PRECISION MEDICINE

an Overview

WITH DALTON

Peter Pekos

Company Vision

"Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

This technical report is intended to provide an overview to key stakeholders including regulatory professionals on precision medicine. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

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Precision Medicine

Precision medicine is an emerging strategy that considers individual variability in genes, environment, and lifestyle to identify, treat, predict, and prevent disease among patients.

Precision medicine has become increasingly feasible due to improved understanding and advancing technologies, such as next-generation sequencing, of individual variability in the human genome.

DID YOU KNOW?

The global market for precision medicine was valued at 43.6 billion USD in 2016 and is estimated to triple in the next decade.

$43.6 b

Genomics

The field of molecular biology known as genomics is concerned with the structure, function, evolution, and mapping of genomes. Next-generation sequencing and biomarkers are examples of how genome characteristics are measured and analyzed.

Precision medicine uses genomics to identify disease-specific variants or biomarkers in a patient's genome to determine the best-suited treatment available to them.

Next-generation sequencing (NGS)

The precise and quick sequencing of genes is made possible by next-generation sequencing technology. Next-generation sequencing works by sequencing fragments of an individual's DNA or RNA molecules and ligating them to adapters, rather than sequencing their full genetic code from scratch. This is then compared to a DNA library that undergoes clonal amplifications and uses algorithms to fill in the blanks. During the procedure, any variations or mutations can be identified.

Biomarkers

Biomarkers are measurable substances within an organism such as antibodies, thyroid hormone levels, or prostate-specific antigens (PSA), whose presence is indicative that a normal biological process, or a pathogenic process such as disease, infection, or toxicity is taking place within an organism.

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Pharmacogenetics

Precision medicine also uses pharmacogenomics (the study of how genes affect a person's response to particular drugs) to develop effective and safe treatment options that are tailored to the variations in a person's genes.

Precision Medicine vs Personalized Medicine

By virtue of its name, the term "personalized medicine" may be easily misinterpreted to mean that every patient can receive completely individualized treatments, which is not the case. Hence, the medical industry is moving away from this term and toward the term "precision medicine," which more accurately infers a treatment approach that considers an individual's unique characteristics, such as genetic variability.

Foundation of Precision Medicine

Precision medicine aims to match each individual patient to the appropriate therapies and at the appropriate dose to initiate the desired response. Hence, it is critical to understand the primary causes for variation in response to treatment: pharmacokinetics and pharmacodynamics.

Pharmacokinetics (PK) is concerned with the movement of drugs within the body. PK variability includes:

- Subject phenotype: weight, body surface area, organ status, age, ethnicity, gender, microbiome
- Subject genotype: polymorphisms in metabolizing enzymes or transporters
- Disease response or advancement over time
- Lifestyle and environmental variables including concomitant medications, diet, and smoking
- Adherence to the prescribed course of action, dosage, and medicine formulation.

Pharmacodynamics (PD) is concerned with the mechanism of action and effects of a drug. PD variability includes polymorphism in drug target or downstream pathway and driver mutations of disease heterogeneity.

Therapeutic drug monitoring is also a key component of precision medicine. Therapeutic drug monitoring provides insight into dosage adjustments that may be needed to meet the predefined target exposure in each patient, lowering response variability. Drug doses may be adjusted based on biomarkers such as glucose/glycosylated hemoglobin, cholesterol, prostate-specific antigens, and blood pressure.

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Examples of Precision Medicine as A Treatment Tool

- The drug Ivacaftor to treat individuals with cystic fibrosis (CF) who have very specific pathogenic mutations in the gene CFTR.
- The use of Primaquine to treat malaria in people who do not have G6PD gene variants.
- The use of Imatinib to treat chronic myelogenous leukemia (CML) in patients whose tumor harbors the Abelson proto-oncogene (abl) and breakpoint cluster region (bcr) fusion mutation.

Example of Precision Medicine as A Predictive Tool

Abacavir is likely to cause multi-organ system hypersensitivity in persons with HIV infection with the HLA-B*5701 gene. Therefore, it is advised that all patients who are administered Abacavir undergo genetic testing.

Example of Precision Medicine as A Preventative Tool

Drugs like warfarin, primaquine (PQ), and imatinib that seem to only work without side effects when a patient has a specific genetic profile.

