

# PRECISION MEDICINE DRUGS *pleonasm or reality?*

The complexity and uniqueness of human metabolism and physiology in the past decade has been highlighted and dissected. Arguments have been made to suggest that our lack of understanding about human individuality has led to the limited efficacy and safety of many marketed therapeutic drugs. The Drug Discovery and Development (DDD) process continues to slowly evolve to address this perpetual problem. More recently with the advent of personalised and precision medicine, there have been efforts made to address individual complexity. An understanding of personalised versus precision medicine is necessary in order to understand such endeavours. This has led to the development of what have been labelled ‘Targeted’ or ‘Personalised Medicine Drugs’. Based on the differences between the N-of-1 model (personalised medicine) and the I-in-N model (precision medicine), we propose that a more appropriate name is ‘Precision Medicine Drugs’. Such issues are discussed herein.

There appears to be a considerable disconnect between the expectation of stakeholders and the pragmatic demands of bringing a therapeutic drug to market<sup>1</sup>. The Drug Discovery and Development (DDD) process was conceived in the early 1960s and has remained relatively unchanged over the past 50-plus years. It continues to be risk-laden, slow, costly and inefficient, as well as delivering products of questionable value in terms of safety and efficacy<sup>1</sup>. For example, cumulative risk is associated with any effort to bring a drug to market. The initial screening of compound libraries (104-106) leads to a single lead compound that has only an ~8% chance of successfully traversing the clinical trials gauntlet<sup>2</sup>. In addition, the failure rate of a drug candidate at each stage of clinical trials is reported to be, 46% (Phase I), 66%

(Phase II) and 30% (Phase III)<sup>3</sup>. The average time required from drug discovery to product launch remains at an eye-watering 12-15 years<sup>4</sup>. Finally, the total capitalised cost of bringing a new drug to market was recently estimated at a staggering \$2.87 billion<sup>5</sup>.

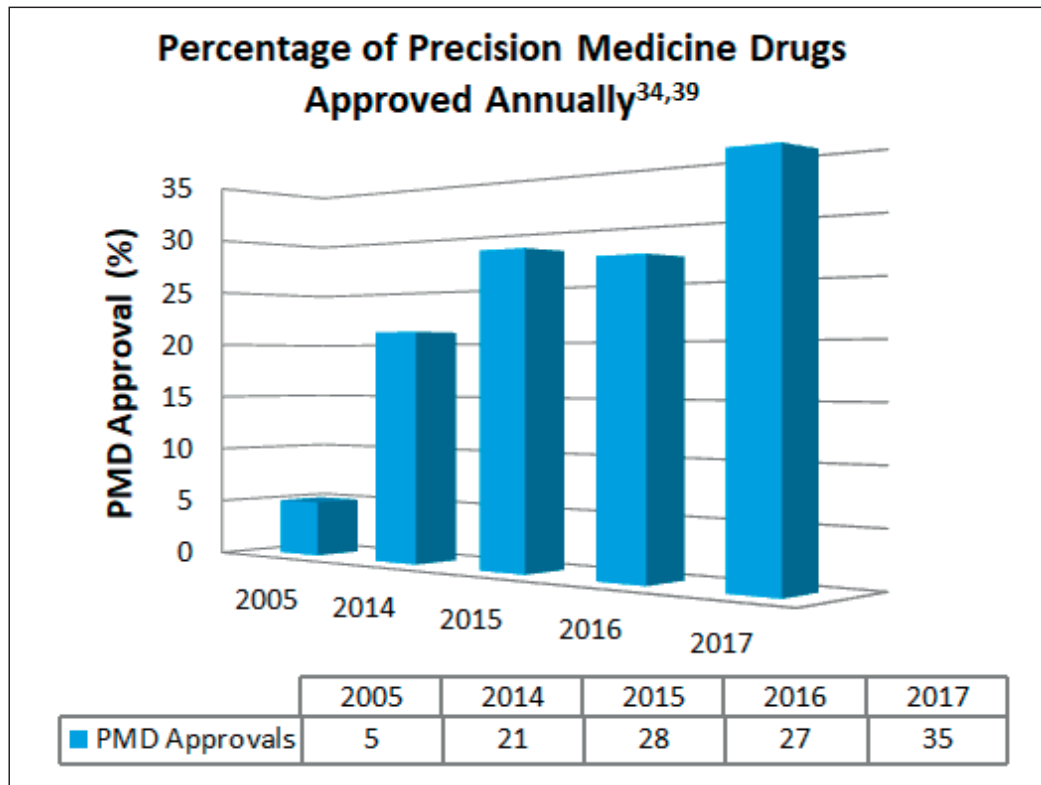
The metrics associated with the DDD process are clearly problematic. There is also a concern about the value proposition of current, marketed therapeutic drug products produced by the DDD process. These issues include:

