US Regulatory Tools for Expedited Antibacterial Development Programs

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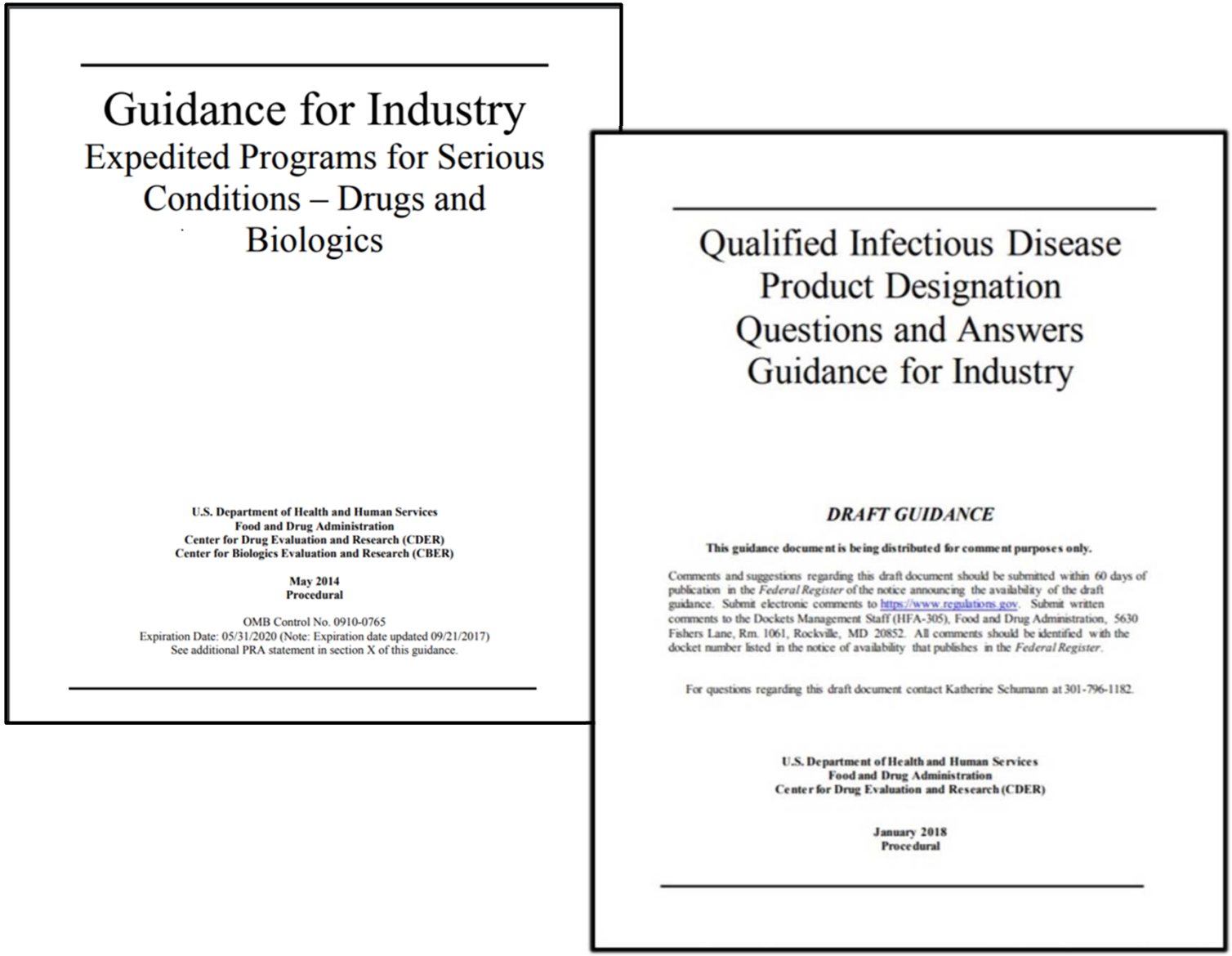
Expedited Programs

- Intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the benefits of the therapies justify their risks
- 21 CFR 312, Subpart E recognizes that patients and physicians are generally willing to accept greater risks or side effects from treatment of life-threatening and severely debilitating diseases while preserving appropriate standards for safety and effectiveness

21 CFR 312 Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses;
Guidance on Expedited Programs for Serious Conditions – Drugs and Biologics May 2014
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf



Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2014
Procedural

OMB Control No. 0910-0765
Expiration Date: 05/31/2020 (Note: Expiration date updated 09/21/2017)
See additional PRA statement in section X of this guidance.

Qualified Infectious Disease Product Designation Questions and Answers Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Katherine Schumann at 301-796-1182.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2018
Procedural

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM594213.pdf

Key Concepts

1. Serious Condition
   - Whether the condition is serious
     - *. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning… Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.*
   - Whether the drug is intended to treat a serious condition
     - must be intended to have an effect on a serious condition or a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition or other intended effects

21 CFR 312.300(b)(1)

Key Concepts

2. Available Therapy
   - Approved or licensed in the United States for the same indication being considered for the new drug, *and*
   - Is relevant to current U.S. standard of care (SOC) for the indication; as SOC for a given condition may evolve, sponsors are encouraged to discuss available therapy considerations with the Agency

Key Concepts

3. Unmet Medical Need

Condition whose treatment or diagnosis is not addressed adequately by available therapy

- Has an effect on a serious outcome of the condition that is not known to be influenced by available therapy
- Has an improved effect on a serious outcome(s) of the condition compared with available therapy
- Has an effect on a serious outcome of the condition in patients who are unable to tolerate or failed to respond to available therapy
- Documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes

Expedited Programs

- Designations:
  - Fast Track
  - Breakthrough
  - Priority Review
- Accelerated Approval

Fast Track Designation

- *". . . if it is intended, whether alone or in combination…, for the treatment of a serious or life-threatening disease.., and it demonstrates the potential to address unmet medical needs for such a disease or condition*"
- Information needed will depend on the stage of drug development
  - Evidence of activity in a nonclinical model, a mechanistic rationale, or pharmacologic data
  - Available clinical data

Fast Track Designation

- Allows for frequent interactions with the review team including pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings
- Allows for submission and review of portions of an application (rolling review)
- Designation may be rescinded if it no longer meets the qualifying criteria

Breakthrough (BT) Designation

- *". . . if the drug is intended… to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints."*

BT Designation

- Preliminary clinical evidence:
  - The drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval
  - Clinical evidence must show that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints

BT Designation

- Intensive guidance on the drug development program, beginning as early as Phase 1
- Organizational commitment involving senior managers
- Eligible for rolling review
- Could be eligible for priority review if supported by clinical data at the time of BLA/NDA/efficacy supplement submission

Priority Review

- An application
  - For a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness
  - Proposes a labeling change based on a pediatric study under 505A (pediatric written request)
  - Is the first application for a qualified infectious disease product (QIDP)
  - For a drug submitted with a priority review voucher

Priority Review

- Examples for significant improvement:
  - Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
  - Elimination or substantial reduction of a treatment-limiting adverse reaction
  - Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
  - Evidence of safety and effectiveness in a new subpopulation

Priority Review

- Review timeline is 6 months, compared to 10 months under standard review
- For applications under the Program (applies to all new molecular entities), the PDUFA review clock will begin at the conclusion of the 60 calendar day filing review period

Accelerated Approval

- A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit
- Must meet the same statutory standards for safety and effectiveness as traditional approval

21 CFR part 314, subpart H; 21 CFR part 601, subpart E ; Section 506(c) of the FD&C Act as amended by section 901 of FDASIA

