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Predicting the Effects of Candidate Drugs: The Future

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Drug Development Involves the Progressive Reduction of Uncertainty Around Hypotheses Related to Benefit and Harm

- Drug discovery process creates predictions that candidate drug will provide benefits and not cause excessive harm
- These predictions are usually incorrect
- Standard battery of *in vitro* and empirical animal toxicology studies seek to predict unacceptable toxicity, organ vulnerability and dose relationship
- This battery works well for predicting safe starting doses, for enabling safety of First in Human (FIH) studies and identifying most major organ toxicities
- Gaps in prediction in specific areas such as more subjective central nervous system (CNS) effects, immunologically-based toxicities, drug induced liver injury (DILI), etc.
- Also may result in false positives, eliminating potentially viable candidates

Intense Interest in Using Novel Methods to Augment or Supplant Current Battery

- Microphysiologic systems, “organs on a chip”, novel animal systems, *in silico* methods
- Understand mechanism of toxicity: “adverse outcome pathway”
 - Define mechanism at genetic, biochemical, cell, organ and system level
 - Requires understanding how *in vitro* system relates to or replicates human pharmacology and physiology
- Popularly touted as replacement for traditional animal studies: this is creating a lot of pressure for regulatory adoption

Multiple Organizations Contributing to Understanding the Process of Integration

- 2007: National Research Council (NRC) of National Academies of Sciences (NAS) issued “Toxicity Testing in the 21st Century: A Vision and a Strategy (Tox21)”
- 2017 NRC: “Using 21st Century Science to Improve Risk-Related Evaluations”
- Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM): A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

FDA Has Also Issued Several Documents and Developed Processes Specific to FDA-Regulated Products

- FDA Predictive Toxicology Roadmap (Dec 2017)
 - Describes processes for gaining knowledge of and experience with new methods
- Commentary: “An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies”, *Regulatory Toxicology and Pharmacology*: 114 (2020)
 - Review of strengths of and gaps in, current primarily empirical approach to nonclinical safety testing for drugs
 - Highlights areas where *in vitro* methods have replaced animal studies
 - Mentions areas where current prediction is less than satisfactory with “Statements of Need”
 - Discusses new emerging paradigms such as the Comprehensive In Vitro Proarrhythmia Assay (CiPA) for certain cardiac toxicities

None of these Documents Describe “What Evidence is Needed” to Make this Adoption Happen

- Most describe processes for gaining understanding of new technologies
 - Training and educational activities
 - Public-private partnerships
 - Laboratory activities
- Do not lay out standards or thresholds for adoption
 - These are often very context-dependent
 - It is likely that very specific activities will need to be carried out to enable regulatory use
 - What pathway will need to be followed? What work accomplished? By whom?

Lessons from Introduction of Other Technologies Into Drug Regulation

- Three disparate examples come to mind from last two decades:
 - Genomic data
 - Novel biomarkers
 - Patient-centered drug development and patient reported outcomes

Each of the above have raised very similar themes that can be generalized to alternative safety methods

Genomic Data

- At turn of century, drug developers were using genomic technologies to explore impact of drug candidates at molecular level
- Great concern was raised that regulators would over-interpret such data and place programs on clinical hold due to findings (e.g., gene expression) of unknown significance
- FDA created a “Voluntary Genomic Data Submission” process and provided guidance that genomic data of unknown significance would not be used against the product!
- Significant efforts at standardization and replicability of platforms was undertaken by public and private entities to improve reliability

Genomic Data: Today

- From today's perspective it is hard to believe this happened!
- Genomic data is part of the bread-and-butter of drug development
- FDA rapidly built up expertise, worked with other regulators worldwide, participated in consortia, issued multiple guidances
- Currently genomic data widely used in predicting drug effects
 - Pharmacogenomics (particularly drug metabolism): still many controversies over predictions versus clinical readouts
 - Companion diagnostics well integrated into drug development
- Controversy remains over relying on fully mechanistic predictions, for example, using gene mutation data plus functional assay to add to list of mutations for which use of a cystic fibrosis drug is indicated

Use of Novel Biomarkers in Drug Regulation

- Availability of reliable biomarkers can significantly speed and de-risk drug development
 - Thousands of biomarkers published on every year; rarely developed into widely usable assays, even more rarely is a broad evidence base generated
 - Pharmacodynamic biomarkers are particularly helpful for efficacy
 - Safety biomarkers rarely evolve
- Early 2000's: no clear pathway for regulatory acceptance of new biomarkers
- Plan: set up public-private partnership (PPP) consortia to advance this science, e.g.,
 - Foundation for the National Institutes of Health (FNIH): “The Biomarkers Consortium”
 - Critical Path Institute (C-Path)
 - Many others

Early Need Became Clear: Standard Terminology

- Different terminologies used in various scientific articles and symposia
- Impeded communication and development of pathways
- NIH-FDA working group developed “BEST (Biomarkers, Endpoints and other Tools) Resource Glossary (2016): 1-year effort
- Defined classes of biomarkers by use i.e.,
 - Susceptibility
 - Prognostic
 - Predictive
 - Response
 - SAFETY

FDA Leadership in this Area: Biomarker Qualification Process

- Beyond analytical validation, what steps need to be taken to enable regulatory use, without proving utility each time?
- Developed concept of “qualification”: a conclusion that the results of an assessment using the model or assay can be relied upon to have a specific interpretation and application in product development and regulatory decision-making.
- Inextricable to qualification is concept of “context of use”: a clearly articulated description delineating the manner and purpose of use for a particular approach. In other words, what kind of decision will the results support? Very often developers were fuzzy about this.

