in NCC after resection, and we see the opportunity for collaboration with the pharma industry using this resource, for example on trials with tumor-agnostic drugs or Asia-prevalent cancer types such as hepatocellular carcinoma and gastric cancer, but we have a big variety of common and rare cancers on file.”

Regulatory Hurdles?

But one area where Yamamoto sees room for improvement is in the Japanese regulatory



“We would like to modify some of the Japanese guidelines for new drug development and are leading the discussions with academia and the government about how to do this.”
– NCC’s Yamamoto

requirement that first-in-human trials with new oncology drugs must be conducted in a hospital in-patient, rather than outpatient, setting and over a 28-day period.

“In the US, most cancer trials are conducted in an outpatient setting, and so the requirement [in Japan] may be a concern for pharma companies. The fundamental medical culture is different, although in reality in Japan some patients continue working during the day but they return to the hospital at night.”

Hospitalization may also increase the number of reported adverse events that are picked up during a trial, even though the actual incidence may not be any higher, he noted. There might also be some benefits to the requirement for some new therapies; CAR-Ts for instance have the risk of cytokine release syndrome.

The design of oncology trials has also changed over the past few years, for example involving the use of expansion cohorts to look at activity in certain tumors, but this approach is not covered in the current regulations, he noted.

The design of trials with tumor-agnostic drugs – which target common mutations across multiple types – are also not clearly described, and may require the guidelines to be changed, as sometimes only a small number of patients are available.

“We would like to modify some of the Japanese guidelines for new drug development and are leading the discussions with academia and the

government about how to do this," the NCC physician said. "The hope is to update these within two years."

Rare Cancer Registry

The NCC launched a rare cancer center several years ago, which is building on its sample bank and in some cases has led to proposals for investigator-initiated clinical trials in rare tumor types with commercialized or investigational drugs. Companies providing product samples for use in such trials have included Chugai Pharmaceutical Co. Ltd. , Novartis AG and Daiichi Sankyo Co. Ltd.

In parallel, the NCC initiated and is leading the Master Key cancer registry project, along with three other university hospitals and 13 pharma firms in Japan, which started in May 2017 and for which the number of participating institutes has now risen to around 900. This is the first attempt globally to foster joint genomic medicine research between a national cancer center and the pharma industry.

Data from the initiative presented at the recent European Society for Medical Oncology (ESMO) meeting in Barcelona, Spain, showed that the incidence of all rare cancers in Japan (around 200 types) accounts for around 15% of total diagnoses. In Japan, soft tissue sarcoma and CNS glial tumors are the most common rare types in the registry.

Over 700 patients were enrolled as of July 2019, 60% of whom have sequencing data, and eight (non-registration) trials are being conducted involving 12% of patients in the registry. Further pivotal trials aimed for approval are needed to provide new options for rare cancers.

New Therapies, Research

"The NCC is one of the facilities to be involved in the conduct of Phase I clinical trials with a novel CAR-T therapy for solid tumors," Yamamoto noted, although further details cannot be revealed at this stage. The therapy, reported in *Nature Biotechnology*, involved the engineering of CAR-T cells to express interleukin-7 and CCL19, which in animal studies achieved complete regression of pre-established solid tumors and prolonged survival, with superior anti-tumor activity compared to conventional CAR-T cells. This work was conducted in collaboration with a large Japanese pharma company.

The NCC is also doing some clinical research on novel cell therapies including one NY-ESO-1-targeting T-cell therapy in synovial sarcoma, for which some work has already been performed in the US.

Yamamoto noted that the NCC itself has generated few drug seeds from in-house original research and that it has no established technology-licensing office, choosing instead to focus mainly on a high-quality tumor sample collection.

More broadly, the physician highlighted the NCC's links and staff exchanges with Japan's regulatory agency, the PMDA, while a number of ex-PMDA and ministry of health, labour and welfare staff have joined the NCC, meaning there are "strong links" between the two.