#### i. Drug safety

Not all approved drugs stand the test of market pressures due to the scrutiny of pharmacovigilance and post-market surveillance. In some cases approved drugs can be removed from the market

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because they manifest safety, effectiveness or economic problems. For example from 1994-2015, the USA Food and Drug Administration (FDA) issued 215 ‘Withdrawal of Application’ notices<sup>6</sup>. During that same time period the FDA actually recalled 26 drugs from the US market predicated primarily on safety concerns<sup>7</sup>.

**ii. Drug effectiveness**

There is now a significant body of evidence that indicates individual patients diagnosed with the same disease indication respond differently to the same therapeutic drug<sup>8</sup>. For example Spears and co-workers analysed the effectiveness of a number of different drug classes against major disease indications<sup>9</sup>. They found that most drugs were 50-75% effective as determined by patient responses. The lowest patient responders occurred with conventional cancer chemotherapy (25%) whereas the highest percentage of patient responders was treated with Cox-2-inhibitors (80%). Therapeutic drugs were reported to be ineffective for Alzheimer’s (70%), arthritis (50%), diabetes (43%), and asthma (40%) patients<sup>9</sup>.

**iii. Pricing**

Approved drug price points are determined by market forces that include drug safety and efficacy

differentiation, market need, patient acceptance, sales and marketing strategy and IP position as well as individual R&D costs<sup>10</sup>. In many cases, pharmaceutical companies have used rampant R&D costs to maximise prices charged to the patient/consumer. Unfortunately, even in such a favourable economic climate, only 3-in-10 approved drugs generate revenues that are at least equal to or greater than average R&D costs<sup>11</sup>.

We have argued in the past that the ‘Blockbuster Model’ has inadvertently led to the ‘wagon-of-woe’ for the DDD process<sup>12</sup>. This model focused on a ‘one drug-one target’ mechanism that was potentially safe and effective in a large, but heterogeneous population. We have suggested the use of more efficient technology usage<sup>13</sup>, decision-making tools<sup>13</sup>, systems biology<sup>14,15</sup>, and personalised/precision medicine<sup>16</sup> in order to overcome the limitations of such a model. More recently, we presented the concept of a combined systems biology-personalised/precision medicine approach to the development of more effective and safe therapeutic drugs<sup>17</sup>, particularly in the treatment of Alzheimer’s Disease<sup>18</sup>. In this manuscript we introduce the concept of ‘Targeted’ or ‘Precision Medicine Drugs’ which is a logical outflow from a combi-

nation of systems biology and personalised/precision medicine approach to DDD.

### Personalised and Precision Medicine

In order to understand the concept and nomenclature of a 'Precision Medicine Drug' it is important to first appreciate the subtle but real differences between the terms Personalised versus Precision Medicine. As with any new and emerging field of endeavour, clear definitions are often a work in progress as terminology evolves and/or disappears. In the case of Personalised and Precision Medicine it is complicated by the fact that these terms are often mistakenly used interchangeably as umbrella descriptors. Hence, the terms Personalised and/or Precision Medicine and how they are practised have broad and confusing interpretations<sup>19</sup>.