Biomarker Qualification Process

- In first decade of 21st Century, FDA set up processes to qualify biomarkers for use in specific regulatory situations (context of use)
- Early years of this program were very fraught—no one really knew what it would take for acceptance of a new biomarker, new concept for regulators
- European Medicines Agency (EMA) also developed a process
- 21st Century Cures Act (2016) established biomarker qualification as a regular part of FDA's duties and set process and timeframe expectations. Some frustration with FDA expressed by various parties
- Processes and timeframes have been established by Agency, robust program ongoing

Predictive Safety Testing Consortium (PSTC)

- In 2006, C-Path established the PSTC, an industry-based consortium intended to share data and information on developing safety biomarkers and seek qualification
- Early candidates included renal safety biomarkers, important since existing biomarkers had low sensitivity for renal injury
- In 2008, both EMA and FDA qualified a panel of kidney safety biomarkers for use in rodents, Pharmaceuticals and Medical Devices Agency (PMDA) followed in 2010.
- In 2018, based on work by PSTC and the Biomarkers Consortium, FDA gave the first ever qualification of a clinical safety biomarker, a panel of assays for renal tubular injury, to be used in situations where animal studies had raised some concern
- This partially addresses one need raised in the 2020 FDA Commentary: how to resolve whether certain animal findings are relevant to humans

Lessons Learned from Biomarker Qualification Efforts of Last Fifteen Years

- It is a lot more work than people think it is; analytical validation is only the first step
- Need to start out with clarity about definitions and what you are trying to accomplish
- Proposal for “Context of Use” should be there from the get-go; fitness-for-use to do what? For example, augment animal study, replace animal study, fill gap in animal results, etc.? May be refined as you learn more about the new approach
- Safety biomarkers are particularly challenging; don’t want to take risks with human lives or with organ safety
- Lack of “gold standard” comparison also makes acceptance difficult

Patient-Centered Drug Development

- Long history of “Patient Reported Outcomes” but idea of “Patient-Centered Drug Development” is new
- Concept is that people with chronic diseases have a good idea of what the worst symptoms are to them and what effects of treatment are desirable or to be avoided
- Goes against “doctor knows best” approach, particularly for rare or chronic disorders
- Also promotes the idea that the people who will bear the risks or receive the benefit need to have input into the benefit/risk assessment
- This set of ideas is having a pretty profound impact

How to Instantiate Patient-Centered Drug Development

- Communication: FDA first initiated “Patient Focused Drug Development Meetings” wherein patients came and described their disease experience in their own words, including symptoms of concern and side effects of treatments. Published “Voice of the Patient” summaries. Patient groups followed with their own
- Development of standardized vocabulary
- Development of standardized assessment techniques: How to collect valid, representative input on burden of disease and treatment, and desired impacts on disease, from those suffering from it?
- Series of technical guidances issued establishing framework
- Patient groups and consortia enthusiastically pursuing data collection
- These efforts have already impacted drug development

Lessons Learned Common to these Efforts

- Adoption of new technologies into regulatory use starts with conversation, familiarity, understanding, non-regulatory use (safe harbor)
- Standardization of terminology and technologies an important next step that can be very labor intensive
- Use of the “Qualification”; “Context of Use”; Fitness-for-Purpose” Framework very useful: need to have a framework! All the efforts discussed here used such a framework in different interactions
- Safety testing is the hardest frontier because of the weight of the decision-making

Other Lessons Learned: Cases Where the Field has Moved

- CiPA Initiative
 - Predicting if candidate drug will have pro-arrhythmic effect has been difficult
 - Current standard (*in vitro* plus dedicated human study) may be over-sensitive
 - Goal is to have full mechanistic understanding and be able to predict from *in vitro* ion channel studies and *in silico* modeling plus human sampling
 - Potential to save time and money and have better discrimination
 - Lesson: extensive understanding of mechanism can drive acceptance
- Ocular and dermal irritation testing
 - Moved away from dedicated animal assay
 - Use of *in vitro* or *ex vivo* models preferred
 - Lesson here: face validity can be important!

How Does this Experience Relate to Development and Regulatory Acceptance of New Methodologies for Safety Testing?

- Need to ensure regulator's familiarity with techniques: Alternative Methods Working Group (AMWG) is doing this at FDA
- Move towards standard definitions and standardized technologies
- Any technology considered for regulatory use has to be proven to be reliable, robust, reproducible and so forth
- Identify a SPECIFIC need (context of use). FDA/CDER Commentary mentions numerous areas of need
- Or MATCH a specific technology of interest to an area of need

Framework for Regulatory Acceptance

- Once you have clearly identified context of use, propose how technology will be fit-for-purpose to meet identified need, and how you will prove it
- This activity is very specific, not broad (biggest error), and can be very hard to think through
- Generally, unless you have very high face validity, will need to run experiments with known human positive and negative readouts, and run in parallel with standard drug development programs through human readout. This will take a while
- Faster than not doing it at all, however

Summary

- FDA and regulators worldwide will incorporate new testing methodologies into regulatory standards if certain standards are met
- If it is intended to replace an existing test, or to stand alone to support decision-making, safety testing must overcome a high bar
- After usual efforts to standardize the new technology, application to a regulatory standard should first consider and define **context of use**
- This means having a clear idea of the unmet need or of the improvement that the new methodology is intended to fulfill
- If clear, then developer can set about seeking to **qualify** the method as fit-for-purpose for that use
- Once qualified, the method can be used for regulatory purposes without additional demonstration of its performance

New Predictive Methods for
Safety Have a Great Future in
Drug Development As Advances
in Science and Technology
Enable Greater Understanding