The PMDA's current chief executive, Dr Yasuhiro Fujiwara, was previously a senior physician at the NCC, and is expected to bring a strong clinical focus to his new role, which he took up in April. (*Also see "New Japan PMDA Head Brings Strong Clinical, Patient Focus To Role" - Pink Sheet, 21 Jun, 2019.*) 🍷

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Innovative Trial Designs Are ‘Life And Death Matter’ For Pharma, Amgen Tells US FDA

BRENDA SANDBURG

While the US Food and Drug Administrative has long emphasized the desire for more innovative trial designs, Amgen Inc. offered the agency specific advice on how it could promote their adoption.

Elliott Levy, Amgen’s senior VP of global development, recommended that FDA hold informal communications with sponsors, in which there is “more asking and less talking.” He also encouraged the agency to more actively share learnings from implementation of guidance with the clinical trial community, such as by publishing case examples on its website or in Q&A documents. And he said it would be helpful for the agency to provide advice on design features it has found unacceptable.

Innovative trial designs are “a life and death matter for the pharmaceutical industry,” Levy stated. “The state of pharma R&D is not well.”

Levy spoke at a 7 November FDA meeting, “Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA’s Office of New Drugs.” The agency convened the meeting to get specific suggestions on policies the office could implement in the near-term. Twenty-five leaders of OND listened to 28 speakers discuss a wide variety of topics.

Levy said that progress in oncology and rare diseases conceals the fact that industry underinvests in many important areas of human health.

"I find it particularly shocking that of 59 new medicinal entities approved by FDA last year, not one is in the area of cardiovascular disease, which is the most common cause of death worldwide," he stated.

Levy said one of the major reasons for underinvestment is the perception, based on fact, that clinical trials in these areas take too long, cost too much, and carry too much risk. He asserted that incorporating innovative methodologies into clinical trials can "dramatically change the prospects for success" in drug development.

As an example, he presented a study Amgen conducted comparing a traditional design and an innovative design for a Phase II trial in lupus. The company modeled three characteristics:

- Probability of making wrong decisions;
- Average number of subjects; and
- Average time to decision making.

Levy said that whether the drug is efficacious or not, the innovative design reduced the probability of reaching an incorrect conclusion, reduced the number of study subjects, and shortened the time to decision.

About two years ago, Amgen launched an in-house Center for Design and Analysis to evaluate advanced trial designs and perform the modeling and simulations needed to support them. The company now considers adaptive designs for most new studies and over half of the studies it conducts incorporate adaptive elements. *(Also see "Amgen's Elliott Levy On Adaptive Design And Real-World Evidence Strategies" - Pink Sheet, 19 Jun, 2019.)*

Common Understanding Needed Among Review Divisions

Levy noted that Amgen is participating in FDA's Complex Innovative Trial Design pilot program

but he said sponsors need more timely advice from the agency.

Launched last year, the program is designed for highly innovative trial designs which require simulations to determine their operating characteristics. The agency is using designs submitted by sponsors as case studies for education and information sharing. *(Also see "US FDA Offers Sponsors More Attention For Sharing Complex Innovative Trial Designs" - Pink Sheet, 3 Apr, 2018.)*

Among other recommendations, Levy encouraged FDA to enhance its statistical capacity on Bayesian adaptive designs and modeling and simulation so that it can provide timely review and advice on use of innovative trial designs. He suggested that the agency consider contracting with third party experts for support while it recruits additional expertise and noted that FDA has retained an external consultant.

Levy also cited the need for consistency within FDA and among regulatory bodies.

"It's important for the divisions which will interpret the results to share a common basis for understanding" innovative trial design methodologies, he said.

On a global level, he said "seeking and building a consensus with multiple regulatory authorities is so time-consuming that it offsets a great deal of the value of using these methodologies."

Levy called on FDA to continue building relationships with health authorities around the world, perhaps by building on the cluster approach and incorporating innovative designs into an existing cluster or forming a new cluster. Initially set up by FDA and the European Medicines Agency, clusters are regular meetings by phone or video conference between global regulators that focus on specific topics. 🌟

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EU Explains How Info Requests Will Be Managed Under Clinical Trials Regulation

VIBHA SHARMA



The European Commission has revised its draft questions & answers document on the EU Clinical Trials Regulation to clarify, among other things, that sponsors would likely receive only one consolidated request for information (RFI) from the member states if there are outstanding concerns about their clinical trial-related applications.