#### Personalised Medicine

Historically, Personalised Medicine emerged in the early 2000s. The Personalised Medicine Coalition (PMC), founded in 2004 to represent the interests of the then fledgling Personalised Medicine community, defined Personalised Medicine as "...an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from those tests with an individual's medical history, healthcare providers can develop targeted treatment and prevention plans"<sup>20</sup>. Other pioneers of Personalised Medicine continued to stress the importance of the individual. The belief was that "actionable understanding of disease and wellness as a continuum of [molecular] network states unique in time and space to each individual human being" is possible<sup>21</sup>. Redekop and Madsen have surveyed that literature and the plethora of competing definitions of Personalised Medicine. They concluded that the most appropriate definition for Personalised Medicine is "the use of the combined knowledge (genetic or otherwise) about a person to predict disease susceptibility, disease prognosis or treatment response and thereby improve that person's health"<sup>22</sup>. They reinforced the idea of specific analyses for treatment of the individual patient.

#### Precision Medicine

The term 'Precision Medicine' was first coined by Clayton Christensen in his book the *Innovator's Prescription* published in 2009<sup>23</sup>. However, the descriptor 'Precision Medicine' did not gain wide acceptance and usage until a report entitled *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* was published by the US

National Research Council (NRC) in 2011<sup>24</sup>. The report laid out a series of recommendations for disease ontology predicated on molecular information content in the form of causal genetic variants or genomic information rather than a symptom-based classification system. This prompted a firestorm of activity, and the initial focus of Precision Medicine was on genetic and genomic underpinnings of disease. For example, the Institute of Precision Medicine provided an early definition that stated: "Precision medicine is targeted, individualised care that is tailored to each patient based on his or her specific genetic profile and medical history. Unlike traditional medicine where one-size-fits-all, practitioners of precision medicine use genomic sequencing tools to interrogate a patient's entire genome to locate the specific genetic alterations that have given rise to and are driving his or her tumour"<sup>25</sup>. This type of approach garnered significant attention, but it was difficult to discern the fundamental differences practiced by the Precision Medicine versus Personalised Medicine communities<sup>19</sup>.

#### Differences between Personalised versus Precision Medicine

The NRC Council Report in 2011 attempted to define and differentiate Precision Medicine from Personalised Medicine. The report stated: "Precision Medicine is the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side-effects for those who will not. Although the term 'personalised medicine' is also used to convey this meaning, that term is sometimes misinterpreted as implying that unique treatments can be designed for each individual"<sup>24</sup>.

It should be noted that the word 'precision' in Precision Medicine is used colloquially to include both accurate and precise scientific measurement<sup>24,26</sup>. However, based on the NCR definition, it is clear that the Precision Medicine approach utilises individuals and defined (sub)-population-based cohorts that have a common network of disease (or health) taxonomy. In addition, it requires an integrated molecular and clinical profile of both the individual as well as the subpopulation-based cohort. Zhang has described Precision Medicine,

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predicated on the individual patient/subpopulation model, as “one-step-up” from the individual patient focus of Personalised Medicine<sup>27</sup>. Implicit in his statement is that Personalised Medicine is based on a single individual ‘N-of-1’ model whereas Precision Medicine uses a ‘1-in-N’ model predicated on widely-used biostatistical data analysis and “big data” analytical tools. Precision Medicine can best be described as an amalgam of Personalised Medicine and modern conventional medicine.

It is clear that Precision Medicine has attracted huge attention and is in the ascendancy compared with Personalised Medicine. The attributes of the 1-in-N model of Precision Medicine have been more fully accepted and rendered into practice compared to the challenging N-of-1 model of Personalised Medicine. A number of disease area specialties have started to query or implement elements of Precision Medicine into everyday practice and treatment of patients and they include such diverse areas as diabetes<sup>28</sup> and Alzheimer's Disease<sup>18</sup>. In particular, the oncology community has been quick to embrace and reduce Precision Medicine to practise in the diagnosis and treatment of a wide variety of cancers<sup>29,30</sup>, and has pioneered the development and use of Targeted or Precision Medicine Drugs.

