Baker McKenzie.

FDA Regulation and Cutting Edge Technology - What Pharmaceutical and Medical Device Companies Should Know

18th Annual Pharmaceutical and Medical Device Compliance Congress

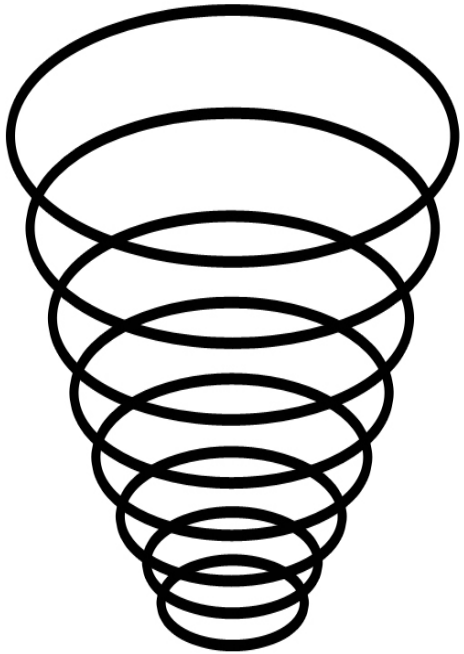
Chia-Feng Lu JD

Challenges we face

We find

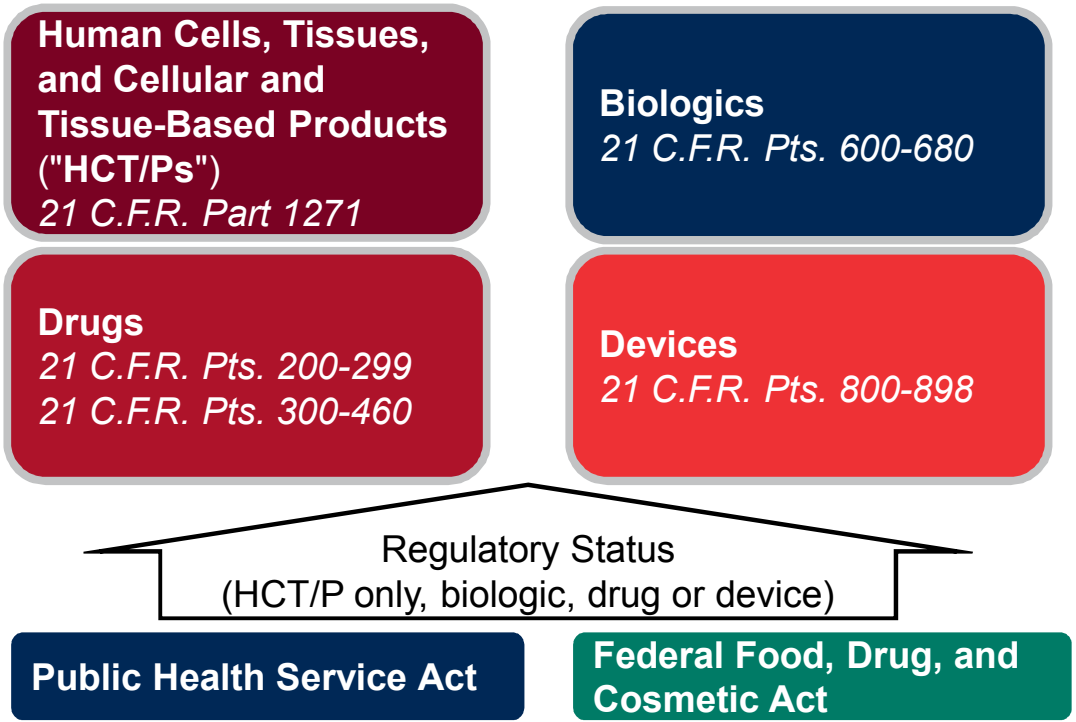
Death Spiral

- Slow introduction of an open innovation model
- Diverse sources of information and application
- Intellectual property practice to product/technology vs. procedure/medical practice
- Different legal definition of regenerative medicine technology, which come with different regulatory strategies and filings
- Less harmonization of the regulatory paradigm worldwide
- Unclear criteria to define the reimbursement approach
- Different levels of medical practice
- Infrastructure of the healthcare delivery
- Intensive capital
- Exit plans tends to be poorly developed ahead



