MASTER CLASS:
EFFECTS ON DEVICES OF PUBLIC LAW 114-255, THE BRAND NEW "21ST CENTURY CURES ACT"

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GREAT IRONY: TSUNAMI BILL WAS USED AS THE CARRIER LEGISLATION FOR THIS LAW

- 21ST CENTURY CURES ACT ("21CCA") BILL WAS ATTACHED TO OBVIOUS MUST-PASS LAW, H.R. 34, WHICH HAD BEEN A
  - ***TSUNAMI WARNING BILL***
- UNRELATED LEGISLATION USED AS THE CARRIER FOR THE 21CCA
- IRONY THAT "TSUNAMI" IS APPROPRIATE METAPHOR>>
- FDA CAN EXPECT A WAVE OF CHANGES WASHING OVER WHITE OAK, MARYLAND, THOUGH ITS CAMPUS IS FAR INLAND
- HOW WILL YOU BE AFFECTED BY THE WAVE OF CHANGE?????

GETTING DEEPER IN TEXT & ANALYSIS

- GPO.GOV/FDSYS
- PUBLIC LAW 114-255
- & SENATE SPONSOR STATEMENTS, CONGL. RECORD – SENATE, DEC. 7, 2016
- ANALYSIS: 2017 EDITION of O'REILLY, West's FOOD & DRUG ADMINISTRATION,
- Vol. 2 chapter 18

Quick Index: Device Law Changes in Subtitle F

- Sec. 3051. ***Breakthrough*** devices.
- Sec. 3052. Humanitarian device exemption.
- Sec. 3053. Recognition of ***standards.***
- Sec. 3054. Certain class I and class II devices.
- Sec. 3055. Classification panels.
- Sec. 3056. Institutional review board flexibility.
- Sec. 3057. CLIA waiver improvements.
- Sec. 3058. ***Least burdensome*** device review.
- Sec. 3059. Cleaning instructions and validation data requirement.
- Sec. 3060. Clarifying ***medical software*** regulation.

HEADLINE CHANGES TO WATCH

- SOFTWARE VIRTUALLY DE-REGULATED
- “REGULATORY YARD SALE”: CLEANS OUT MANY CLASS I & II DEVICES FROM FDA 510(K) CLEARANCES THROUGH EXEMPTIONS
- FEWER DEVICE CHANGES WILL REQUIRE FDA REVIEWS
- AND SEE HISTORIC CHANGE IN DRUGS: NEW DRUG APPROVAL MECHANISM & NORMS EXPRESSLY ALTERED
- COMPARE: DRUG MAKERS WON QUICK,EASY PROMOTION OF NEW INDICATION FOR INSURER FORMULARIES, WITH NO PRIOR APPROVAL
- UNIVERSITIES & HOSPITALS’ IRBS ARE LOCKED OUT OF MOST TRIALS

SOFTWARE IS BIGGEST CHANGE

- Much narrower FDA role in hospital & personal software
- Tough procedural hurdles constrain FDA regulating these products
- Patients will get software apps faster, but largely without FDA as the gatekeeper of product effectiveness
- Unintended humor: sec. 3060 titled “Clarifying”, but it’s Mystifying
- Chose to use dense and inconsistent wording, headed for court
- Result is good for Plaintiff’s litigators
- New 520(o) [§3060] now leaves defects and consequences to liability lawsuits beyond FDA – did not expand device preemption of lawsuits

LOBBYISTS PAID BY INDUSTRY BLEW IT

- LIFESTYLE SOFTWARE IS NOT REGULATED IF "**UNRELATED**" TO THE DIAGNOSIS, CURE, MITIGATION, PREVENTION, OR TREATMENT OF A DISEASE OR CONDITION;
- HEALTHCARE ADMIN "BACK OFFICE" SOFTWARE IS NOT REGULATED
- IF IT HAS MULTIPLE FUNCTIONS AND ONE IS A DEVICE-LIKE FUNCTION BUT ANOTHER IS NOT, THEN 3060 SAYS IT WILL NOT BE A DEVICE
- CURIOUS WORDING: BUT EVEN SO, when assessing the safety and effectiveness of the device function or functions of such product, FDA "may assess the impact that the software function or functions described in subparagraph (A) have on such device function or functions"
- Would the lobbyist who wrote this please stand up and explain it???

THE BIG W.T.F.???

- Lobbyists wrote the key conditional phrase in new 520(o)(1)(E):
- Software product NOT a device if it can
- acquire, process, or analyze a medical image
- or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system,
- “enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.” How many arguments will this produce??

What did the lobbyists miss?

