RUOs, IUOs, ASRs, BMTs & LDTs

Bradley Merrill Thompson
EpsteinBeckerGreen
April 20, 2012

Agenda

- RUO and IUO Policy
  - June 2011 Proposed Guidance
  - The Great Debate
  - Comments on the Guidance
  - Brad's predictions on what changes FDA will make
  - Enforcement
- Marketing RUOs, IUOs and ASRs
  - Application notes
  - Social media/collaboration websites
  - Contracts leading up to FDA clearance
- LDT Policy
  - Brad's predictions

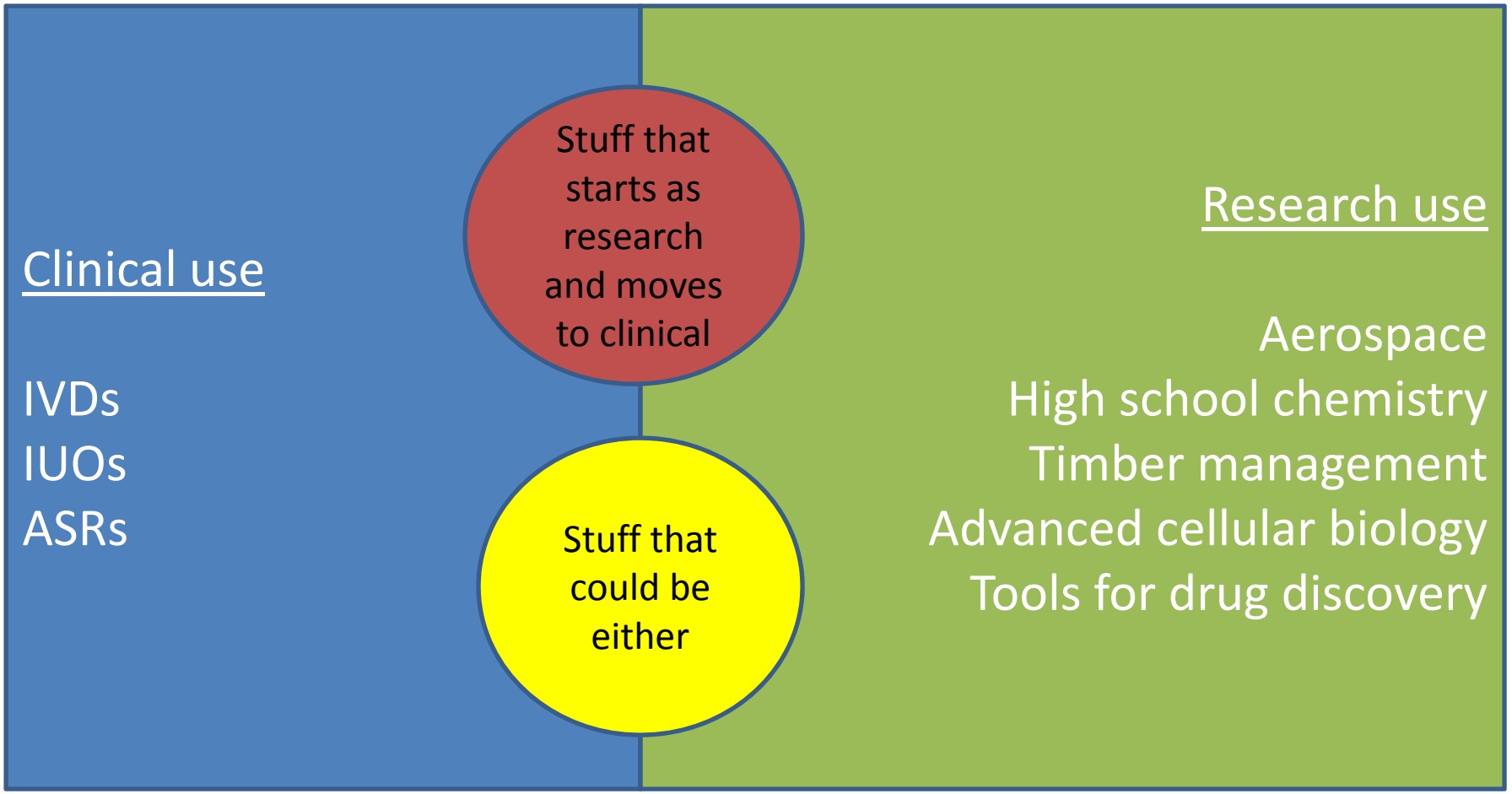
RUO/IUO Guidance
Scope of Research

- RUOs include products that will lead to IVDs. Some examples include:
  - Tests that are in development to identify test kit methodology, necessary components, and analytes to be measured;
  - Instrumentation or other electrical/mechanical components under development to determine correct settings, subcomponents, subassemblies, basic operational characteristics, and possible use methods;
  - Reagents under development to determine production methods, purification levels, packaging needs, shelf and storage life, etc.