Comparison of Expedited Programs for Serious Conditions

	Fast-Track Designation*	Priority-Review Designation*	Breakthrough-Therapy Designation	Accelerated-Approval Pathway
Criteria	• Nonclinical or clinical data demonstrate potential to address unmet medical need	• Provides improvement in safety or effectiveness over existing therapies	• Preliminary clinical data demonstrates substantial improvement over existing therapies	• Provides meaningful advantage over existing therapies • Demonstrates effect on a surrogate endpoint or intermediate clinical endpoint
Features	• Frequent FDA feedback • Eligible for priority review • Rolling review	• 6 month review period (instead of 10 months)	• All benefits of Fast-Track Designation • Intensive guidance beginning Phase 1 • Organizational commitment involving senior FDA managers	• Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict an effect on IMM or other clinical benefit

*Products with QIDP designation are eligible for fast track designation and priority review
IMM: Irreversible morbidity or mortality

Expedited Programs for Anti-Infective Products

- Fast Track (FT) Designations
  - For products with FT designation we have accepted rolling reviews, if requested
  - Most QIDP products also have FT designation

Expedited Programs for Anti-Infective Products

- Breakthrough Designation:
  - BT designation has been granted for some anti-infective products
- Accelerated Approval:
  - Clinical endpoint can usually be measured in a fairly short time frame (2-4 weeks); so less need for a surrogate endpoint
  - Subpart H approval of bedaquiline for MDRTB was based on sputum culture conversion

https://orphandruganaut.wordpress.com/2014/06/18/fda-breakthrough-therapy-designation-43-for-insmed/
https://us.gsk.com/en-us/media/press-releases/2013/gsk-and-mmv-announce-fda-breakthrough-therapy-designation-for-tafenoquine-for-plasmodium-vivax-malaria/
http://investors.achaogen.com/releasedetail.cfm?releaseid=1027613
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/204384Orig1s000ltr.pdf

QIDP Designation

- Antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections, including…
- Provides for the following incentives
  - Additional 5 years marketing exclusivity
  - Priority review for the first application for a QIDP
  - Eligible for fast track designation
- Designation can be requested at any time before submission of the marketing application
  - Designation cannot be withdrawn by FDA, unless the request contained an untrue statement of material fact

GAIN Provision (Title VIII of FDASIA under section 505E of the FD&C Act)
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM594213.pdf

QIDP Designation

- Granted for approximately 77 novel antibacterial and antifungal products (156 designations)
- Recently approved products with QIDP designation received priority review