- Locking in ambiguous phrases in the terms of a statute
- Means there will eventually be multiple lawsuits over its meaning
- Between industry and the agency
- But FDA knows it has the upper hand
- FDA wins if at least 2 of 3 non-scientist generalists, ages 45-75,
- Sitting as judges in an appeals courthouse somewhere
- Say “That’s really vague and confusing to us, so FDA wins”
- Deference principles make it important for industry to be clear!

Your Device as an Accessory is Not Tied to the Device it Supports, for Classification Purposes

- FDA must classify an “accessory” based on the intended use of the accessory…
- …“notwithstanding the classification of any other device with which such accessory is intended to be used.”
- So if it is an accessory which is a phone app which helps to read an implantable Class III device like a pacemaker (hypothetically)
- FDA cannot classify the phone app automatically as Class III
- Because of new 513(b)(9)

And the Public Citizen Critics Complained:

- Amendments “Exempt(ed) certain types of medical software from FDA oversight without providing for regulation by another federal agency, meaning problems with medical software will be difficult for regulators to address when they arise.”
- Meaning: Halfway Between FDA & FCC in “no regulator” zone
- Possible FTC could be involved with some extreme benefit claims
- Liability lawyers prefer to sue where the company cannot claim the government had approved or licensed that product; this is like an “un-preemption” by leaving safety remedy only to litigation

Barrier to FDA control of Software: “Yuuge!”

- No FDA control of this medical software **unless all these happen** –
- FDA finds software is “reasonably likely to have serious adverse health consequences”;
- FDA publishes formal finding in Federal Register about this software,
- FDA publishes “rationale and identification of the evidence”
- Waits min. of 30 days from date of Federal Register for public comments
- Federal Register final order [maybe will need OMB-OIRA to agree]
- Lawsuit vs FDA usually follows, by software sponsor citing new 520(o)
- Only takes 3 of 4 judges to disagree with FDA (1 DistCt & 2 CtApps panel)

Next: What is a Breakthrough Device?

- History by Sponsor Sen. Burr “Must represent breakthrough technologies, have no approved alternatives, offer significant advantages over existing approved alternatives, or their availability must be in the best interest of patients.” Cong Rec S6791 (12/7/16)
- That last phrase swallows everything: who gets to decide “best”?
- Critics of the measure, such as Public Citizen’s Health Research Group, say the designation of “breakthrough” devices is too broad, and could lead to clearance of devices that aren’t ready for the market.
- Critics: “False Cures Act” would “eviscerate the already far-too-weak safety rules for medical devices”.

Red Flag: Re-useable Devices [§510(q), 3059]

- If you file a 510(k) after approximately June 2017
- For a device that FDA lists as “reusable”
- And FDA has listed this device in Fed Register notice of “reusables”
- Then you must include
- Instructions for Use re Cleaning, Disinfection & Sterilization
- And sponsor must submit Validation of the Instructions
- With the validation data as part of the 510(k)
- That proves the device will be sterile once the directions are followed

MEANWHILE OVER IN DRUGS -- HISTORIC CHANGE IN PRE-MARKET APPROVAL NORMS

- Huge shift in forcing FDA Reviewers to move away from the 1962-2016 standard of proof based on ***Controlled Clinical Trials***
- Entire Structure was built on reliance upon scientific testing/analysis
- New 3022: FDA must accept more claims, infer more, rely on industry post-market reporting of adverse events, after the sharp scolding by Sen. Alexander in Act's history (Cong Rec S6794 12/7) & new text
- "Real World" Data is the new Norm for Less Rigor in Approval; Sen. Alexander said 12/7 "(M)odern trials are so tightly controlled that the results are often artificial or irrelevant to how a medicine will be used and refined in actual medical practice."

KEY SWITCH AWAY FROM CONTROLLED TRIAL

- NEW 3022 Allows use of "***real world evidence***" to support the approval of a new indication of an FDA-approved drug, and to support or satisfy postapproval study requirements. (Explained by Sen. Alexander, 12/7 Cong Rec. S6794)
- "Real world evidence" means ***data*** regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.
- Expect Big Fight: How much of this "Other" source info justifies approval?
- Critics dissent: "The sources of real world evidence include ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities. This will weaken the standards for FDA review and approval of supplemental new drug applications (sNDAs) and lower the bar for the type of evidence needed to meet post-approval requirements." (PCHRG)
- Would FDA fight about inadequate trials, when law & history show changes?

WILL THOSE DRUG PROOF CHANGES "SPILL OVER" TO PMAA?