Where we stand

FDA's legal authority



- Registration and Listing Requirements
- Adverse Event Reporting
- Donor Eligibility Requirements
- Requirements to prevent the introduction, transmission or spread of communicable diseases
- Other requirements

- Formulation
- Preparation
- Intended use

HCT/Ps – two regulatory tiers

Risk determines the level of regulation:

Tissue ("361 HCT/P") – *lower risk*

- Section 361 of PHS Act
- Premarket review and approval not required; Product regulated solely under Tissue Regulations to control communicable disease (21 CFR 1271)
- Establishment registration and product listing required (21 CFR 1271-Subpart B)
- Good Tissue practices (21 CFR 1271-Subpart D)
- Other requirements

Therapeutic ("351 HCT/P") – *higher risk*

- Sections 351 & 361 of PHS Act, FD&C Act

- Degree of manipulation
- Homologous use v. Non-Homologous Use
- Combined with another article
- Systemic effect and/or dependence on metabolic activity (autologous use? allogeneic use in a first-degree or second-degree relative? reproductive use?)

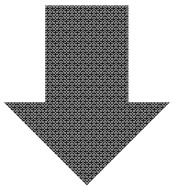
Regulatory approach 1 – HCT/P

Definition: Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient (21 CFR 1271.3 (d)).

- Minimally manipulated
- Homologous use
- Not combined with another article (with limited exceptions)
- Either (i) the product does not have a systemic effect and is not dependent upon metabolic activity of living cells for its primary function; or (ii) the product has a systemic effect or is dependent upon metabolic activity for its primary function, and is for autologous, allogeneic or reproductive use

- Vascularized human organs for transplantation;
- Whole blood or blood components or blood derivative products;
- Secreted or extracted human products, such as milk, collagen, and cell factors;
- Minimally manipulated bone marrow for homologous use and not combined with another article; and
- Cells, tissues, and organs derived from animals other than humans

Regulatory approach 2 – drug, biologic or device



- Minimally manipulated
- Homologous use
- Not combined with another article (with limited exceptions)
- Either (i) the product does not have a systemic effect and is not dependent upon metabolic activity of living cells for its primary function; or (ii) the product has a systemic effect or is dependent upon metabolic activity for its primary function, and is for autologous, allogeneic or reproductive use

Fail to meet criteria

Drug	Biologic	Device
▪ IND / New Drug Application (NDA) ▪ Requires pre-market review and approval ▪ Must show that the product is safe and effective ▪ Compliance with Current Good Manufacturing Practices (cGMPs) ▪ "Well Characterized" ▪ User Fees ▪ Other requirements (incl part of CFR 1271)	▪ IND/ Biologic License Application (BLA) ▪ PHS Section 351 ▪ The cellular or tissue product is safe, pure, and potent and that the facility in which the product is manufactured, processed, packed, or held meets established quality control standards ▪ User Fees ▪ Other requirements (incl. part of CFR1271)	▪ Investigational Device Exemption (IDE) ▪ 510(k) clearance or Pre-Market Approval ▪ Compliance with Quality System Regulations (QSR) ▪ User Fees ▪ Other requirements (incl. part of CFR1271

- Umbilical cord stem cells treated with enzyme to increase engraftment are considered biological products and are subject to INDs and BLAs because this processing constitutes more than minimal manipulation.
- Autologous adipose tissue enzyme digested and processed for urinary incontinence and treatment of impotence is considered a biological product and not a 361 HCT/P because this is a non-homologous use.
- Allogeneic adipose-derived stem cells seeded onto a bone scaffold for filling, augmenting or repair of pathologically or surgically created bony voids is considered a biological product, and not a 361 HCT/P, because the product is dependent upon the metabolic activity of living, unrelated allogeneic cells for its primary function.