### Precision Medicine Drugs

We have discussed above the limited efficacy of currently available therapeutic drugs. These efficacy limitations also apply to blockbuster drugs. For example, the effectiveness of Cymbalta (duloxetine- treatment for depression) only applies for 1-in-9 patients, Copaxane (glatiramer acetate – multiple sclerosis) is 1-in-16 patients and for Nexium (esomeprazole – heartburn) it is 1-in-25 patients<sup>31</sup>. Even more stunning is the report that the widely prescribed class of blockbuster statin drugs, used in the management and treatment of elevated cholesterol levels, is only effective at a 21% response ratio<sup>32</sup>. Such poor efficacy has led to a reassessment of the clinical trial process<sup>31</sup>. Imagine if a manufacturing and QA/QC process resulted in your smart phone only working 10-20% of the time in an emergency situation!

The classical form of clinical trials requires the compilation of a number of specific measurements from thousands of selected patients. This is a costly, time-consuming, risky and inefficient process. In an attempt to enhance clinical trial design and potentially account for patient variability, a number of other approaches have been utilised. A ‘basket’ clinical trial utilises a specific biomarker, often

a genetic marker in oncology trials, and a mode of action for the candidate drug against a number of related disease indications. In contrast, an ‘umbrella’ trial tests the effectiveness of a myriad of drug candidates against a single disease indication<sup>31</sup>. More recently, Schork has suggested an N-of-1 clinical trial, in which a systems-level analysis of data is collected on an individual patient who is being treated with a therapeutic agent<sup>31</sup>. In all cases the intertwining of appropriate biomarkers, companion diagnostics and mechanistic understanding of the drug mode of action are driving such efforts.

### Definition of a Precision Medicine Drug

The oncology research and clinical communities have pioneered the development of ‘Targeted Therapies’. It was long recognised that in a patient population with the same clinical disease state, heterogeneity of the molecular etiology and development of the tumour led to different therapeutic responses by individual patients. However, a targeted therapy may be effective in a sub-population of patients who have different underlying molecular similarities. The PMC has extended this concept beyond just the oncology sector. When evaluating New Medical Entities (NMEs) approved by the FDA, PMC categorised personalised medicines as “those therapeutic products for which the label includes reference to specific biological markers, identified by diagnostic tools, that help guide decisions and/or procedures for their use in individual patients”<sup>33,34</sup>. However, we would propose, based on our discussions above concerning the differences between personalised (N-of-1 model) versus precision (1-in-N model) medicine that it is more appropriate to refer to them as ‘Precision Medicine Drugs’.

It is important to note that the physician utilises the biological marker(s) listed on the drug label in prescribing the Precision Medicine Drug. This should not be confused with Companion Diagnostic biological markers. There appears to be widespread agreement that a Companion Diagnostic is a biomarker(s) used in a specific context that provides biological and/or clinical information that enables better decision-making about the development and use of a potential drug therapy<sup>35</sup>. In recent years the use of Companion Diagnostics has found broad applicability in clinical trials and are used in the optimised selection of clinical trial patient populations. In particular they have found use in selection or exclusion of patient groups for treatment with that particular drug in determining responders and non-responders to the

therapy, as well as early indications of adverse toxicological effects<sup>35,36</sup>.

**Case studies of Precision Medicine Drugs**

**Herceptin:** Herceptin (trastuzumab) is a humanised monoclonal antibody and targets the HER-2 receptor in breast cancer patients. This drug was developed and sold by Genentech/Roche. The FDA and EMA both approved its use in 1998 and 2000 respectively for the treatment of breast cancer, but only for patients for HER-2 (+) patients. Herceptin became the first Targeted or Precision Medicine Drug to be approved, although at that time such terminology was not in common usage<sup>37</sup>.