Precision Medicine

Patient's genome

Sample (i.e., biomarker)

Genome sequencing/ testing (i.e., NGS)

Genome analysis

Pharmacogenetic interpretation

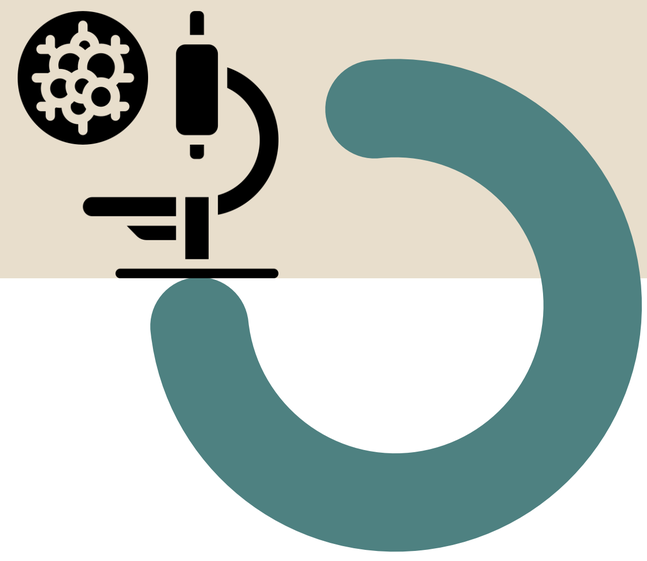
Precision medicine application (diagnostic, treatment, prediction, prevention)

Precision Medicine and Cancer

Certain gene or protein changes can affect how cancer responds to certain treatments. Therefore, before starting treatment, health care providers may take a biopsy to test the cancer cells for certain gene and protein changes to help determine which treatments are likely to work best.

The two types of treatment most commonly used in oncology precision medicine are targeted drug therapy (drugs designed to attack a specific target on cancer cells) and immunotherapy (medicines used to help the body's immune system attack the cancer).

For more on oncology treatments, view our latest whitepaper, *Drug Development in Oncology: An Overview.*



Challenges in Precision Medicine

- Relies on evidence outside of traditional randomized, drug-centered clinical trials
- Absence of concise regulatory guidance
- Higher setup costs
- Higher medication prices for specific subgroups of patients
- Legal, social, and ethical issues
- Patency and intellectual property concerns
- Privacy, confidentiality, and patient rights concerns

All these issues impact safety, effectiveness, and sustainability.

DID YOU KNOW?

In the US, The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was enacted to ensure that personal medical information stored, accessed, or processed adheres to a set of privacy guidelines.

Next Step & Opportunities in Precision Medicine

- Elevating mechanistic understanding, such as why the body reacts negatively to a treatment and what triggers differences in efficacy
- Improving manufacturing capabilities
- Further exploring current technologies (i.e., omics including proteomics, metabolomics, and genomics)
- Advancing in new technologies (i.e., CRISPR)

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Regulatory

The emergence and evolving field of precision medicine necessitate that global regulatory bodies adopt an integrated policy framework that balances the needs of patients, industry, and science without impeding the development of this revolutionary sector. This may entail adopting new approaches to product approval.

Although regulatory guidance among global regulators is still in development, the FDA provides can serve as an example on how to approach precision medicine.

In 2015, precisionFDA was introduced - a cloud-based site for community research and development that enables users from across the globe to share data and tools to test, pilot, and validate existing and novel bioinformatics approaches to next-generation sequencing processing.

In 2020, the FDA published several guidance documents on the manufacturing and clinical development of gene and cell-based therapeutic products, which provided updated guidance on the process to obtain approval for the commercialization of new therapeutics, including when and under what circumstances the use of a new drug must be preceded and/or accompanied by a diagnostic or screening test.

In 2021, the FDA provided further clarity on developing new drug products in the age of individualized medicine, specifically for the development of antisense oligonucleotide (ASO) products, as it is the most advanced individualized genetic drug products thus far, by releasing a new draft guidance on investigational new drug (IND) submissions for individualized ASO drug products.

The CDER has also been developing infrastructure programs and review capacity to be on the leading edge of precision medicine initiatives.