What we foresee

CD19-targeting chimeric antigen receptor T cell (CAR-T) therapy

- Up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
- Orphan Drug designation, Breakthrough Therapy designation, Priority Review
- More than one month earlier than PDUFA date
- Pivotal open-label, multicenter, single-arm Phase II ELIANA trial, the first pediatric global CAR-T cell therapy registration trial examining patients in 25 centers in the US, EU, Canada, Australia and Japan+ Advisory committee meeting
- Box warning + RMES (with ETASU)

- Adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
- Orphan Drug designation, Breakthrough Therapy designation , Priority Review
- More than one month earlier than PDUFA date
- Full approval based on mid-stage study + No advisory committee meeting
- Box warning + RMES (with ETAUSU)

How it works - Yescarta

- Remove T cells from patients via leukapheresis and shipping them to Kite's manufacturing facility in El Segundo, Calif. where the cells are genetically engineered to target cancer cells expressing the CD19 receptor. Kite sends patients' engineered cells back to their treatment center where the therapy is infused into the patient to attack leukemia cells.

- Kite Connect will help patients and physicians track shipments and manufacturing of their individualized Yescarta therapies as well as assist patients with health insurance questions and connect them with third-party resources to assist with travel to treatment center.

Overture

"*However, with all of the medical potential, also comes novelty and uncertainty as this field matures. There are a small number of unscrupulous actors who have seized on the clinical promise of regenerative medicine, while exploiting the uncertainty, in order to make deceptive, and sometimes corrupt, assurances to patients based on unproven and, in some cases, dangerously dubious products.*"

"*This comprehensive policy will establish clearer lines around when these regenerative medicine products have sufficient complexity to fall under the agency's current authority, and then define an efficient process for how these products should be evaluated for safety and effectiveness*"

Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine
August 29, 2017

FDA's current action

- Create of a new regulatory framework to promote patients' efficient access to regenerative medicine therapies with high quality
- Strengthen enforcement against the promotion or the distribution of illegal products
- Include gene therapy products (that permanently alter tissue and produce a sustained therapeutic benefit as part of the products) into the scope of RMAT product
- Report by Nexight to develop standards for regenerative medicine therapies
  - Examine challenges in the areas of product testing, performance characteristics, testing methodologies, scientific protocols, product quality, ingredient specifications and compliance criteria.
  - Identify the way to identify key quality and safety standards and how to decide whether developing each standard is feasible.
  - Outline a roadmap for carrying out these preferably public processes.

Call upon FDA's strong commitment

Regenerative Medicine Advanced Therapy (RMAT) (Sections 3035 and 3036)

- FDA must report annually to Congress on:
  - The number of RAT applications filed, approved, withdrawn or denied
  - The number of RATs granted accelerated approval or priority review
- Requires a coordinated effort to develop standards and definitions to support the development, evaluation, and review of regenerative medicine therapies and RAT
- Requires the Secretary to review and update relevant regulations and guidance following development of such standards and definitions

Status

30 RMAT requests, acted on 26 of them and granted 7

(as of September 12)

ATIR101 (Allodepleted T-cell ImmunotheRapeutics)

- Intended use:
  An adjunctive to hematopoietic stem cell transplantation to provide for a safe donor lymphocyte infusion from a partially matched family member without the risk of causing severe graft-versus-host-disease. The product's T-cells help to fight infections in remaining tumor cells as the immune system regrows.
- Orphan drug designation
- RMAT designation - A single-regimen, open-label Phase II trial
  - safe infusion
  - no causality of acute grade III-IV GVHD and showed a significant reduction in transplant-related mortality and a significant improvement in overall survival