- DOES THE PMAA PROCESS FOLLOW TIGHT PATIENT CONTROLS IN THE PIVOTAL STUDIES?
- WOULD THE SPONSOR PREFER TO GET APPROVAL WITH "REAL WORLD EVIDENCE"?
- WILL THE COMBINATION OF THE TRUMP REVOLUTION & THE NOVEL STARTUP OF THE NEW PROCESS IN DRUGS BE A SIGNAL TO DEVICE REVIEWERS TO LOOSEN UP WHAT EVIDENCE THEY WILL ACCEPT?

NEGOTIATE & LOCK-IN DEVICE PLAN EARLY

- Benefit of agreement to plan – more predictability of cost & delay
- Critics said law would “bind the FDA to a specific clinical testing plan that would be difficult to modify without consent of the company testing the device.”
- Critics said agreements made before the FDA has had opportunity to view the results from initial testing, “unacceptably prevent the FDA from responding to scientific evidence, and will almost certainly lead to poorly-informed FDA decisions and immense harm to patients.”
- Again > Tradeoff of Certainty for Investors versus Flexibility of the FDA review team in asking for more data to flesh out new insights

HAMMER “LEAST BURDENSOME” INTO FDA

- “Least Burdensome” Language could be a Big Burden on FDA, major constraint in rule going through OIRA when critics attack rule’s burdens
- “How can we regulate less?” is an uncomfortable question for a career scientist at FDA to ask, because of culture/tradition to more thoroughly review to protect patients
- 3038’s Rare Congressional Decree: Mandatory Training of FDA career scientists is commanded
- Then the FDA careerist must be tested
- Then the tested group’s record of awareness must be audited
- Then FDA must report to Congress that audit was passed
- Big role of postmarket data warrants some “burden” on sponsors

Back to School Will NOT Be Fun For MD/PhDs

- Historic: 1st Time Congress Scolded FDA Staff by such Commands
- Train & Test Staffers on: Who must be on product review panels now?
- Must a reviewer accept foreign data?
- Must a reviewer accept company data?
- Is this device approval requirement the Least Burdensome option?
- If not, why not loosen it to require less?
- Common Theme: Train FDA staff, then Test them, then Audit
- Did the reviewer answer correctly on Least Burdensome? If not, then?

Congress Says: FDA Must Clarify 510(k) Duties

- 3059 Compels FDA to issue final “guidance”, *not* a regulation
- Regarding when a premarket notification
- Is required to be submitted
- For a modification or change
- To a legally marketed device
- This is the 3rd time Congress has spoken to this messy issue

EXEMPTING MY DEVICE: HOP ON THE LIST

- What devices do not need FDA clearance under new §3054?
- By March> exemptions of Class II device types, no more clearances needed
- By April > exemptions of Class I device types
- Then every 5 years, search for new device types to exempt
- Caveat: Lack of any FDA affirmative approval may have liability consequences – haste onto the market in a regulated product field suggests lack of protection that led to harm

When Must FDA Follow Private Standard?

- Much more power for industry consensus device standards in §3053
- Long history of industry associations fixing easy-to-meet norms for selves
- 3053 Forces the retraining of FDA staff re acceptance of industry norms
- Maybe resistance among FDA is based on staff's prior involvements
- Now will be Forced to train, test and audit FDA staff
- Update GHTF now makes foreign standards more likely to displace creation of a more stringent US norm
- Critics say it "compels the FDA to review and adopt or reject international standards, which may be drafted by industry, within an extremely brief review timeframe of 60 days. Once adopted, these standards will be used to regulate cleared medical devices in the United States."(PCHRG)

“HUMANITARIAN” DEVICE QUICK APPROVAL

- Concept was Novel Device Experiment used to save small base of extremely needy users - Now a much larger 8,000 patient trial base
- HDE needed because small base of patients was deemed not worth investment in full trials and production at very early stage
- Number in base has been 4,000
- 21CCA doubles number to Larger patient pool > now 8,000 users
- “Probable benefit” decision sounds like guesswork
- Standards must be set in a timely FDA guidance very soon

WHERE A COMBINATION PRODUCT IS REVIEWED DEPENDS ON ITS MODE OF ACTION

- FDA "shall not determine that the primary mode of action is that of a drug or biological product solely because the combination product has any chemical action within or on the human body." [3038]
- Major change from the 1938 law's drug/device "BRIGHT LINE"
- Then assign review task to FDA Center based upon "single mode of action of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product."
- Objections > quick meeting > additional test > fast status decision

FASTER COMBINATION PRODUCTS [§3038]