21st Century Cures Act

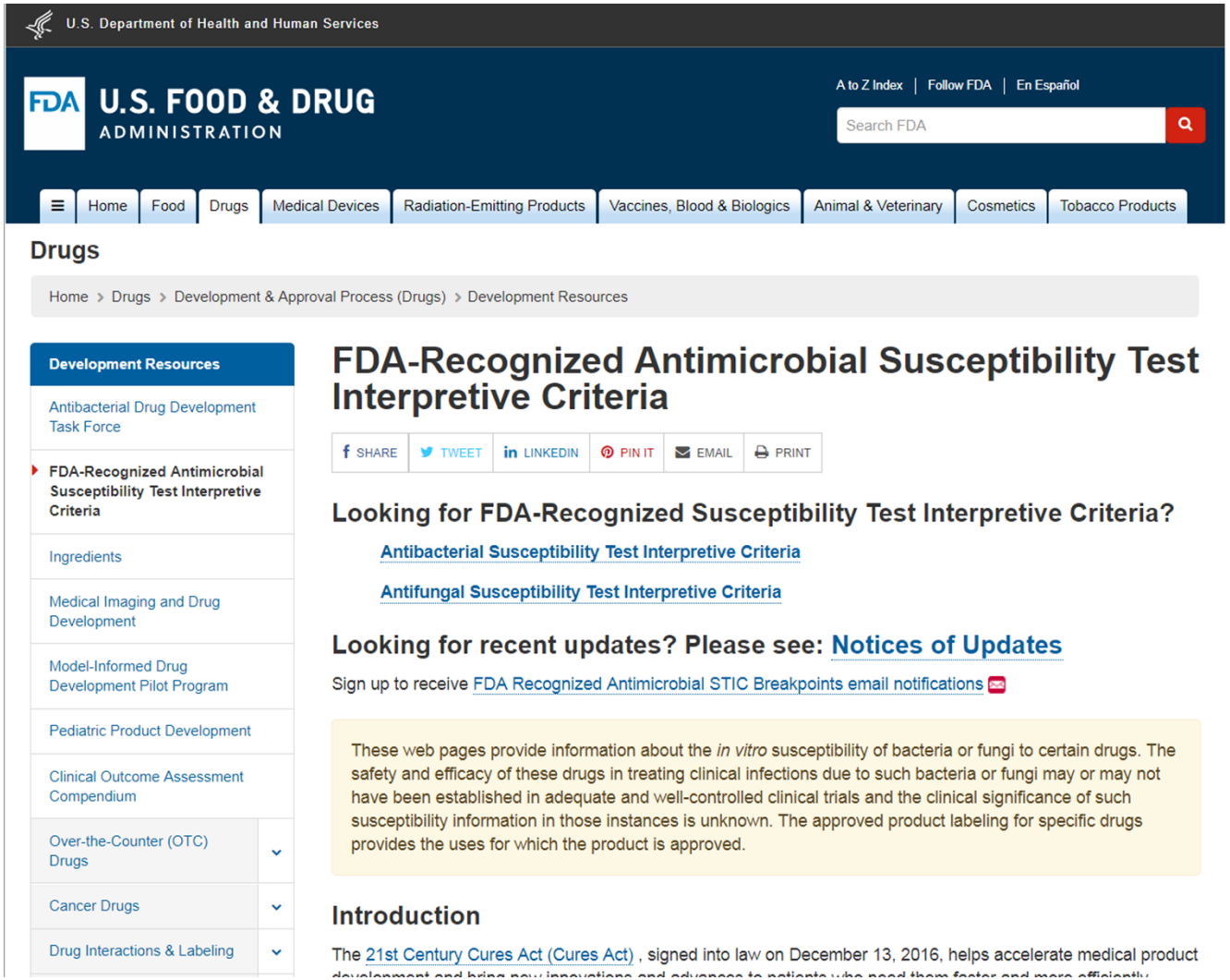
- Signed into law on December 13, 2016
- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
  - Section 3044. Susceptibility test interpretive criteria for microorganisms; antimicrobial susceptibility testing devices
  - Section 3042. Limited Population Pathway for antibacterial and antifungal drugs (LPAD)
  - Section 3041. Antimicrobial Resistance Monitoring

https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf

21st Century Cures: Breakpoints

- FDA website for breakpoints:
  - www.fda.gov/STIC
- Federal Register notice:
  - https://www.federalregister.gov/documents/2017/12/13/2017-26790/21st-century-cures-act-announcing-the-establishment-of-the-susceptibility-test-interpretive-criteria
- Labeling guidance:
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588747.pdf

STIC Website



www.fda.gov/STIC

Drug Labeling

- The Microbiology subsection of labeling for drugs approved after December 13, 2017 will include the following:
  - *For specific information regarding susceptibility testing methods, interpretive criteria, and associated test methods and quality control standards recognized by FDA for DRUG, please see: https://www.fda.gov/STIC*
- An applicant can seek breakpoints that differ from those listed on the website
  - Will need to provide data to support the proposed breakpoints
- Application holders have 1 year following establishment of website to remove breakpoints from approved drug labeling
  - replace with reference to the website
  - can be submitted as annual reportable change

Section 506(h): LPAD

- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
- Standards for approval under 505(c) and (d) or standards for licensure under 351 of Public Health Service Act are met
- Written request from the Sponsor that the drug be approved as a limited population drug