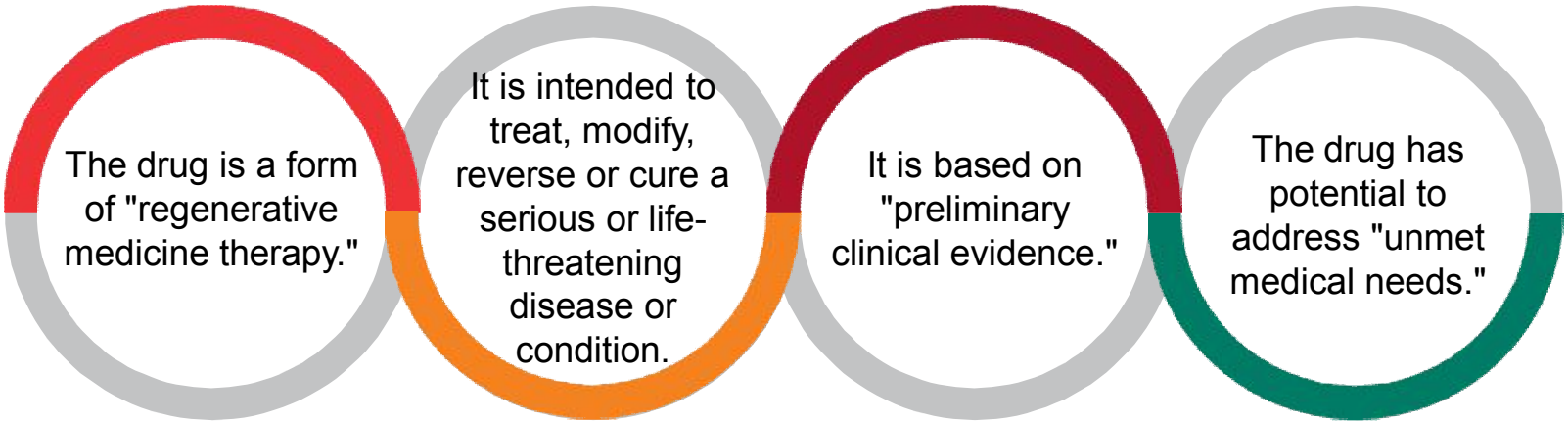
Regenerative Medicine Advanced Therapies

21st Century Cures Act, Section 3033(a)

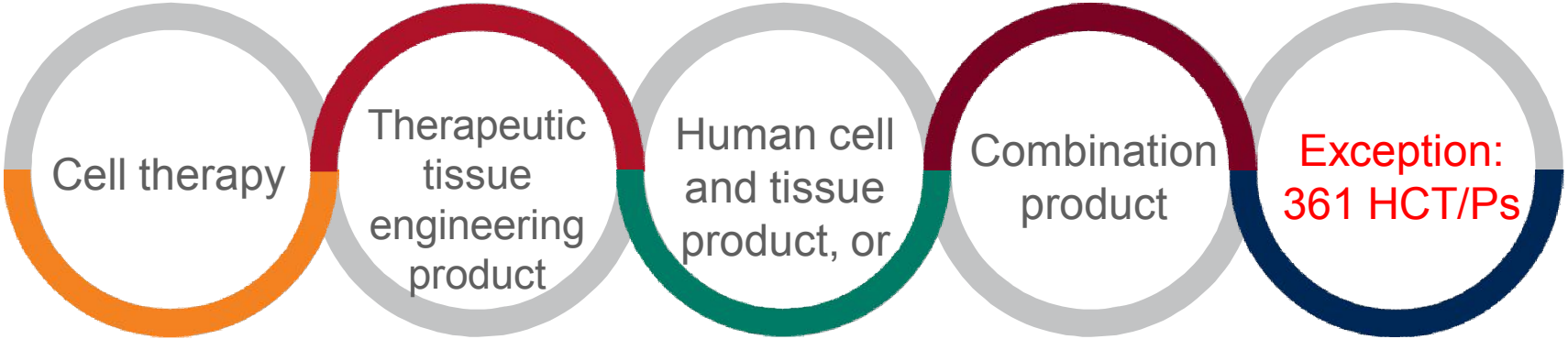
- Creates new Section 561(g) of the FDCA
- Creates new "Regenerative Medicine Advanced Therapies" (RMAT) designation
- Establishes procedures for requesting RAT designations
- Makes RATs eligible for:
  - Same "actions" as breakthrough therapy
  - Priority review
  - Accelerated approval

