Recent FDA Initiatives to Support Development of Individualized Cell and Gene Therapies and Rare Disease Therapies

Last month, FDA issued a **Request for Information** (RFI) in the Federal Register seeking information and comments from interested stakeholders regarding "critical scientific challenges and opportunities to advance the development of individualized cellular and gene therapies (CGTs)." Individualized CGTs are therapies "developed for a single patient (or a very small number of patients) based on designing or engineering a product that specifically targets the mechanism underlying a patient's (or small number of patients') illness."

FDA's request focuses on three core areas:

1. Manufacturing: Manufacturing and product quality challenges and opportunities for individualized CGTs in light of, for example, small batch sizes, tailoring of batches to individual patients, and need for rapid testing and release.

On this topic, FDA asks:

i. *Given the challenges to develop consistent manufacturing strategies for CGTs designed for a very small number of patients or an individual patient, how can manufacturers leverage their prior experience manufacturing one CGT to support subsequent development and approval of another related, but distinct CGT (potential areas for leveraging may include manufacturing process validation, control strategy, assay validation, and drug product stability studies)?*

ii. *When the batch size of a CGT is very small, what are some challenges and solutions regarding the volume of product (or number of vials) needed for batch release testing, stability testing, retention of reserve samples, and comparability studies?*

iii. *What are some challenges and solutions for individualized CGTs that need to be tested and released rapidly, either because the product has a very short shelf life or because the patient's clinical status may be rapidly declining and treatment is urgently needed?*

iv. *For many individualized CGT products, each batch is tailored to an individual patient (e.g., autologous CAR–T cells, tumor neoantigen vaccines, certain genome editing products). For such products, what are some challenges and solutions for assuring that each batch has adequate potency to achieve the intended therapeutic effect?*

v. *What are some challenges and solutions for individualized genome editing products that aim to treat monogenic diseases for which the target gene has different mutations in different*

patients?

2. Nonclinical development: The use of nonclinical data to support individualized CGTs, considering the lack of relevant animal models in many instances, the uniqueness or limited applicability of individualized CGTs, and the potential of using prior knowledge from other CGTs—for example, where gene therapy vector products use the same vector backbone.

On this topic, FDA asks:

i. *What nonclinical studies could be leveraged in support of a related product using similar technologies? What nonclinical studies are important to conduct with each final clinical product?*

ii. *What nonclinical development approaches could be considered when there are no relevant animal models or animal models are unable to replicate each individual disease/condition?*

iii. *For patient-specific products where evaluating each individual product is infeasible or impractical, what is the role for nonclinical studies conducted with representative product(s)?*

iv. *What are the opportunities and challenges with using computational approaches to support nonclinical development?*

3. Clinical Development: Clinical development of individualized CGTs, considering for example the infeasibility (for ethical or other reasons) of conducting randomized controlled studies, novel endpoints, and limitations in statistical analyses.

On this topic, FDA asks:

i. *What are challenges and strategies/opportunities with interpreting efficacy data from individual patients (including expanded access) and small groups of patients? What opportunities are there in leveraging prior and/or collective experiences?*

ii. *What strategies can be utilized to accumulate and interpret safety data in personalized/individualized CGTs?*

iii. *For genetic disorders with clear genotype-phenotype associations for disease manifestations or severity, what opportunities are there for tailoring treatments and study design to specific genotypes/phenotypes?*

FDA also requested input on several additional significant questions:

i. *What additional major scientific challenges to advance the development of individualized CGTs should be considered?*

ii. *What existing best practices or scientific approaches should be leveraged to address any of these challenges? Are there specific opportunities for collaborations to advance the development of individualized CGTs?*

iii. *Are there specific areas where flexibility in regulatory approaches would improve the*

feasibility of developing and commercializing individualized CGTs?

Comments are due on November 20, 2023.