This is designed to help ensure that all stakeholders can comply with the strict evaluation timelines specified in the CTR for the assessment of initial clinical trial applications, applications for substantial clinical trial modifications, and applications for the subsequent addition of a member state concerned (MSC).

“In general, it is expected that due to time limitations, only one request for information will be feasible during the assessment period,” says the updated Q&A guidance document on the CTR (Regulation No 536/2014).

The RFI, the document states, would focus only on critical issues that would need to be addressed by the sponsor, so as to allow the trial’s authorization or authorization with conditions and to avoid the application being rejected. “In case of an authorization with conditions, it is expected that the conditions... are linked to matters that were raised during the RFI phase,” it adds.

To enable a timely response from the sponsor and to avoid unnecessary rejections of trial applications, the guideline states that the reporting member state (or MSC in the case of part II of the clinical trial application) would formulate the RFI “with clear and concise instructions to the sponsor on how to address the considerations stemming from the assessment.”

The sponsor, for its part, would be expected to respond to all questions in the RFI. Where changes are needed to the clinical trial documentation (eg the protocol, investigational medicinal product

dossier, investigator's brochure, etc), the sponsor should also submit an updated version of the relevant documents.

Other Updates

The revised document also provides clarity on various other topics, such as supporting transparency, what information should be included in a layperson summary if a trial were to end prematurely, and the sponsor's responsibilities regarding changes to a clinical trial that are not substantial modifications but are relevant for the supervision of the trial.

On transparency, for example, it clarifies that the regulatory assessment report on parts I and II of the clinical trial application would be made public at the time of decision unless a deferral is requested by the sponsor at the time of submitting the initial trial application.

On the publication of layperson summaries of clinical trial results, which are mandated under the regulation, the commission had earlier stated that these should "at a minimum" reflect the primary and patient-relevant secondary endpoints. However, in cases where a trial is terminated early due to unavailability of trial subjects or due to lack of data,



On transparency, for example, it clarifies that the regulatory assessment report on parts I and II of the clinical trial application would be made public at the time of decision unless a deferral is requested by the sponsor at the time of submitting the initial trial application.

the revised Q&A document states that the layperson summary should exclude information on primary endpoints.

Instead, the summary should include a statement to indicate that a sound statistical analysis of the information was not possible due to insufficient data and it should state the reason for this, for example, due to evidence of lack of efficacy, safety events, poor recruitment, etc.

The EU CTR entered into force in 2014, but its provisions cannot take effect until the Clinical Trial Information System – which includes a new EU-wide submissions portal and trials database – has undergone an independent audit and been confirmed as fully functional. Once this has been done, the European Commission will publish a notice to this effect, and the CTR's provisions will apply six months later.

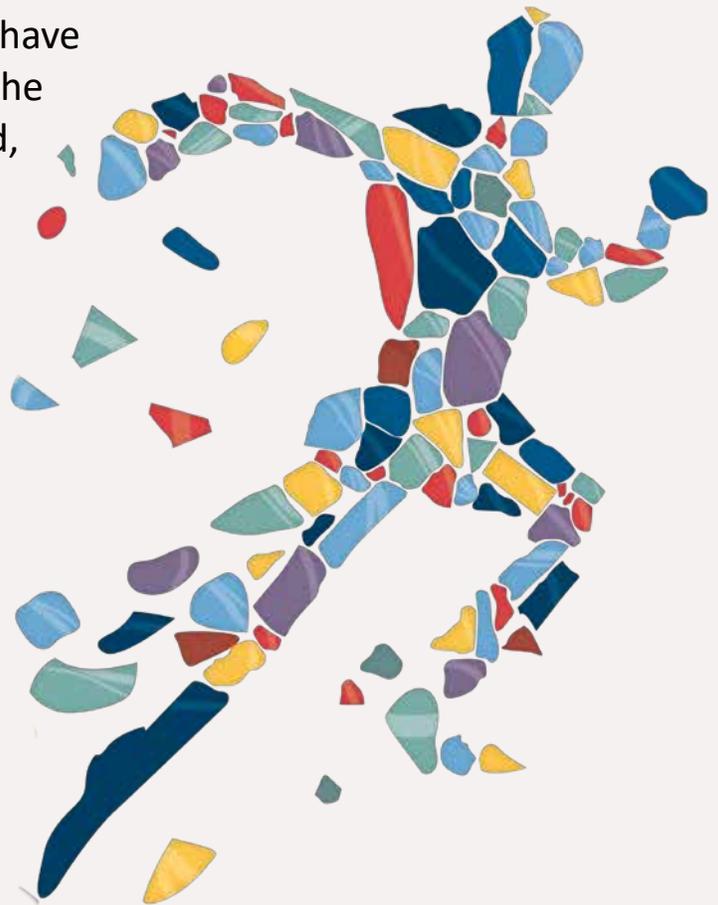
The original go-live date was October 2018, but this has been postponed because of technical difficulties with the development of the IT systems, and the