- LARGEST IMPACTS MAY BE FELT HERE AS SPONSORS FLEE DRUG CATEGORY FOR LESS REGULATED DEVICE STATUS
- “PERSONALIZED” THERAPY CLEARED WITH FEWER CONTROLS
- TEXT WAS TAILORED BY LOBBYISTS TO SCOLD FDA DRUG REVIEWERS
- FORCES A FASTER, BINDING DECISION ON REVIEWERS
- FDA:90 DAYS FOR APPROVAL OF DESIGN FOR STUDY OF NEW COMBO
- FDA:75 DAYS TO BINDING DECISION AT AN FDA-SPONSOR MEETING

CRITICS OF COMBINATION PROVISIONS

- PubCitizen: Pressures FDA to choose “device” path. Allowing the manufacturer to challenge FDA’s initial classification. Sponsor can “demand documented scientific proof that the “primary mode of action” of the product is that of a drug in cases where the product has been classified as a drug.
- Critics: “The primary mode of action is often unclear because the product is complex, not sufficiently studied, or otherwise difficult to discern. Placing the burden on the FDA to provide a scientific rationale will result in *more products being classified as devices* in such cases of uncertainty. “
- Will “lock the FDA into inflexible agreements on all aspects of clinical studies very early in the development process, including post-approval studies. This will make it extremely difficult for the FDA to request more information based on concerns that arise after clinical testing has begun.”

TEST DATA FROM OUTSIDE USA [§3101(q)]

- 2012 Act shifted reviewers' approach toward non-USA data
- 2016 Act makes less costly Indian & Chinese testing likely to be used as support for biologics like vaccines
- FDA now is told to accept "consistent parallel scientific advice"
- More FDA test/BIMO inspector teams must be sent outside USA
- Real doubt has existed among some FDA reviewers re reproducible quality of foreign clinical test results; Congress wants a change
- If criteria for evaluating drug effectiveness change, would mean a significant loss to CROs and universities that dominated US research

SURPRISE HIT ON LOCAL IRBs [§3056]

- ***Cuts out role of local IRBs*** for each university or hospital, as participants in an approval cycle for a new drug or device; still will have role in those few products which are local and not national, e.g. surgical patient consents.
- "RACE TO THE BOTTOM" potential for IRBs to win nationwide assignments
- Congress freezes out HHS rules that were more protective of patients
- 2 IRB systems diverged over the decades; now the FDA IRB rule "wins" over HHS more protective norms
- UNPLEASANT SURPRISE TO UNIVERSITY HOSTS OF DRUG/DEVICE TRIALS
- ASSUMES SPONSOR CAN HAVE A SINGLE NATIONWIDE DECISION RE DRUG'S ACCEPTABLE RISKS TO PATIENTS, TIED IN TO MORE USE OF FOREIGN DATA

How was FDA Bashed?

SENATOR ALEXANDER, CONG.REC. S6794, 12/7/16:

- Senate fixates on fixing FDA's "institutional culture of control, delay and abuse of regulatory discretion"
- New law "requires the FDA merely to evaluate the use of real-world evidence, and this wouldn't be the first **political instruction that the bureaucracy has defied."**
- New law is a "compromise" that seeks "a more rationale and humane drug development system".
- Adaptive trial designs target sub-groups, to "allow research to succeed or fail faster at some fraction of the current expense".

Can Sponsor Stack FDA Device Panels? [§3055]

- Classification has big implications for a device: Class II far cheaper than III
- Panels are required to augment FDA on classification choices
- Now law gives more power to mixed-background product review panels
- Can device sponsor leverage this to pick its preferred classification panel?
- FDA uses Fedl. Adv. Committee Act (FACA) today in picking panels
- Now industry gets 3 more voices on its product's review committee
- 1 more from outside FDA with relevant technology knowledge
- 2 more from outside FDA, of persons with clinical knowledge
- Significant exception from prior FACA conflicts of interest norms

DIAGNOSTICS [§3057]

- Changes to CLIA law on lab testing: Very Arcane Field
- Changes seem to favor Lab Developed Tests (LDTs)
- Likely to cause shifts in the diagnostics market
- No later than Jan. 2019, CLIA waiver final policy is due [3057]
- Removes 2008 Policy on CLIA Waiver Applications for Manufacturers of In Vitro Diagnostic Devices
- New policy effv. 2019”includes the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy.”

DOES NEW MONEY OFFSET NEW BURDENS? LET'S NOT BE CONFUSED...2017: $20 MIL

- Funding Auth'y for FDA for new responsibilities: $20 mil thru 9/30/17
- Authorization is Not Appropriation; Watch Trump's OMB & HHS in '17
- Sen. Leahy: "Whereas this bill contains $6.3 billion in upfront cuts to offset funding for its many efforts, these funds are not in fact guaranteed each year." (Cong. Rec. 12/7 at S6790)
- Funding for NIH of $4.8 billion for three signature Obama administration research programs, over the next 10 years: the "moonshot" against cancer, the BRAIN Initiative, and the Precision Medicine Initiative.
- Additional staffing authorizations for science jobs at FDA

IS IT REAL “NEW MONEY” FOR FDA TO USE?