At the end of last month, FDA also **announced** a pilot program "to help further accelerate development of rare disease therapies." The program, titled Support for clinical Trials Advancing Rare disease Therapeutics ("START"), will include selected sponsors with an active IND for products meeting certain eligibility requirements. Products regulated by CBER are eligible for the program only if they are a gene or cell therapy treatment for a rare disease or condition that is "likely to lead to significant disability or death within the first decade of life." Products regulated by CDER are eligible only if they are "intended to treat rare neurodegenerative conditions, including those of rare genetic metabolic type." Participants selected for the pilot program will "be able to obtain frequent advice and regular ad-hoc communication with FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population."

FDA will accept applications to the START program beginning January 2, 2024 and until March 1, 2024.

Mark Your Calendars: This Halloween, Don't Miss FDA's LDT Webinar

The U.S. Food and Drug Administration (FDA) has announced an upcoming **webinar** on its **proposed rule** on the regulation of laboratory developed tests (LDTs).

The webinar is scheduled for **October 31, 2023 from 1:00 – 2:00 PM ET** and will include an overview of the proposed rule, a description of the proposed phaseout of FDA's general enforcement discretion approach to LDTs, and a question and answer session. Stakeholders must submit questions by **October 23, 2023** to be considered for the discussion.

For our detailed analysis of the 83-page proposed rule, please see our two-part Insight series: **Part I: Underpinnings of FDA's Proposed Rule** and **Part II: FDA's Proposed Phaseout Policy – Key Considerations & Open Questions**.

If you have questions on the proposed rule or its potential impact, contact the authors or a member of the **Goodwin Life Sciences Regulatory & Compliance** team.

FDA’s Proposed Rule for Oversight of Laboratory Developed Tests: Part II: FDA’s Proposed Phaseout Policy – Key Considerations & Open Questions

 After an over decade-long discourse amongst interested stakeholders, on October 3, 2023, FDA unveiled its **proposed rule and policy** to increase oversight over LDTs.

If finalized as proposed, FDA would implement a new “phaseout policy” that would, across five stages and within four years, apply the same regulatory requirements applicable to in vitro diagnostics (IVDs) on the majority of clinical laboratories offering tests as LDTs. Once implemented, tests offered as LDTs that do not meet the applicable regulatory requirements, including premarket review and the quality system regulation, may be expected to come off the market.

In our **first post** in this Insight series, we recapped the underpinnings of the proposed rule and policy, including the significant discussions contained in the proposed rule on (1) the rationale for the agency’s proposed phaseout policy and (2) FDA’s legal authority for issuing the rule.

In this Insight, we provide our full analysis of FDA’s proposed five-stage phaseout policy and the open questions that remain. Read the full Insight **here**.

FDA’s Proposed Rule for Oversight of Laboratory Developed Tests: Part I: Underpinnings of FDA’s Proposed Rule

On October 3, 2023, the U.S. Food and Drug Administration (FDA) published its widely anticipated **proposed rule** on the regulation of laboratory developed tests (LDTs). The proposed rule and policy are the latest in an over decade-long discourse amongst interested stakeholders – laboratories, IVD manufacturers, regulatory agencies, Congress, providers, and patients – as FDA has sought to enhance oversight over LDTs.

In this Insight, we recap the underpinnings of the proposed rule and policy, including the two lengthy discussions contained in the proposed rule on (1) the rationale for the agency's proposed phaseout policy and (2) FDA's legal authority for issuing the rule. Stay tuned next week for our additional analysis of the details of FDA's proposed five-stage "phaseout" policy and the open questions that remain.

Contact the authors or a member of the Goodwin **Life Sciences Regulatory & Compliance** team for any questions. Read the full Insight **here**.