The development history of Herceptin is instructive in the evolution of Targeted and Precision Medicine Drugs. In the late 1980s, Professor Slamon (UCLA) and Professor Gullick (ICR-

London) reported that some human breast cancers manifested overexpression of the HER2 gene, as well as the protein product her-2, resulting in a poor prognosis for the patient. Gullick in conjunction with Dr Barnes (Imperial Cancer Fund Research Unit, Guys Hospital) reported that HER-2 (+) tumours were much more aggressive than HER-2 (-) tumours<sup>37</sup>. The fact that her-2 protein was present at high concentrations indicated it was a good target for therapeutic intervention to treat HER-2 positive tumours. Dr Sliwkowski and colleagues (Genentech) developed a monoclonal antibody to target her-2 protein, and the antibody was ultimately named Herceptin.

**Gleevec:** Gleevec (imatinib) is a 2-phenyl amino pyrimidine derivative and acts as a specific inhibitor of a number of tyrosine kinase enzymes.

**Table 1:** Precision Medicine Drugs approved by FDA in 2017. Data taken and adapted from PMC Progress Report<sup>39</sup>

	BRAND	DRUG NAME(S)	INDICATION(S)	LABEL BIOMARKER
1	Kisqali	Ribociclib	Advanced breast cancer	HR and HER2
2	Bavencio	Avelumab	Metastatic Merkel cell carcinoma	PD-L1 levels
3	Zejula	Niraparib	Recurrent epithelial ovarian, fallopian tube or peritoneal cancers	BRCA mutation
4	Austedo	Deutetrabenazine	Huntington's Disease associated Chorea	CYP2D6
5	Ingrezza	Valbenazine	Tardive dyskinesia	CYP2D6
6	Brineura	Cerliponase alfa	CLN2 type Batten disease	TPPI
7	Alunbrig	Brigatinib	Metastatic non-small cell lung cancer	ALK
8	Rydapt	Midostaurin	Acute myeloid leukaemia	FLT3
9	Imfinzi	Durvalumab	Advanced urothelial carcinoma	PD-L1
10	Nerlynx	Neratinib maleate	Reoccurring breast cancer	HER2
11	Vosevi	Sofosbuvir, Velpatasvir Voxilaprevir	Hepatitis C	HCV genotype
12	Idhifa	Enasidenib	Refractory acute myeloid leukaemia	IDH2
13	Mavyret	Glecaprevir & Pibrentasvir	Hepatitis C	HCV genotype
14	Verzenio	Abemaciclib	Advanced breast cancer	HR and HER2
15	Mepsevii	Vestronidase	Mucopolysaccharidosis type VII (Sly syndrome)	MPS VII
16	Hemlibra	Emicizumab-kxwh	Hemophilia A	Factor VIII antibody



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The drug was developed and is now sold by Novartis. The FDA and EMA approved the drug in both the US and Europe respectively in 2001, for the treatment of chronic myeloid leukaemia (CML). However, the drug was approved and thus prescribed only for patients with Philadelphia chromosome BCR-ABL-positive CML<sup>38</sup>. The journey of Gleevec began with the observation by Nowell and Hungerford in the early 1960s that a number of patients diagnosed with CML had an abnormally short chromosome. This characteristic chromosome was named the 'Philadelphia chromosome' after their home city. Additional research revealed that 95% of patients with CML had this unique chromosomal marker. Subsequently, Heisterkamp demonstrated that when the Philadelphia chromosome is formed the result produces a fusion gene labelled BCR-ABL. This 'new' gene produces a fusion protein, abl with bcr (breakpoint cluster region), termed bcr-abl which was recognised as a potential disease specific, drug-gable target<sup>38</sup>.

Dr Druker (Oregon Health and Science University) and Dr Lydon (then Ciba-Geigy Pharmaceuticals which merged with Sandoz to create independent entity Novartis in 1996) investigated the druggability of the fusion protein bcr-abl. The rationale was that patients with CML would have the BCR-ABL gene and hence the fusion protein bcr-abl, conferring highly specific efficacy. One such drug candidate, known then as STI-571, later renamed Imatinib, inhibited bcr-abl by binding proximal to the ATP binding site. This caused a conformational change in the enzyme resulting in a 'self-inhibited conformation', and thus curtailment of activity. In the first Phase I clinical trial of the drug, the majority of patients went into remission, and even five years later >98% were still in remission<sup>38</sup>. This mechanism-based approach led to yet another successful Targeted/Precision Medicine Drug to enter the market.