Scope of Reserach

- FDA says RUOs include products that will always be used in research.
  - I disagree: research products are entirely unregulated by FDA and should not be put in the RUO category.
- FDA says RUOs do not include any IVD product that is intended for use in a clinical investigation or clinical diagnostic use outside an investigation (for example, in clinical diagnosis).

Types of Research Uses



Meets the medical device definition

Does not meet the medical device definition

Marketing

- In addition to overt expressions by the manufacturer such as those present in labeling and advertising, intended use may be shown by the circumstances surrounding the distribution of the product and the manufacturer's knowledge that its product is offered and used for a purpose for which it is neither labeled nor advertised.
- FDA will assess the following marketing practices as evidence of an intended use :
  - Written or verbal statements in any labeling, advertising, or promotion of the IVD product, including any performance claims, clinical information, product names, or descriptors, that claim or suggest that the IVD product may be used in a clinical investigation or for any clinical diagnostic use;
  - Written or verbal statements in any labeling, advertising, or promotion of the IVD product that suggest that clinical laboratories can validate the test through their own investigational procedures and subsequently offer it for clinical diagnostic use as a laboratory developed test;
  - Sales to clinical laboratories that the manufacturer knows, or has reason to know, use the IVD product in clinical diagnostic use in an investigation or otherwise, and support (including technical support) for those activities.
  - Past history of promotion of the product

Halting Sales

- [RUO manufacturers] should not sell such products to laboratories that they know use the product for clinical diagnostic use.
- If a manufacturer learns that a laboratory to which it sells its RUO… product is using it in clinical diagnosis, it should halt such sales

RUO Clinical Test Validation

8. Should [an RUO] manufacturer … help with the validation and verification of performance specifications of an LDT or other test that the manufacturer knows is used in clinical diagnosis that utilizes its product?

- No.

RUO IFU

6. Should the manufacturer include instructions for use with an IVD product labeled RUO or IUO?

- In certain circumstances, such as when the use of an IVD product labeled RUO is limited to laboratory research that is unrelated to the development of IVDs …, general instructions for using the product (for example, mixing proportions, incubation times, etc.) may be provided.
- However, no clinical interpretive information, discussion of clinical significance, or other indications of clinical applicability should be included with any … RUO….
- For those products that are in the research phase of IVD development, there is unlikely to be a need for instructions for use, as such products are still in their formative stages.

The Great Debate

Defense Attorney Brad	US Attorney Brad
My client should not be held responsible for what its customers do with the products they buy.	The government isn't doing that. Often what the customer does reflects something about how the seller promoted the product.

The Great Debate

Defense Attorney Brad	US Attorney Brad
There is an obvious flaw in that analysis. Sometimes customers do what they do because of their own ideas and research.	That doesn't make your client innocent. New medical devices need to be reviewed based on the true intended use. To figure out that true intended use, we look at your client's (1) Words, (2) Deeds and (3) Knowledge. If your client made and sold a pacemaker, but called it a grapefruit and made no medical claims, would you say it wasn't a medical device?

The Great Debate

Defense Attorney Brad	US Attorney Brad
That's a bunch of theory, but its not how product development happens in the real world with regard to RUOs. Clinical labs do research on their own, and figure out how they want to use chemicals. Uses change over time.	We get that, and that's why FDA adopted a guidance that lets your client sell until they realize, or should realize, their customers are using their products clinically. At that point, we expect your client to cut off that clinical use and go to FDA to secure clearance.

The Great Debate

Defense Attorney Brad	US Attorney Brad
But that's not the law. Intent is not determined sale by sale, customer by customer. The company has one intent for its whole market. We can't be the police and check to see what each customer is doing with our product.	Where does our policy say that you have to police your customers?