regulation will now not take effect until 2020. ❖

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Drug Development and Manufacturing Solutions Bridging the US and Japan

Over 25 years ago, we were the first Contract Research Organization (CRO) in Japan. We have since expanded our services broader into the drug development and manufacturing field, and our footprint into the U.S. Combining our Japanese high quality service standards with our extensive industry expertise, CMIC Group can bridge your needs between the U.S. and Japan.



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US FDA Expects Updates On Investigational Gene Therapy CMC Improvements

BOWMAN COX



The US Food and Drug Administration repeatedly emphasized in the final version of its guidance on chemistry, manufacturing and control information for investigational gene therapies its expectation that sponsors will continually improve manufacturing processes and analytics during development – and that they will update their investigational new drug applications (INDs) accordingly.

The agency sprinkled the final guidance document with observations and suggestions that were not in the July 2018 draft, a reflection perhaps of the learning that has occurred at the agency in the subsequent 18 months. The final guidance document still asks for lots of CMC information even though industry had complained that the draft version called for submission of nearly as much CMC information for INDs as for biologics license applications. (*Also see “Gene Therapy: Industry Seeks Greater Clarity In Final FDA CMC Guidance On INDs” - Pink Sheet, 8 May, 2019.*)

There were complaints that the draft:

- Commingled discussions of application assessment and facility inspection issues;
- Lacked clarity on how it applied to drug substances versus drug products;
- Lacked clarity on applicability to ex vivo versus in vivo gene therapies; and
- Appeared to apply to INDs in some cases and BLAs in others.

If anything, the final guidance adds more detail on inspection-related issues such as quality unit responsibilities. But there appears to be more clarity on the challenge of distinguishing drug substances from drug products, and on ex vivo/in vivo differences.

The Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Organization agreed that it would be better for the FDA to segregate its gene therapy CMC advice by

phase. However, the final document is organized the same way as the draft.

The CMC guidance document is one of six on gene therapy manufacturing and clinical development the agency issued on 28 January in final form. The FDA also issued a draft guidance document on interpreting the sameness of gene therapy products proposed as orphan drugs.

Changes In General Provisions

The final version adds a footnote saying the guidance does not apply to vaccines against infectious diseases, bacteriophage products, live biotherapeutic products, fecal microbiota for transplantation products or allergenic products.

The final version clarifies that the products excluded from a requirement to file the common technical document electronically rather than on paper because they are not intended for commercial distribution include investigator-sponsored and expanded access INDs.

And it adds a caveat about the exclusion of devices from the eCTD requirement: while the exclusion applies to in vitro diagnostics devices, it does not apply to devices such as scaffolds that are used in gene therapy delivery or in combination products.

New eCTD requirements drove the agency's efforts to produce the guidance. The agency had hoped to issue the guidance before eCTD requirements took effect, the FDA's Denise Gavin explained the day the draft was published. (*Also see "FDA's CMC Guidance For Investigational Gene Therapies Reflects Broader CMC Evolution" - Pink Sheet, 11 Jul, 2018.*)

Detailed recommendations on CMC information for Module 3 of the eCTD were revised, and the FDA added details about the types of amendments that should come with a reviewer's guide or a document that tracks the changes, clarifying that they include changes to manufacturing processes,

assays for critical quality attributes and changes in manufacturing sites or contractors.