New category - Advanced Regenerative Therapies

Criteria

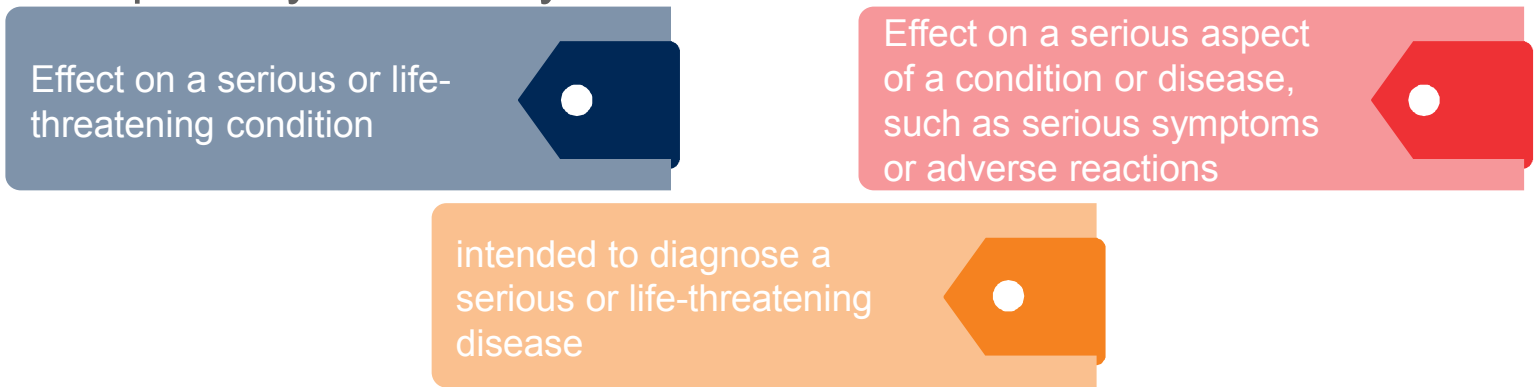


Factor one - Regenerative Medicine Therapy

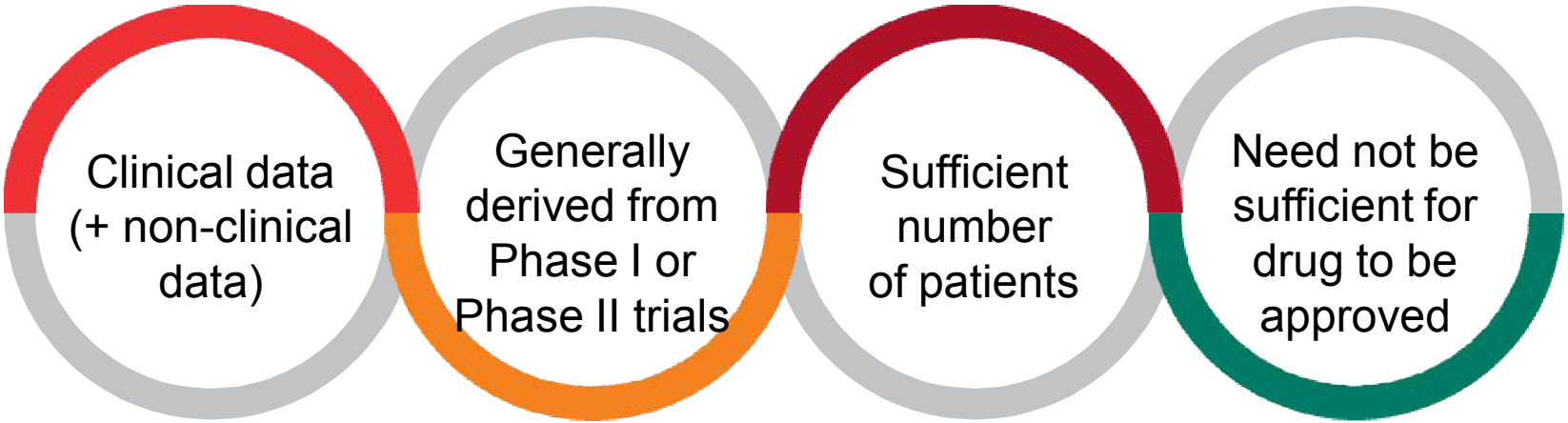


Factor two - serious or life-threatening disease or condition

- Condition causes death or irreversible morbidity with substantial impact on day-to-day functioning.
- Multiple ways to satisfy definition:



Factor three - preliminary clinical evidence