- NO, READ THE DETAILS OF SECTION 1002 VERY CAREFULLY
- OFFSET MEANS THIS IS NOT EXTRA MONEY ADDED TO NORMAL APP.
- ANNUAL APPROPRIATION FOR FDA IS NOT INCREASED, BUT IT MUST INCLUDE THIS FUNDING
- THIS IS LIMITED TO DRUG & DEVICE ITEMS IN THE NEW 21CC ACT
- LIMITED ALSO TO INNOVATION ITEMS TIED TO THIS NEW LAW
- ACTUALLY ONLY $20 MIL IN 2017, $60 MIL IN 2018, $70 MIL IN 2019
- FDA TOTAL BUDGET OVER $4 BILLION

CRITICS OBJECTED TO ANY NEW SPENDING

- Republicans required Offset of new spending on FDA activities[1002]
- Cut 30% of Prevention & Public Health Fund ($3,500,000,000)
- Removes funding of chronic illnesses studies, Alzheimer's reduction, hospital acquired infections, etc. (Kaiser News)
- Cuts in Medicare payments for drug therapies & medical equipment

NET: HOW WILL 21-CC ACT CHANGE FDA?

- **FDA negotiated wording on "priority review for breakthrough devices,**
- **third-party quality system assessment,**
- **valid scientific evidence,**
- **humanitarian device exemption application,**
- **health software and the**
- **Clinical Laboratory Improvement Amendments (CLIA) waiver study design guidance for in vitro diagnostics."** (Inside Health Policy 12/10/15)
- NEW COMMISSIONER'S JOB IS DRIVEN BY ALLEGIANCE TO SEC. PRICE
- REAL TEST WILL BE REACTION TO DEATHS WHICH ARE TIED BACK TO FAST APPROVAL OF SOME HARMFUL PRODUCT; HOW WILL CONGRESS REACT AT THAT POINT, IF FATAL RISK COULD HAVE BEEN CAUGHT UNDER PRIOR SYSTEM OF PRE-MARKET CONTROLLED CLINICAL TRIALS?

Will Congress Monitor the Act's Results? YES!

- Elizabeth Warren:"I will fight it because I know the difference between compromise and extortion."
- Bernie Sanders: these are "corporate giveaways that will make drug companies even richer"
- Budget: 1002 requires spending reports to Congress on these changes
- New Provisions "will ensure an all-hands-on-deck approach..with the goal of expediting the development and review of breakthrough technologies" . "THE IMPORTANCE OF HOLDING THE AGENCY ACCOUNTABLE FOR ITS ACTIONS AND INACTIONS—ALL THE WAY FROM FRONT LINE REVIEWERS TO THE COMMISSIONER—HAS NEVER BEEN MORE IMPORTANT" (S.6792, SEN. BURR, 12/7/16)

How Much Was Spent Lobbying This Law?

- *Kaiser Health News 12/4/16: data by Center for Responsive Politics*
- Reports by 58 Drug makers, 24 Device makers, 26 Biotech firms
- Spending $192,000,000 on this bill & related legislation
- Lobbying by 60 schools, 36 hospitals, dozens of medical groups
- They spent over $120 million on this & related legislation
- Mental/psych groups spent $1,800,000 on this & related legislation
- 24 Patient advocacy groups spent $6,400,000 & related legislation
- 12 Health IT firms spent $35,000,000 & related legislation

SORRY FOR THE INFORMATION OVERLOAD ☺

- ROUGHLY 150 PAGES OF DETAILED LANGUAGE TO SCOUR THROUGH
- FULL OF CROSS-REFERENCES TO OBSCURE SUBSECTIONS
- LOTS OF REASONS TO PAY LOBBYISTS TO WIN YOUR HIDDEN VICTORY

  YES, LITIGATION VS. FDA IS LIKELY

  WATCH NEW ATTY GEN SESSIONS' WILLINGNESS TO FIGHT FOR FDA
- FUTURE COURT CASES WILL TURN ON AMBIGUOUS TERMS
- KEY IS HOW DEC. 7 CONGRESSIONAL RECORD HISTORY STATEMENTS AT S6790-S6795 ARE INTERPRETED BY 3 JUDGES (1 DIST., 2 APPS CT)
- IN MEANTIME, WATCH HOW SEC. PRICE DIRECTS FDA'S ACTIVITIES