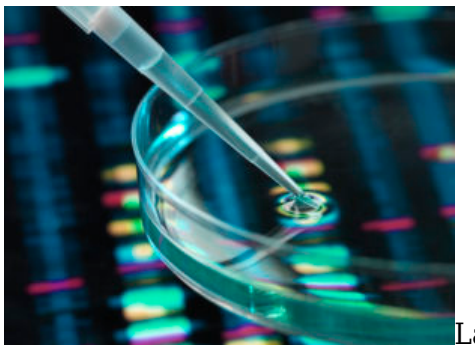
FDA Proposes Phased Approach to Regulating Laboratory Developed Tests

On September 29, 2023, the U.S. Food and Drug Administration (FDA) posted and scheduled for publication its long-awaited **proposed rule** concerning FDA regulation of laboratory developed tests (LDTs). If enacted, the proposed rule would amend the Agency's regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act; and this includes when the manufacturer of the IVD is a laboratory.

Upon finalization of the rule, FDA proposes to phase out its general "enforcement discretion" approach for LDTs so that tests manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs.

Comments to the proposed rule are due 60 days after the date of publication of the proposed rule in the Federal Register. We will provide our full analysis of the proposed rule in the coming days. Contact the authors or a member of the Goodwin **Life Sciences Regulatory & Compliance** team for any questions.

Is it Biosimilar or Interchangeable? It Won't Be Easy to Tell Under FDA's Latest Draft Labeling Guidance



Last week, **FDA released** a draft guidance, "**Labeling for Biosimilar and Interchangeable Biosimilar Products**" that—when finalized—will revise and replace its July 2018 final guidance, "**Labeling for Biosimilar Products**." FDA noted that this 2023 Draft Guidance reflects recommendations based on the "valuable experience about labeling considerations" that FDA has gained through its approval of 42 biosimilar products, including four interchangeable biosimilar products.

Notably, the 2023 Draft Guidance provides further recommendations regarding when to use a biosimilar or interchangeable biosimilar product name, and when to use the reference product name in labeling:

- The biosimilar or interchangeable biosimilar product's proprietary name[1] (or if the product does not have a proprietary name, its proper name[2]) should be used when –
    - Information in the labeling is *specific to the biosimilar (or interchangeable biosimilar) product*, including such references to the product in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections, and/or
    - For "directive statements and recommendations for preventing, monitoring, managing, or mitigating risk," including such references to the product in the BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections.

- When referring to the *drug substance* in the labeling, the biosimilar or interchangeable

biosimilar product's proper name should be used.

- When information *specific to the reference product* is described in the biosimilar or interchangeable biosimilar product's labeling (for example, data from clinical trials of the reference product in the ADVERSE REACTIONS and CLINICAL STUDIES sections), the reference product's proper name should be used.

- In sections of the labeling containing *information that applies to both the biosimilar (or interchangeable biosimilar) product and the reference product*—such as BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS—the labeling should use the core name of the reference product followed by the word "products."[3]

FDA acknowledges that the application of these recommendations is highly context-dependent and may not always be clear, but recommends that biosimilar and interchangeable biosimilar product sponsors evaluate all statements in product labeling carefully to determine the most appropriate product identification approach in each instance.

Another noteworthy aspect of the 2023 Draft Guidance is the Agency's recommendation regarding the biosimilarity statement and footnote in the HIGHLIGHTS section of a biosimilar or interchangeable biosimilar product's labeling.[4] Previously, FDA recommended a biosimilarity statement for a biosimilar product and an interchangeability statement for an interchangeable biosimilar product. The 2023 Draft Guidance now recommends a statement and footnote in the HIGHLIGHTS section that the product is biosimilar to the reference product, *regardless of* whether the product is a biosimilar or an interchangeable biosimilar to the reference product. In the **Federal Register notice** announcing the 2023 Draft Guidance, FDA acknowledges that this marks an "evolution in our thinking" and explains that "a labeling statement noting that certain products within a 351(k) [Biologics License Application] have been approved as interchangeable, and explaining the interchangeability standard, is not likely to be useful to prescribers, who can prescribe both biosimilar and interchangeable biosimilar products in place of the reference product with equal confidence that they are as safe and effective as their reference products." FDA further states that "information about interchangeability is more appropriately located in the Purple Book rather than labeling."