Designation request

When

- Concurrent with submission of IND
- With any amendment to the IND

How long

- Within 60 calendar days of receipt of request

Where

- CBER, Office of Tissues and Advanced Therapies (OTAT)

What do you receive

- RAT designation
- Written description of rationale for denying designation

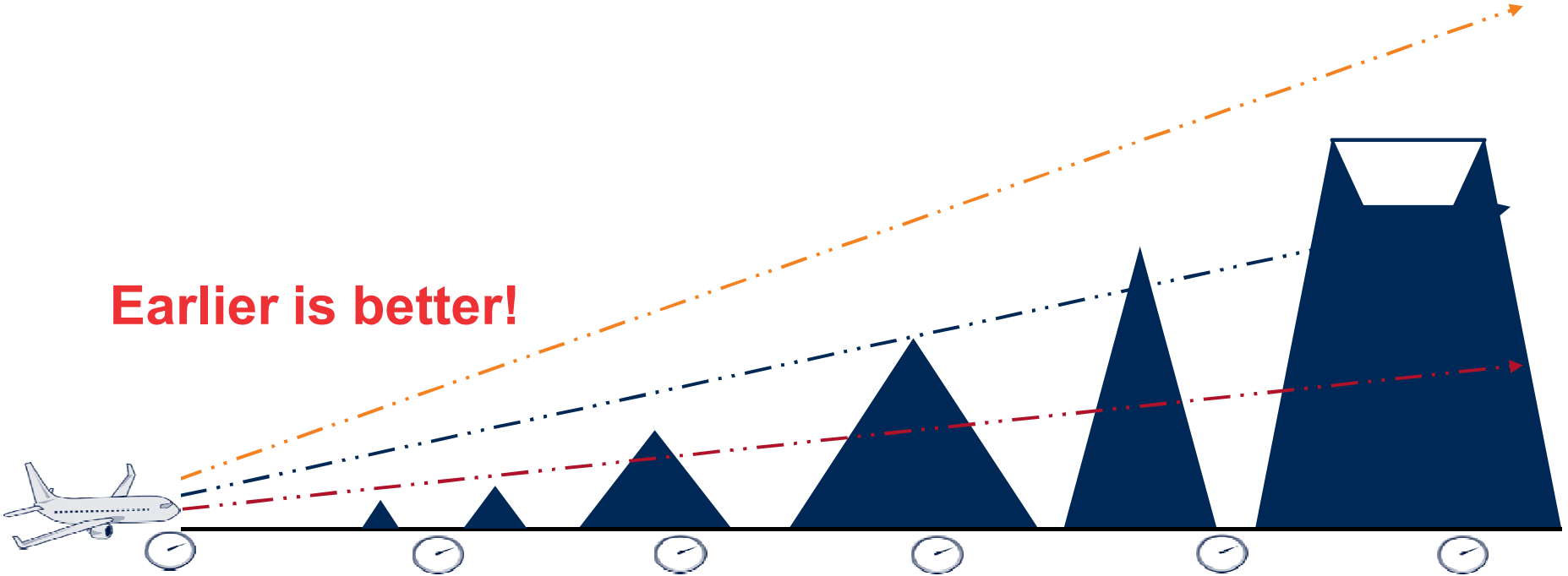
Benefit – expedient development and review

