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Drug Manufacturing And Development In The Age Of Precision Medicine

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Drug Manufacturing And Development In The Age Of Precision Medicine

Growing demand for patient-centered health care presents fresh challenges for pharmaceutical product development and manufacturing. As precision medicine gains traction in research and development pipelines and the pharmaceutical marketplace, specialist providers are leveraging cutting-edge technologies to offer flexible services and capabilities that address this complex new environment.

There are multiple drivers for health care tailored to individual patients. They include demand for more cost-effective and efficient care in the face of trends such as population aging, associated chronic diseases, and escalating health care expenditure; the growing complexity of disease management, as science continues to unlock the causes, mechanisms and consequences of ill health; increased patient awareness or empowerment, facilitated by digital technologies and media; and opportunities or incentives for patients to take a more active role in managing their own health.

These broader currents are reflected in the emergence of precision medicine, both as a tool for more streamlined, targeted and productive pharmaceutical R&D and as a product platform to ensure that each patient gets the right medicine at the right time, in a format optimized for their needs. Underpinning those efforts are scientific advances ranging from data analytics and biomarkers to genomics and systems

biology, as well as novel techniques for enhancing drug formulation and delivery.

Of the 44 therapeutic new molecular entities (NMEs) approved by the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) in 2019, 11 or 25% were personalized medicines as defined by the US-based Personalized Medicine Coalition (PMC)[1]. The trend was even more pronounced in 2017 and 2018, when the PMC classified 34% and 42%, respectively, of NMEs as personalized medicines.

Improving Health Outcomes

Precision medicines can enhance both therapeutic effectiveness and drug safety, whether directly through better targeting of disease pathways, or indirectly through improved treatment facility and adherence. Without personalization, drug treatments for cancer, Alzheimer's disease, arthritis and diabetes may be ineffective for as much as 75%, 70%, 50% and 43%, respectively, of the patient populations taking these therapies, PMC notes[2].

A number of studies indicate that around 5.3% of all hospital admissions – typically, the most expensive care component of any health system – are associated with adverse drug reactions, PMC adds. Moreover, precision medicines that improve therapeutic effectiveness or present fewer side-effects may encourage patients to comply with their treatment regimens, particularly in the case of chronic diseases, such as hypercholesterolemia, where non-adherence to therapy is more likely to exacerbate the condition[3].

Precision medicine is here to stay. Personalized therapies account for more than one in every four drugs approved by the US FDA over the past six years, PMC highlights in its latest annual research report. With the "extraordinary pace of scientific innovation" in this field, the Coalition states, "the science is leading the health system away from one-size-fits-all, trial-and-error medicine and toward the utilization of molecular information to improve outcomes and make the health system more efficient"[4].

Formulating Precision Medicines

While scientific innovations are expanding the frontiers of drug discovery and development to produce a new generation of highly targeted medicines, these products must also be presented in formulations and delivery systems capable of accommodating novel modalities such as nucleic acids or monoclonal antibodies. At the same time, both new and existing medicines, as well as the health systems that want these products to be used as safely, effectively and consistently as possible, benefit from being offered in formats aligned with precision-medicine strategies.

In broad terms, this is about ensuring that each patient has access to a drug tailored at every level to his or her individual needs and circumstances. Flexible, personalized dosing is particularly valuable in populations where drug administration and adherence issues are most prevalent, such as the elderly or children.

These patients may not just need help with physical challenges such as swallowing pills or keeping to a medication regime. They may also be more susceptible than the general population to the negative impact of off-target drug effects. Precision formulations also bring added value in therapeutic areas where controlled drug delivery is an important element of therapy. One example would be extended-release dopamine agonists used to treat Parkinson's disease.

How CMIC Supports The Precision Medicine Agenda

CMIC Group is a Pharmaceutical Value Creator and Japan's largest contract research organization. As a one-stop shop for drug development and manufacturing services, from preclinical and clinical through to commercialization and post-marketing surveillance, it has the experience and agility to handle a broad range of drug formulation, delivery, dosage and presentation requirements. These include powders/granules, capsules, injectables, lipids, semi-solid dosage forms and topical solutions, as well as oral solid formats such as immediate/sustained-release and orally disintegrating tablets (ODTs).

In terms of finished products, solid-dosage forms still account for a large share of the worldwide market for contract development and manufacturing of medicines. That share was 41% in July 2018, according to a breakdown by PharmSource. Nonetheless, there is also a good deal of market diversification.

This reflects, for example, the primacy of injectable dosage forms (27% of the global contract market in July 2018, according to PharmSource) among the more targeted biologicals now dominating the new-drug landscape. But it also underlines the need for alternative formats, such as specialty (21% of the worldwide market) and semi-solid/liquid dosage forms (11%), that favor choice and convenience in addressing the full range of patient needs in a more personalized health care environment.