Other notable elements of the 2023 Draft Guidance include recommendations regarding how to describe pediatric use data in a range of scenarios and how to incorporate immunogenicity data. With respect to immunogenicity data, the 2023 Draft Guidance suggests that a contextual paragraph[5] generally be included in the relevant CLINICAL PHARMACOLOGY subsection before describing the available immunogenicity data for the reference product and the biosimilar or interchangeable biosimilar product. The 2023 Draft Guidance also outlines the Agency's expectations for patient labeling—such as a Medication Guide, Patient Information, or Instructions for Use—for a biosimilar or interchangeable biosimilar product, if the reference product has such patient labeling.

Information on how to submit comments on the 2023 Draft Guidance can be found at **https://www.regulations.gov/docket/FDA-2016-D-0643.**

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[1] The proprietary name of a biosimilar product is a brand name determined by the sponsor. The fictitious example provided in the 2023 Draft Guidance is "NEXSYMEO."

[2] The proper name of a biosimilar product is the nonproprietary name designated by FDA that consists of a biological product's core

name plus a unique four-letter suffix. The fictitious example provided in the 2023 Draft Guidance is “replicamab-cznm.”

[3] The fictitious example provided by FDA in the 2023 Draft Guidance is “replicamab products”.

[4] The fictitious example provided by FDA in the 2023 Draft Guidance is “NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf)” and the accompanying footnote is “Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT’S PROPRIETARY NAME]* has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration) described in its Full Prescribing Information.”

[5] The Agency’s suggested paragraph is, “The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of [*proper name of reference product*] or of other [*core name*] products.”

Modernizing the FDA’s 510(k) Program for Medical Devices: Selection of Predicate Devices and Use of Clinical Data in 510(k) Submissions

 On September 6, 2023, the US Food and Drug Administration (FDA) released a trio of draft guidances in its efforts to “strengthen and modernize” the 510(k) Program and provide for more “predictability, consistency, and transparency” for the 510(k) premarket review process. In this post, we discuss the two new draft guidances with broad applicability to the 510(k) Program:

- “**Best Practices for Selecting a Predicate Device to Support a Premarket Notification [510(k)] Submission**”
- “**Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions**”

The two draft guidances address a number of fundamental issues of concern with the 510(k) process.

Read the full client alert **here**.

LDT Proposed Rule Remains Under OIRA Review

Throughout August 2023, the Office of Information and Regulatory Affairs, Office of Management and Budget, Executive Office of the President ("OIRA") has **held stakeholder meetings** regarding a proposed rule which, if enacted, would amend the U.S. Food and Drug Administration's ("FDA's") regulations to make explicit that laboratory developed tests ("LDTs") are devices under the Federal Food, Drug, and Cosmetic Act. The next stakeholder meeting on the proposed rule is scheduled for September 6, 2023.

Per its **website**, OIRA received the proposed rule from FDA on July 26, 2023. The proposed rule was initially **published** this past spring on the Biden Administration's Unified Agenda of Regulatory and Deregulatory Actions with a target publication date of August 2023. The forthcoming stakeholder meeting on September 6th suggests that OIRA may continue its review process well into September, if not later.

The publication of the proposed rule would mark the first significant FDA action on LDTs since its two 2014 draft guidances (available **here** and **here**) and 2017 **discussion paper**. The proposed rule is also expected to be controversial after prior U.S. Department of Health & Human Services statements concerning regulation of LDTs and legislative attempts to further define the LDT regulatory framework. Once cleared by OIRA, the proposed rule will be published in the Federal Register and subject to public comment.

We will continue to monitor for updates on the LDT proposed rule. Contact Goodwin Life Sciences Regulatory & Compliance team members for any questions.

Common FDA Bioresearch Monitoring Violations: Updates from FY 2022 to Now

 The Bioresearch Monitoring (BIMO) Program, operated by the U.S. Food and Drug Administration (FDA), conducts on-site inspections and data audits in order to effectively monitor the compliance of all FDA-regulated research.