- The FDA's dedication to all product development phases
  - "Timely advice" from the FDA to make data gathering for clinical development "as efficient as practicable" is given
  - More focused on manufacturing issues
- The FDA's key staff members' accessibility
  - Access to senior managers and experienced review staff
- The FDA's partnership with sponsors in the development program
  - Cross-disciplinary project lead will facilitate review and liaise with sponsor
  - Ensure trial design as efficient as possible
    - Discuss any potential surrogate or intermediate endpoint to be used to support the accelerate approval of the product
- Eligibility for priority review

Strategy we should adopt

What we should deal

Develop the issue checklist



Ask yourself at pre-clinical stage

- What tools and therapies provide the greatest protection for your assets
- How you can leverage your portfolio to generate income
- Use of government funding in research and development vs. the restriction of the licensing or utilization of asset
- Royalty monetization
- Will the regulatory clearance and approval constitute the necessary condition to obtain the reimbursement
- What is the desirable regulatory status of the technology
- Will it be possible to develop the technology in accordance with the desirable regulatory pathway

Product development strategy

Do you know

- How to determine how your technology shall be developed or launched as a drug, device, combination product, or regenerative advanced therapies
- How to negotiate with FDA if your technology is classified to an undesirable regulatory pathway; how to persuade FDA to grant favorable product designation
- How to relieve the regulatory burden and lessen requirements
- How to expedite product development if a regenerative medicine product is composed of different regulated articles, such as drug+device; or biologics+device
- How to assure the regenerative medicine production site's readiness to pass the regulatory authority's inspection in the setting of scale-up
- How to assure the import or export / product supply across national borders without being delayed due to regulatory issues
- How to manage the internal stakeholders in the regulatory agency's review process

Commercial launch

Do you know

- How to accurately forecast the right or acceptable price from the payor, like Medicare or Medicaid, or pharmacy benefit manager
- How to consider the price or clinical utility for the combination product or regenerative medicine if with drug/biologics, device, HCT/Ps components
- How to introduce the target product profile or concept to KOLs before the regulatory approval and clearance without violating any laws and regulations
- How to find and engage the proper KOLs in the patient advocacy group, healthcare professional community, and payor group, as well as regulator
- How to assure the supply chain and distribution channel in compliant with federal and state laws
- How to assure the stable access to the local or foreign cell bank if appropriate

Licensing & M&A

Do you know

- How to incorporate new thinkings reflected from the new paradigms into the formulation of your value proposition of the R&D asset
- How to conduct the due diligence and understand the regulatory as well as IP issues emerging under the new framework related to target asset or company in regenerative medicine
- How to formulate the term sheet or deal structure if there remains the uncertainty of product development approach
- How to identify the most promising technology by considering the impacts from the new measures stipulated by the new framework
- How to assure the best talents and employees remain after the acquisition

Let's talk about the other…

Explosion of digital health products and U.S. government reaction

- The availability of digital health products is growing exponentially.
- Realizing this, FDA's Digital Health Innovation Action Plan outlines the Agency's vision for fostering digital health innovation while continuing to protect and promote the public health.
- FDA and Congress are looking to actively regulate only a subset of those products which "medical devices" and present a higher risk to patients.
- However, scrutiny and regulatory expectations are growing for higher risk digital health and other MedTech devices.