Conducted mainly in Japan and the United States, CMIC's pharmaceutical-development activities span:

- **Pre-formulation research.** Physicochemical evaluation, including particle engineering (e.g., micronization) and Good Laboratory Practice supply (manufacturing and stability assessment).
- **Formulation and process development.** Dry (slugging/roller compaction) and wet (fluid-bed, high-shear) or hot-melt granulation, tableting, encapsulation (active pharmaceutical ingredients, powders, granules and tablets), coatings (particles, tablets).
- **Packaging design.** Blister packaging, sachets, bottles, clinical-use cards.
- **Good Manufacturing Practice** (GMP) Supply (~30 kg/sub-batch/250 kg/batch).
- **Assay method development/validation,** stability testing.

Exhibit 1

Dosage Form Capability Of CMIC's R&D

Line-Ups (Dosage Forms)		Equipment (Solid)
• Powder, fine granule, granule • Capsule • Immediate release tablet • Orally disintegrating tablet • Modified release tablet	• Injectables • Lyophilized products • Lipid formulation for injection • Semi-solid dosage form Hydro-gel Suppository • Solution for topical application	• Granulator 5 Kg Scale 30 Kg Scale • Blister packaging (AL-AL available) • Bottling • Secondary packaging

The Group's contract development and manufacturing organization, CMIC CMO, also offers development services for injectable medicines. These include liquid and lyophilized formats for low-molecular weight compounds, proteins such as monoclonal antibodies, and semi-solid products (e.g., suppositories, ointments, creams and lotions). Process development and characterization, GMP supply and commercial manufacture of these dosage forms is handled at GMP facilities in Ashikaga and Toyama, Japan. Pharmacokinetic and toxicity study services are also available through CMIC Pharmaceutical Science (CPhS).

Innovations In Drug Development And Manufacturing

CMIC Group is committed to innovations in drug development and manufacturing that extend the options for personalized therapy. To this end, it has formed alliances with companies such as Accu-Break Pharmaceuticals, whose Accu-Break® technology allows tablets to be divided easily into

Exhibit 2

CMIC's Pharmaceutical R&D Service

API	FIH to Pa	Beyond P2b
Preformulation (~100g)	Formulation Dev I (~1kg)	Formulation Dev II (~30kg)
• Evaluation of physio-chemical properties: Cystallinity, Hygroscopicity, Solubility, etc. • Crystal engineering • Micronization • Assay development • Excipient compatibility • Preparation of PIC/PIB • Tox Supply • Evaluation of original products	• Lab scale experiment: Dry blend, wet granulation, encapsulation, tableting • Evaluation of formation & stability property • Clinical packaging development • GLP Supply • Animal PK/TK Supply • Improvement of existing formulation	• Dry granulation • High shear & fluidbed wet granulation • Hot melt granulation • Encapsulation, tableting • Powder coating • Film coating • Commercial packaging development

Formulation Development	IND Support	Clinical
Demo batches (5~30kg)	GMP Supply (5~30kg)	NDA Filing
• Process characterization • Assay validation • Spec development for clinical images • Spec development for raw materials • Preliminary stability assessment • In Vitro BE evaluation	• GMP Supply • Release testing • Quality assurance release • Stability assessment for products • Tech-Transfer • Filing document support • Support product life cycle management • Alternate formulation • Product improvement	

precise doses customized to individual patients; Aprecia Pharmaceuticals, which uses 3D printing to manufacture ODTs at high drug doses and in multiple formats; and Freund-Vector Corporation, for its advanced Granurex® granulation and powder/spray coating technology.

Under an agreement with **Accu-Break Pharmaceuticals**, CMIC CMO will act as an exclusive contract-manufacturing agent for the proprietary Accu-Break® technology in Japan and the US. Accu-Break® creates bi-layer tablets compromising, in equal volumes, a heavily scored active top layer and a placebo substrate bottom layer.

The drug-free layer serves as a 'break zone' that enables the active layer to be split readily and accurately into precise doses. This type of tablet is needed when individual patients need different doses, or where formulations are tailored to children or the elderly, and strict dose adjustment is paramount. The Accu-Break® technology can also be used to design and manufacture tablets with multiple deep scores, which is difficult to achieve with conventional tableting technology.

Tablet-splitting is a common means of adjusting drug doses, facilitating ingestion or saving money on medicines. It is especially prevalent with narrow therapeutic-index drugs taken by the elderly, such as warfarin and digoxin. At the same time, these are among the medicines most often implicated when elderly patients require emergency hospital care. One reason for these emergency visits may be the difficulty older patients have in subdividing conventionally scored tablets of narrow therapeutic-index drugs into accurate fragments that maintain dosing integrity[5].

CMIC CMO already has GMP facilities in place for manufacturing Accu-Break® Tablets, both for investigational use and in commercial quantities. Moreover, it has successfully developed a product using this technology for submission as a New Drug Application through the 505 (b)(2) pathway in the US. The new product will allow patients with early disease onset to use lower dosages of medication and maintain their drug blood levels at the optimum physiologic range.