As a follow up to our **June 2022 post**, we highlight the most common violations identified in Fiscal Year (FY) 2022, in addition to those observed thus far in FY 2023. BIMO conducted 766 inspections in FY 2022. The majority of these inspections (approximately 79%) were of drug, biologic, or medical device study clinical investigators, institutional review boards (IRBs), sponsors, clinical research organizations (CROs), and sponsor-investigators. Some of the most common inspection outcomes are highlighted below. Our methodology included a search of FDA's Warning Letter database for FY 2022 and 2023, to date, for letters issued by BIMO and the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health to IRBs, CROs, clinical investigators, sponsors, and sponsor-investigators.

FY 2022:

BIMO conducted 504 inspections of clinical investigators (468 of which were assigned to FDA's drug, biologic, and device Centers), making up over half of BIMO's inspections conducted in FY 2022. Inspections of IRBs, sponsors, CROs, and sponsor-investigators assigned to FDA's drug, biologic, and device Centers comprised another 138 inspections in FY 2022. Of the 504 clinical investigator inspections, only 9 resulted in a classification of "Official Action Indicated" (OAI) and 87 resulted in a classification of "Voluntary Action Indicated" (VAI). The most common inspection observations included: (1) failure to comply with Form FDA 1572 requirements and protocol compliance; (2) failure to follow the investigational plan and protocol deviations; (3) inadequate and/or inaccurate case history records and inadequate study records; (4) inadequate accountability and/or control of the investigational product; (5) safety reporting and failure to report and/or record adverse events; and (6) inadequate subject protection and informed consent issues.

Of the Warning Letters that were issued in FY 2022 to clinical investigators, the most common observations were:

- **Failure to ensure that a clinical investigation was conducted according to its investigational plan.** This finding in various Warning Letters included failure to properly consent participants, failure to properly randomize participants, and/or failure to properly screen potential participants to ensure they met a protocol's inclusion and exclusion criteria prior to enrollment in an investigational plan. For example, in one **Warning Letter**, an investigator did not ensure that subjects randomized to a specific intervention group received the assigned investigational drug for that intervention group and did not adhere to the blinding protocol.
- **Failure to submit an IND application for the conduct of a clinical investigation with an investigational new drug.** For example (and similar to trends observed in FY 2021), the

> FDA noted that one **clinical investigator** failed to submit an IND for the use of a product that was determined by the FDA to be a drug. The study design demonstrated that the investigational product was intended to cure, mitigate, and/or treat a disease or condition and therefore, an IND application should have been submitted to the FDA prior to commencing any research activities. Another **Warning Letter** included a finding that a protocol comprised of a combination product (a drug and device component) required an IND application.

BIMO conducted 81 inspections of sponsors and CROs in FY 2022 (all but one were assigned to FDA's drug, biologic, and device Centers). Of these, 0 resulted in a finding of OAI, though 15 were classified as VAI. The most common inspection observations included: (1) failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan; (2) failure to meet the abbreviated requirements for investigational device exemptions (IDEs); (3) failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; (4) accountability for the investigational product; (5) failure to comply with Form FDA 1572 requirements; (6) financial disclosures; (7) failure to submit an Investigational New Drug (IND) application and IND safety reports; and (8) failure to submit current list of all participating investigators to FDA at the six-month interval after FDA approval of the study.

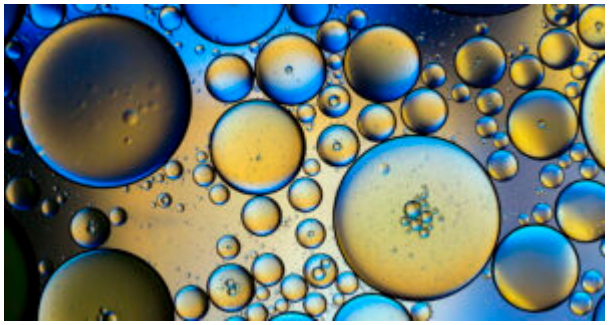
FY 2023 Trends (to date):