The Great Debate

Defense Attorney Brad	US Attorney Brad
Well, the FDA policy may not say we need to police our customers, but it says that we will be held responsible for what we “have reason to know”. That suggests that we have to be vigilant. And there’s absolutely nothing in the underlying statute to impose that obligation on my client.	That’s not what the government meant. That language is aimed at companies that are willfully ignorant. Your client can’t just cover it’s eyes, hum real loud, and pretend it doesn’t know how its customers are using its product. I go back to my pacemaker example. You can’t sell a pacemaker, and then act shocked that customers use it for regulating heart rhythms.

The Great Debate

Defense Attorney Brad	US Attorney Brad
This interpretation of intended use is new and different, and the government didn't go through rulemaking to impose it, so it's not law.	It's not new and different. We might've stated it a little bit differently, and perhaps a bit clumsily, but we never did let people sell pacemakers without any claims and get away with it.

The Great Debate

Defense Attorney Brad	US Attorney Brad
Well, the government caused this problem, so you shouldn't be taking it out on us.	Excuse me? What the %$&*$$#!!! are you talking about?

Osmosis

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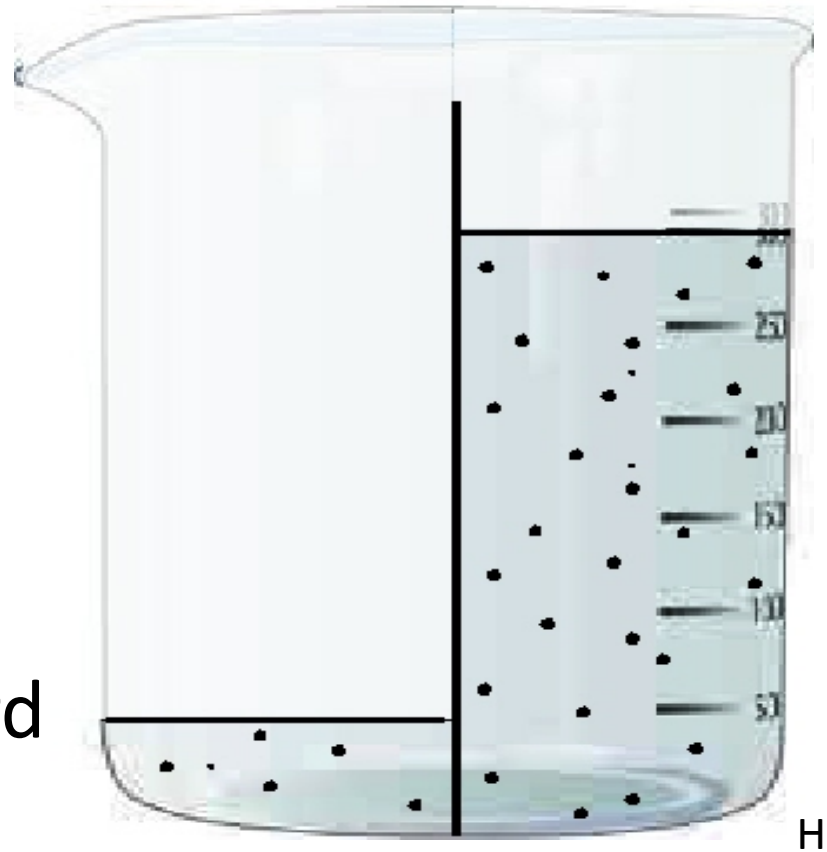

IVD Standard

LDT Standard

The Great Debate

Defense Attorney Brad	US Attorney Brad
You created an unsustainable system, and you are dragging your feet in fixing the root cause which is this dual standard that you allow for lab developed tests.	Tough. The law is the law. I don’t care what temptations it creates.

The Great Debate

Defense Attorney Brad	US Attorney Brad
Well, not only is the system unsustainable, it doesn't help patients. Either IVDs are way over-regulated, and therefore slow to reach the marketplace, or LDTs are way under regulated and putting patients at risk. One of those has to be true.	We do plan to change it someday, but for now you must toe the line.

The Great Debate

Defense Attorney Brad	US Attorney Brad
But what if an RUO my client sells is actually the standard of care as part of a lab develop test? Don't you care about patients?	Certainly we care, and we will take that into account on a case-by-case basis. But every time we propose a guidance that has some sort of structured phase-in period, you guys in industry whine that it's a rule and has to go through rulemaking. So, we'll just any use our judgment on a case-by-case basis, and we don't like what your client is doing.