As the FDA and other health authorities continue to develop clearer regulatory pathways in precision medicine, life sciences industries must prepare to quickly adopt shifts in regulations related to precision medicine.

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Dalton's
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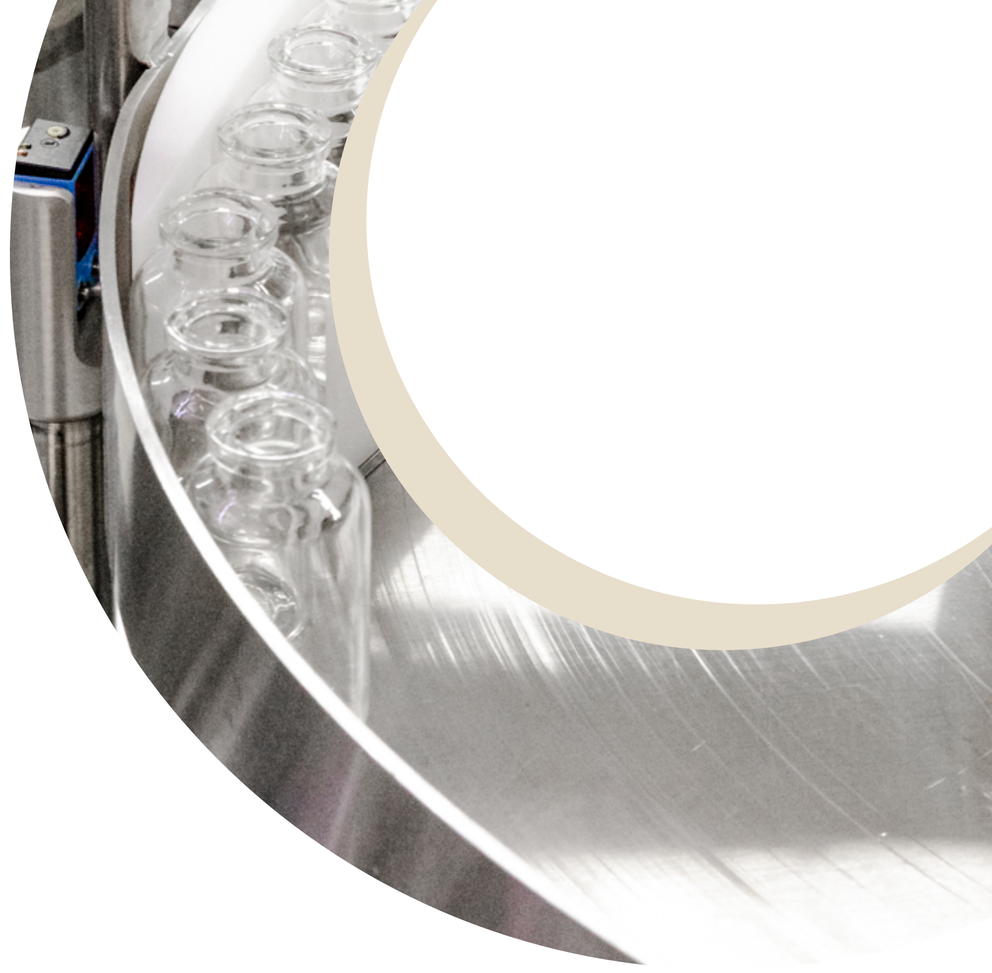

We bring over 35 years of experience developing products for our clients that are compliant, transferable, and scalable.

At Dalton we can help with drug innovation through our cGMP APIs. Our skilled scientists can support your drug discovery process through API synthesis for all stages of pre-clinical and clinical trials as well as small scale commercial manufacturing. We provide integrated process development, API manufacturing and finished dose manufacturing at a single location with the expertise required for developing a process that is robust, transferable, and scalable to meet your requirements.

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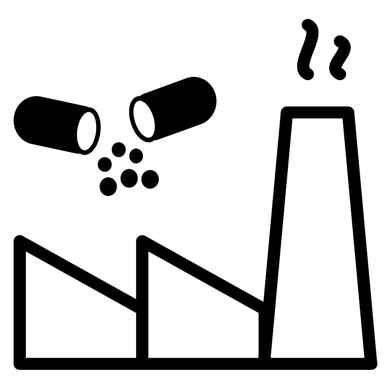

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