In 2023, we have already observed six Form FDA 483 Warning Letters issued to clinical investigators and IRBs, three involving the failure to submit an IND for the conduct of a clinical investigation with an investigational new drug, two involving failure to follow the clinical investigation according to its investigational plan, and one involving overall lack of IRB oversight and IRB compliance. For example, in a 2023 **Warning Letter** issued to an IRB, the FDA noted that the IRB: (a) failed to review proposed research at convened meetings at which a majority of IRB members were present; (b) failed to maintain adequate documentation of IRB activities, including keeping an active list of active IRB members; and (c) failed to ensure that information provided to study subjects as part of the informed consent process was done in accordance with applicable FDA regulations. Although sponsors may often make the decision to utilize a central IRB to oversee the conduct of a clinical investigation, some participating sites may be required to utilize their own local IRB, and it is important to remember that any IRB which does not adhere to FDA's requirements can introduce a compliance risk for studies it is engaged to oversee.

Sponsors, clinical investigators, CROs, and IRBs should review the FDA's **BIMO Compliance Program Guidance Manuals** regularly to ensure that they understand their responsibilities when carrying out clinical research involving human subjects. Sponsors, clinical investigators, CROs, and IRBs should ensure inspection readiness at all times while bioresearch is ongoing and following completion of bioresearch that may support marketing applications submitted to the FDA. Ensuring diligence in the research site selection process, careful monitoring during clinical trials, and corrective actions when deviations occur can help manage the risk of inspection findings of noncompliance or Warning Letters issued by the FDA. The Goodwin Life Sciences Regulatory & Compliance team provides regulatory counseling on FDA's Good Clinical Practice requirements and the resolution of BIMO inspection findings and Warning Letters when they occur.

Contact our team to learn more.

Psychedelics & Drug Development — Key Considerations for Healthcare Industry and Life Sciences Companies as Congress Seeks to Tap Into Psychedelics' Therapeutic Potential



Based on recent regulatory changes at the state and local level and the efforts by the federal government and certain foreign agencies, investors, clinical trial sponsors, life sciences companies, and investigators operating in the psychedelics industry may have reason to be optimistic about the future regulatory landscape for therapeutic psychedelic product candidate development, approval, and commercialization. The proposed Breakthrough Therapies Act is one such reason.

On March 8, 2023, US Sens. Cory Booker (D-NJ) and Rand Paul (R-KY) **introduced** an **updated version** of the Breakthrough Therapies Act. If passed, the bipartisan bill would amend the federal Controlled Substances Act (CSA) to enable the Drug Enforcement Administration (DEA) to reclassify from Schedule I to Schedule II drugs and biologics, including therapeutic psychedelics, that receive breakthrough therapy designation or are authorized for expanded access by the US Food and Drug Administration (FDA). Therapeutic psychedelics are Schedule I substances and include LSD, MDMA, and psilocybin. According to the bill's sponsors, the "legislation [would] remove regulatory hurdles that inhibit research and compassionate use access to potentially lifesaving treatments that are heavily restricted by Schedule I of the [CSA]."

The bipartisan effort behind the Breakthrough Therapies Act signals the federal government's evolving position on psychedelic substances, their therapeutic potential, and access. This evolution, discussed in greater detail in our Client Alert, presents an important opportunity for investors, clinical trial sponsors, life sciences companies, and investigators.

Accordingly, we have identified and answered 8 key questions that stakeholders should consider as they develop and innovate in the psychedelic space:

- What Is the Difference Between a Schedule I and a Schedule II Drug?
- What Diseases and Conditions Can Potentially Benefit From Therapeutic Psychedelics?
- What Are the Key Provisions of the Proposed Breakthrough Therapies Act?
- How Does a Drug or Biologic Obtain Breakthrough Therapy Designation From FDA?
- What Is Expanded Access?
- What Are Some Key Limitations in the Proposed Breakthrough Therapies Act?
- What Is the Status of Therapeutic Psychedelics at the State and Local Level?

- What Regulatory Changes Are on the Horizon for Therapeutic Psychedelics?

Read the full client alert **here**.