Overview of the Over-the-Counter Drug Monograph Process

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Outline

- **Purpose of this public meeting**
- **FDA history regarding the over-the-counter drug review (OTC monograph), and regarding user fees**
- **Overview of the OTC monograph process**
- **Potential benefits of additional resources for monograph review activities**

Purpose of this Public Meeting

- **The Prescription Drug User Fee Act (PDUFA) and other FDA user fee programs have provided vital resources that have enabled more timely evaluation of the safety and efficacy of many drugs, biologics and devices**
- **No user fee program exists for OTC monograph drug products, and funds from other user fee programs cannot be used for monograph work**
- **Over 100,000 monograph drug products; used by millions of Americans every year**

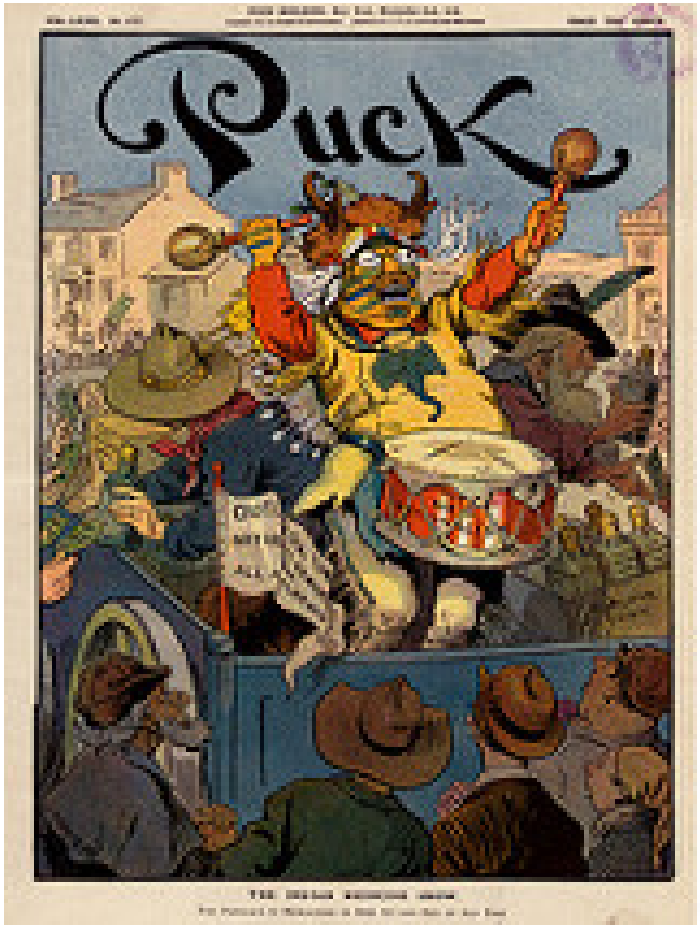
Purpose of Meeting (cont.)

- **FDA critically under-resourced in this regulatory area**
- **FDA is seeking public input regarding a possible user fee program as a way to provide stable, predictable funding for assurance of the safety and efficacy of OTC monograph drug products.**
- **Monograph policy reform is not a topic of this meeting; FDA is addressing policy reform as a separate process**

Overview of the OTC Drug Review Process

Key Points in FDA History

- **FDA is the oldest comprehensive consumer protection agency in the US federal government**
- **Prior to the late 1800s, a hodgepodge of state laws addressed consumer protection from unsafe or misrepresented therapeutic products**


Puck


KICKAPOO INDIAN PRAIRIE PLANT
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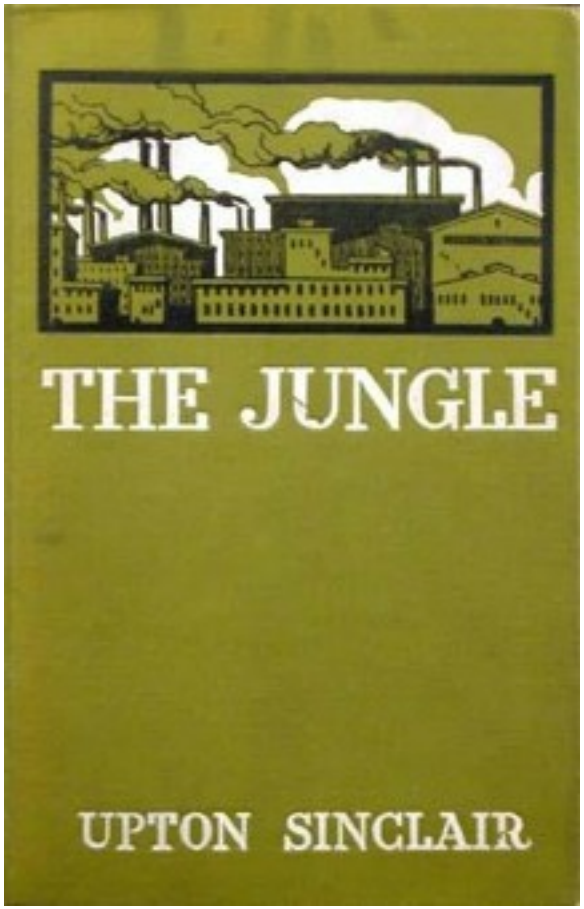
1862: The Bureau of Chemistry