Judge Judy's Decision

- I find that the law is:
  - The government can take into account a company's words, actions and knowledge when determining the use intended by the seller.
  - When it comes to knowledge, in the absence of any words or deeds suggesting an intended use, precedents suggest that the use must be very high, indeed a preponderance, before I will impute intent on the seller.
    - So I will not impute an intended use just because one or even a few buyers uses the product in a certain way.
    - Further, I do not expect the seller to stop selling merely because it found out that a customer or two is using it in a way that was not intended.
    - But I do expect the seller's words and actions to conform to their intent, which may mean that the seller has taken steps to avoid an unintended but perhaps predictable "intended use".

Additional RUO Guidance Comments

1. Consider allowing ASR kits
2. Add a grace period
3. Allow contract manufacturing
4. Address more clearly drug clinical trials
5. Carve out an exemption for low volume tests
6. What about products used by laboratories for both research and clinical uses.
7. The halt sales thing isn't very practical.
8. Clarify the intent behind the product codes for imports.
9. The guidance isn't very clear regarding the meaning of research.
   a. What about educational uses: are those research?
   b. Why did you add the words "novel and fundamental"?
   c. Why are you including both research products on their way to becoming diagnostic products, and pure research products?

Final Comments Offered

- Society needs RUOs because labs make very important LDTs from them.
- You're messing with innovation
- You'll frustrate the other Obama folks who are trying to advance science that depends on RUOs
- Your baby is ugly

RUO Enforcement

- September 14, 2011 Warning Letter to International Immuno-Diagnostics from San Fran District
  - Your TSH product insert identifies it for "For Research Use Only Not For Use in Diagnostic Procedures." However, the product states that it is intended for "the quantitative determination of the thyroid stimulating hormone (TSH) concentration in human serum."
  - Your HDV Ab product insert identifies it "For Research Use Only Not For Use In Diagnostic Procedures." However, language in the product insert indicates that the device is intended for the determination of Hepatitis Delta Virus (HDV Ab) concentration in human serum and plasma.
- Letter actually cites the draft RUO guidance

Congressional Letter

- On March 19, 2012, four Congressmen wrote FDA asking many of the same questions posed in the comments.
- Consequences unclear as of this writing

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Application Notes

- Defined as “Instructions and recommendations from the vendor provided in addition to the normal reference manuals.”
- The analysis always starts with intended use.
  - What is my true intended use?
  - Do all of my words and actions support that intended use?
    - If there’s a predictable risk of use in a clinical application, have I taken appropriate steps to avoid that?
  - Are the application notes consistent with my true lawful intended use?

Collaboration Website

- Can we bring together researchers through a social media platform so they can collaborate and develop new tests using our products?
  - Probably not ourselves, but this is akin to continuing education, so look to the CME guidance.
- Key elements of an unrestricted grant to independent body
  - Use your existing policy for unrestricted grants
  - Have a grant agreement
  - Follow FDA's 1997 CME guidance document

1997 CME Guidance Factors

- Here are a few of the 12 factors
  - Control of content and selection of moderators
  - Disclosures
  - Focus of the program
  - Relationship between the manufacturer/sponsor and the program organizer
  - Audience selection
  - Ancillary promotional activities

RUO Contracts Leading up to FDA Clearance

- How about selling research products (instruments and reagents), and then converting them to clinical when we get our clearance?
  - Abandon prior agreement
  - Start supporting cleared clinical uses
- Not as a predetermined strategy
- If everything done properly at the start, can go back and change agreement

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The Future of LDTs

- According to FDA 2012 guidance development plan, the agency will draft 3 guidances on:
  - Framework for Regulatory Oversight of Laboratory Developed Tests
  - FDA Notification and Medical Device Reporting for Laboratory Developed Tests
  - Quality System Requirements Guide for Laboratory Developed Tests

Brad's Predictions

- Expect (maybe):
  - The approach to be risk based, where tests that present equal risk are dealt with equally regardless of who makes them
  - FDA to approach this incrementally and cautiously, carving out the highest risk first before expanding the program
  - That the elements of the quality system imposed on laboratories will be selected to fill the gaps in CLIA, and to be flexibly written
  - The evidence of clinical validation to be on par with what is expected of traditional manufacturers
- But don't blame me if I'm wrong because I'm just guessing.

QUESTIONS?