"The technology facilitates and simplifies dose adjustment during initial titration," states Michael O'Donoghue, senior director of operations at CMIC CMO USA. "Later, as the disease progresses, it allows the patient to personalize the amount and timing of dosage on an as-needed basis, therefore avoiding overdoses that cause motor complications." The Accu-Break® technology can also be used in other therapeutic areas where multiple dosages are needed, as well as in pediatric and veterinary medicine.

CMIC CMO is developing business opportunities in Japan for ZipDose®, **Aprecia Pharmaceuticals'** 3D printing (3DP) technology for the manufacture of high-dose orally disintegrating tablets. The ZipDose® platform uses 'powder-liquid' or 'binder-jetting' 3DP technology, developed at the Massachusetts Institute of Technology in the US, to assemble dosage forms layer by layer.

This eliminates the potential for particle disruption (especially important with modified-release formulations and taste-masked ODTs), and enables multiple dosage strengths to be produced using a single blend. It also gives manufacturers the flexibility to create tablets of multiple shapes, sizes and characteristics – for example, with different ingredients in different parts of the tablet.

Dosage forms can be designed to disperse on contact with liquid or to be swallowed whole using the 3DP technology. Moreover, ZipDose® produces tablets that disperse in the mouth

within five seconds, and with very little water. "ZipDose® technology uniquely addresses the need for high-dose orally disintegrating tablets to reduce the burden on patients who have difficulty swallowing, as well as on caregivers and health care professionals who seek better ways to improve administration adherence," says Makoto Matsukawa, chief executive officer of CMIC CMO.

The ZipDose® platform is also fast and efficient. At commercial scale, the current iteration of the 3DP technology (which is being upgraded) can produce more than 10,000 tablets per hour. Freedom of structural design allows the tablet interior to be closer to a powder, by printing with a minimal amount of binder in the tablet core, in addition to achieving high porosity.

The ZipDose® method is particularly effective for controlling the disintegration of a large ODT. It means a high volume of powder can be formed into an orally disintegrating tablet, and drug levels of more than 1,000 mg can be accommodated in a tablet with excellent rapid-disintegration properties. Furthermore, tablets can be manufactured without damaging bitterness-masking or release-control particles.

All of this creates opportunities for flexible dosing and controlled drug release, enhanced taste-masking, and entirely new dosage forms, thereby maximizing innovative value at launch, in-market differentiation, patient accessibility, and lifecycle management. The ODT market worldwide is projected by Persistence Market Research to expand at a compound annual growth rate of 11.5% from US$11.4 billion in 2017 to US$27 billion in 2025. In Japan, ODTs account for 7.1% of all tablet revenues, compared with just 1% in the US.

ODTs are applicable across disease areas, although the capacity to combine solid and liquid dose forms makes them especially suitable for drug administration to pediatric and elderly patients, as well as patients with more general difficulties in swallowing tablets or capsules. Once again, the end-benefits are reduced dosage errors, more convenient, patient-centric administration, and better medication compliance.

CMIC also has access to **Freund-Vector Corporation**'s Granurex® conical rotor-granulation and powder/spray-coating technology. Traditionally, granulation, bead coating and particle coating in pharmaceutical manufacturing have relied on fluid-bed, top spray and Wurster (bottom-spray) coating processes. With advances in precision metal machining, the rotor is now conical and the gap between the stator (the stationary part of the rotary system) and the rotor can now both be fixed and significantly smaller than with a traditional flat rotor.

This fixed small gap enables very low process-airflow volumes to be distributed at high velocity. Combined with the kinetic energy generated by the spinning rotor disk, it means the micronized active pharmaceutical ingredient (API) can be granulated into small and uniformly shaped spherical particles carrying high drug loads. These may be further refined through conical rotor-powder coating, or spray coating, to incorporate extended release, enteric-release or taste-masking properties.

With the Granurex® technology, high drug-loaded granulations and coated beads can be processed at significantly higher speeds than with traditional granulation and sphere-coating technologies. The Granurex® processes are also directly scalable, so process times remain the same as the scale increases from R&D through to commercialization, saving time and money throughout the product lifecycle. Moreover, the technology can be used to coat API particles directly, making it ideal for direct taste-masking of APIs and creating unique drug-release profiles for powders, granules, tablets and capsules.

Microneedles And More

CMIC has also established partnerships with several companies for access to **medical microneedles** that improve transdermal drug absorption. One advantage of transdermal drug delivery over oral and injectable formulations is ease of confirming drug administration from the outside the body. Discontinuing drug administration is also simpler and more immediate with transdermal delivery.

At the same time, a limited number of medicines are available in topical formulations. Microneedles can be used across a wide range of transdermal formats to facilitate drug absorption through the skin. The size of the needles avoids patients feeling any pain when the transdermal patch or device is applied.

CMIC will continue seeking out opportunities to expand its existing drug development and manufacturing capabilities, in line with fast-evolving demand for more precise approaches to pharmaceutical intervention. Better-targeted medicines bring significant benefits to patients, health systems and society at large. But they must also be available in formulations and delivery systems that optimize uptake and adherence across the full spectrum of patient needs.

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