LPAD: Additional Requirements

- Labeling: To indicate that safety and effectiveness has only been demonstrated with respect to a limited population
  - All advertising and labeling will include “Limited Population” in a prominent manner, and
  - The prescribing information will contain the statement “This drug is indicated for use in a limited and specific population of patients”
- Promotional Materials:
  - Pre-submission of promotional materials at least 30 days prior to dissemination of such materials

Facilitating Antibacterial Drug Development

- Flexibility in clinical trial requirements:
  - Streamlined development programs; use of wider NI margins for products that have the potential to address an unmet need; single trial in some instances
  - One trial in an indication to support a single trial in a different indication, e.g., one trial each in cUTI and cIAI
  - Some use of prior effective antibacterial therapy allowed to make trials feasible
  - Some flexibility in choice of comparator for NI trials
- Public workshops
- Guidances
- Public-Private partnerships
- Research activities

Interactions with the Division

- We recommend early and frequent interactions, especially if you have a program/product that might not fit into available guidances
  - In the last two years, the Division has granted ~ 140 meetings/year
- PIND consultation process
- Early discussions around CMC aspects of the program

Recent Antibacterial Drug Approvals

- Dalbavancin: ABSSSI, May 2014
  - Two trials in ABSSSI
- Tedizolid: ABSSSI, June 2014
  - Two trials in ABSSSI
- Oritavancin: ABSSSI, August 2014
  - Two trials in ABSSSI
- Ceftolozane-tazobactam: cUTI and cIAI, December 2014
  - One trial each in cIAI and cUTI
- Ceftazidime-avibactam: cUTI, cIAI, HABP/VABP, February 2015
  - Phase 2 data for initial approval*; followed by a trial each in cIAI, cUTI, HABP/VABP
- Delafloxacin: ABSSSI, June 2017
  - Two ABSSSI trials
- Meropenem-vaborbactam: cUTI, August 2017
  - Single cUTI trial
- Secnidazole: Bacterial Vaginosis (BV), September 2017
  - Two placebo-controlled trials

ABSSSI: Acute Bacterial Skin and Skin Structure Infections; cUTI: complicated urinary tract infections;
cIAI: complicated intra-abdominal infections; * Limited Use; subsequently revised to remove limited use labeling
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Clinical Trials - Lessons Learned

- Clinical trials continue to teach us important lessons that are often unexpected
  - Daptomycin: CABP didn't meet NI margin; binding to surfactant
  - Doripenem and tigecycline: Higher mortality and lower cure rates in VABP
  - Ceftobiprole: Lower cure rates in VABP
  - Delafloxacin: Monotherapy may not be sufficient to treat some patients with uncomplicated gonorrhea
  - Solithromycin: Trial in gonorrhea did not meet NI margin
  - Eravacycline: cUTI trials didn't meet NI margin; successful trial in cIAI

Silverman. J Infect Dis. 2005; Pertel. Clin Infect Dis 2008; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm http://www.fda.gov/drugs/drugsafety/ucm369580.htm; Ambrose Clin Infect Dis 2010; Udy Int J Antimicrob Agents. 2012 Awad et al. Clin Infect Dis 2014; http://www.melinta.com/news.php?c=41; https://www.fiercebiotech.com/biotech/another-setback-for-cempra-s-solithromycin-time-gonorrhea; http://ir.tphase.com/releasedetail.cfm?ReleaseID=930613; http://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-top-line-results-ignite3-phase-3-clinical

Summary

- Provided a summary of the expedited programs available for products that treat a serious condition and address an unmet need
- Discussed how the available expedited programs have been used to facilitate antibacterial drug development
- Provided an overview of 21st Century Cures as it relates to antibacterial drug development
- Encourage early interactions and continued dialogue with the Division as drug development progresses

U.S. FOOD & DRUG ADMINISTRATION

Thanks!

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