Steps by FDA and Congress have done to ease the burden of traditional MedTech regulation

- FDA—published the Food and Drug Administration Safety and Innovation Act (FDASIA) Health IT report proposing a new framework for Health IT.
- FDA—limited its oversight focus to mobile medical apps that present higher risk to patients, while choosing not to enforce compliance for lower risk mobile apps.
- FDA—not actively regulating technologies that receive, transmit, store or display medical device data.
- FDA—led international efforts to converge on regulatory principles for Software as a Medical Device (SaMD) through the International Medical Device Regulators Forum (IMDRF).

Steps by FDA and Congress have done to ease the burden of traditional MedTech regulation

- FDA—created a mechanism to respond to queries on digital health product regulation.
- FDA—Launched an Entrepreneurs in Residence program to take advantage of thought leaders and others with real experience in software development to build and structure the Agency's digital health function.
- Congress—excluded from the "device" definition certain types of software products under the 21st Century Cures Act. The exclusion includes certain software that supports administrative functions, encourages a healthy lifestyle, serves as electronic patient records, assists in displaying or storing data, or provides limited clinical decision support.

Plans of FDA to further ease the burden of traditional MedTech regulation

- Establish a program to pre-certify the quality of a firm's software development and validation practices to lessen the amount of data or time needed for review of a device premarket submission or to avoid a premarket submission altogether. A pilot program is just beginning. FDA is also considering the role of third party certification in facilitating FDA determinations about pre-certification.
- Explore ways to use "real world data" (RWD) and "real world evidence" (RWE) efficiently in its regulatory programs, e.g., to support in whole or in part medical device marketing authorization decisions.

Plans of FDA to further ease the burden of traditional MedTech regulation

- Issue new draft or final clarifying guidance documents on a long list of digital health topics, including new guidance to be consistent with and provide greater clarity on the 21st Century Cures Act software provision.
- Build Agency bench strength and expertise in its digital health unit.

Challenges for digital health products actively regulated by FDA

- Moving forward, there will be substantial regulatory emphasis on medical device cybersecurity controls and monitoring as well as device interoperability controls.
- Through final guidance documents, FDA has provided clarity on its expectations for medical device cybersecurity, also collaborating with stakeholders to form a community to exchange cybersecurity information.
- Congressional bills have been introduced to address medical device cybersecurity concerns.
  - The Internet of Medical Things Resilience Partnership Act would task the FDA and other stakeholders with developing recommendations and guidelines for boosting cybersecurity and resilience of networked medical devices.

Challenges for digital health products actively regulated by FDA

- The Medical Device Cybersecurity Act of 2017 aims to protect patient safety from medical device cyberattacks and improve medical device security through several proposed measures.

- These and other activities led the FDA recently issued its final device interoperability guidance which is intended to help manufacturers design and develop safe, effective, and interoperable medical devices by outlining important design considerations and providing clarity on the agency's recommendations for submitting interoperability-related information in premarket submissions and labeling.

Chia-Feng Lu
Baker McKenzie
Chia-Feng.Lu@bakermckenzie.com

- ✓ Regulatory strategy
- ✓ Pricing & reimbursement
- ✓ Pharma compliance
- ✓ Business development & licensing
- ✓ Policy advocate & legislative procedure
- ✓ IP related matter

Chia-Feng Lu represents life sciences companies and industry associations in strategic regulatory and legislative processes before various government agencies and health authorities to guide and develop new legislation and policy, to frame effective approaches to working with the various agencies on compliance and investigation issues, and to help clients develop strategic plans to obtain agencies' approvals or clearances of their innovative products.

In addition, he assists investment banks, private equity firms, and venture capital groups in their evaluations of regulatory developments and the resulting business impacts, as well as regulatory uncertainty with respect to novel technology and compliance; he also advises life sciences companies on corporate strategy planning, partnerships, licensing, and M&A deals. He has served as an adjunct faculty member of a number of leading academic and an advisor to numerous government agencies.

Thank you very much

Baker McKenzie.

www.bakermckenzie.com