The discussion of general information about the quality overall summary in Module 2 of the eCTD removes a request to distinguish between drug substances that are used in vivo and ex vivo.

Vectors Viewed As Playing Multiple Roles

A discussion of drug substance and drug product information for the quality overall summary in Module 2 was expanded to address the role of viral vectors. The final guidance says viral vectors used to transduce cells ex vivo should be considered critical components. However, vectors used in the final formulation to administer genetic material should be considered drug products, but may also be active pharmaceutical ingredients, "depending upon the manufacturing process and formulation of the finished dosage form," the final guidance document says.

The final version adds a sentence to a discussion of the difficult necessity of distinguishing gene therapy drug substances from their drug products that says for developers to add a separate drug substance section for vectors they use to modify cells ex vivo.

Changes In Module 3 Recommendations

There were changes in recommendations on how to fill out Module 3 of the eCTD, the part that contains detailed quality information.

Sequence data including data collected to support the genetic stability of the vector should go in the 3.2.R "Regional Information" section of Module 3 rather than, as proposed in the draft, the 3.2.S.3.1 "Elucidation of Structures and other Characteristics" section.

The FDA added a recommendation to update the description of the drug substance manufacturing process and process controls as product development proceeds.

Representative certificates of analysis for materials used in manufacturing should go in Section 3.2.A.2 of the eCTD, "Appendices – Adventitious Agents Safety Evaluation," rather than, as suggested in the draft, Section 3.2.A.1, "Facilities and Equipment."

Additional pointers and advice appear throughout the final version of the document. For example, in a discussion about cells collected by leukapheresis, the FDA added an observation that well-designed process controls and standard operating procedures for manipulating and handling in-process materials can reduce variability in the manufacturing process, the drug substance and the drug product. And in a discussion about donor screening and testing for allogeneic cells, the FDA adds a reminder that the laboratories used must be properly certified. The FDA added a reference in a section on process validation to its January 2011 process validation guidance. That section retains a discussion about expectations for good manufacturing practices oversight and quality unit responsibilities.

The FDA added a point to a section on process-related impurities, saying that sponsors should provide quality data, risk assessments and/or details of their process and product control strategies to mitigate potential risks posed by their manufacturing systems such as non-vector DNA like plasmid DNA, helper virus sequences and cellular DNA.

There is a new suggestion in the section on specifications to ask the FDA how to define the drug substance and drug product and meet release requirements in cases where the design of the manufacturing process and controls makes it difficult to distinguish the drug substance from the drug product. There is a new suggestion in the section on analytical procedures to, when possible, trend assay performance to learn more about the method and how to improve it during product development.

The FDA added a recommendation in a section on batch analysis to "gain adequate experience

with new clinical manufacturing processes prior to making clinical material."

The agency stressed that such experience is especially critical after technology transfer to a new manufacturing facility, when manufacturing processes change during development and when the plan is to use multiple manufacturing facilities.

New Drug Product Provisions

The FDA added a recommendation to a section on the compatibility of the drug product with the diluent used for reconstitution or the delivery device: because in-use and in-device stability issues can impact product performance and add risk to clinical study treatments, the agency recommends carefully controlling and assessing drug product compatibility and the final steps of product preparation and administration. Also added was a suggestion in the section on drug product purity that assays should be phase appropriate and may evolve during development as the sponsor gains understanding about the impurities present or changes the manufacturing process.

The agency significantly revised and extended its discussion of what should go into the Section 3.2.A.1 appendix on facilities and equipment. There is more detail on how to describe the quality unit, and some recommended reading on quality systems. And the agency notes there that statutory drug cGMP requirements apply to all stages of clinical investigation under section 501 of the Food, Drug & Cosmetic Act, but that regulatory requirements in Title 21, Section 211 of the Code of Federal Regulations do not apply to most Phase I INDs.

The final guidance adds a note that information specific to a regulatory region can go in the eCTD's regional section, including vector and plasmid sequencing information and delivery device information. ••

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Company Description

CMIC stands for Current Medical Information Center. In 1992, Dr. Kazuo Nakamura founded CMIC as the first Contract Research Organization (CRO) in Japan.

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