### Current perspectives of Precision Medicine Drugs

Last year (2017) the Center for Drug Evaluation and Research (CDER) at the FDA approved 46 NMEs. However, 16 of them were classified as Precision Medicine Drugs by the PMC, representing an annual high of ~35% of total NMEs approved<sup>39</sup>. These are all listed in **Table 1**, and it is noteworthy that almost 50% of these drugs (seven out of 16) were for disease indications other than oncology. This was the highest percentage yet reported of Precision Medicine Drugs approved by the FDA in any one year. In 2005 only 5% of approved drugs were classified as Precision Medicine Drugs, but

there has been a steady and consistent increase over the past decade as highlighted in **Figure 1**. Note that the data was obtained from the annual reports provided by the PMC and summarised in its latest publications<sup>34,39</sup>. In addition, three gene therapies were approved for the first time ever, in the treatment of acute lymphoblastic leukaemia (Kymriah), large B-cell lymphoma (Yescarta) and retinal dystrophy (Luxturna). Finally and of note, the first Precision Medicine Drug biosimilar was approved in 2017. Herceptin (see above) was approved by the FDA in 1998, and now in 2017 Ogivri (trastuzumab) was approved as a biosimilar for HER-2 (+) breast cancer<sup>39</sup>.

Last year was also pivotal for the number of marketed Precision Medicine Drugs that were approved for new indications. They included Revlimid (lenalidomide), Ibrance (palbociclib), Tecentriq (atezolizumab), Kalydeco (ivacaftor), Zykadia (ceritinib), Opdivo (nivolumab), Zelboraf (vemurafenib), Alecensa (alectinib), Adcetris (brentuximab vedotin), Sprycel (dasatinib), Sovaldi (sofosbuvir), Bosulif (bosutinib), Perjeta (pertuzumab) and Tassigna (nilotinib) for "new molecularly defined subsets of patients"<sup>39</sup>. Dr Janet Woodcock, the Director of CDER, stated that: "[These expanded] approvals point to an encouraging future for 'precision medicine' – an approach for disease treatment that tailors medical therapies, including medications, to the needs of individual patients<sup>39</sup>."

In another watershed moment, the FDA approved the Precision Medicine Drug Keytruda (pembrolizumab) for the expanded indications of patient treatment with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch-repair deficient (dMMR) solid tumours<sup>40</sup>. The groundbreaking approval was predicted on the fact that only the presence of a specific biomarker was required, and not a conventionally defined disease indication. This clinical trials data that afforded such an outcome consisted of 15 different conventional oncological indications! This is in stark contrast to traditional oncology drugs that have been approved for treatment of specific cancers located in specific organs and/or tissues in the body. This is an exciting harbinger for the future of Precision Medicine Drugs and the impact they will have on the quality of therapies offered patients.

### Conclusions

In the early 2000s one of us (Dr Stephen Naylor) formed a personalised medicine company, Predictive Physiology and Medicine Inc. The company provided a patient's predictive molecular

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profile in areas such as cardiovascular and neurological health and wellness. At that time there was a great deal of focus on providing individual tools for the prevention, prediction and diagnosis of disease states. However, there was little progress on the impact of personalised medicine in DDD, but significant discussion about how the costly, time-consuming and risky DDD process could provide therapeutic drugs for individual patients. The conclusions at the time were that such efforts were prohibitively expensive and economically unfeasible. However the advent of precision medicine and its focus on the grouping and identification of sub-populations (1-in-N model), as well as the tools to identify such populations led to the concept and implementation of Precision Medicine Drug discovery and development. In 2005 only 5% of all drugs approved by the FDA were Precision Medicine Drugs. Last year that percentage had risen to an all time high of 35% (Table 1), and in 2018 is predicted to go even higher. The pharmaceutical sector has recognised the value of such an approach, and it is clear that Precision Medicine Drugs are here to stay. They are indeed a reality and not a pleonasm!

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