1906: The Pure Food and Drug Act



1937: The Elixir Sulfanilamide Tragedy

1938: The Federal Food, Drug and Cosmetic Act

- **Mandated premarket review of the safety of all new drugs**
- **Banned false therapeutic claims in drug labeling, and no longer required the FDA to prove fraudulent intent**
- **Authorized factory inspections**
- **Added enforcement authorities**
- **Remains the foundation of FDA regulatory authority today**

1951: The Durham-Humphrey Amendment

This Week In FDA History - Oct. 26, 1951

Photo courtesy of Kremers Reference Files University of Wisconsin

Former vice president and senator Hubert H. Humphrey Jr., who was a pharmacist in South Dakota before beginning his political career, co-sponsored the 1951 Durham-Humphrey Amendment.

October 26, 1951: The Durham-Humphrey Amendment is passed. The bill requires any drug that is habit-forming or potentially harmful to be dispensed under the supervision of a health practitioner as a prescription drug and must carry the statement, "Caution: Federal law prohibits dispensing without prescription."

Durham-Humphrey Amendment (1951)

Establishment of Two Drug Classes

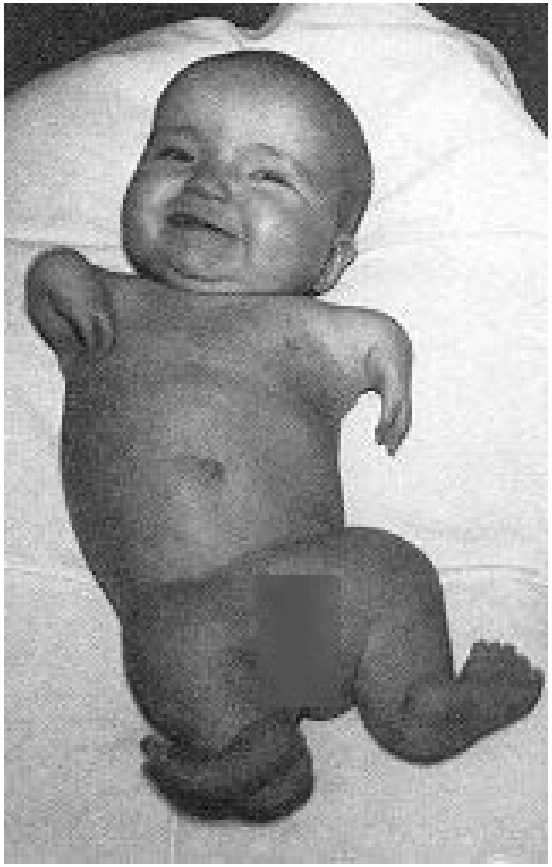
- **Rx legend (prescription)**
  - Requires practitioner supervision, because of toxicity or potentiality for harmful effect, or method of use
  - Labeling indicates that it is by prescription-only
- **OTC (nonprescription)**
  - Drugs that do not meet the definition for an Rx drug

OTC Drug Products

OTC drug products generally have these characteristics:

- **Can be adequately labeled such that**
  - **The consumer can self-diagnose, self-treat, and self-manage the condition being treated**
  - **No health practitioner is needed for the safe and effective use of the product**
- **Drug has low potential for misuse and abuse**
- **Safety margin is such that the benefits of OTC availability outweigh the risks**

1962: The Thalidomide Tragedy



1962: Kefauver Harris Amendment

- In addition to premarket evaluation of safety, manufacturers had to demonstrate efficacy
- Was the basis for the current New Drug Application (NDA) system
- Created a dilemma for what to do about OTC drug products
- Estimated 100,000 to 300,000 OTC products on the market at that time
- Monograph process established in 1972 by regulation as a means to address the safety and efficacy of hundreds of thousands of existing OTC products without requiring each to have a separate New Drug Application

Two Paths to Market for OTC Drugs

OTC drugs can enter the market under one of two paths:

- **under an approved new drug application (NDA or ANDA), or**
- **by conforming to a monograph**

Both NDA and Monograph Review Focus on Science

Both paths involve a scientific decision by FDA

- **NDA: FDA reviews the safety and effectiveness of the *product***
- **Monograph: FDA reviews the safety and effectiveness of the *ingredient***

History of OTC Drug Review (The OTC Monograph)

- **In 1970s, Advisory Review Panels reviewed therapeutic classes of OTC drugs and put products into three categories:**
  - Category I: GRASE (Generally Recognized as Safe and Effective)
  - Category II: not GRASE
  - Category III: insufficient data available to determine if safe and effective

- **Examples of GRASE conditions include:**
  - Active ingredients
  - Dosage strength
  - Dosage form and route of administration
  - Patient population (age, gender) and indications for use
  - Required labeling: Uses, Warnings, Directions

What is an OTC Drug Monograph?

- **A sort of "rule book" for marketing requirements for an OTC drug**
- **A list and explanation of GRASE conditions (GRASE = Generally Recognized As Safe and Effective)**
- **If a sponsor follows the "rule book" exactly, it can market a monograph drug without coming to FDA for premarketing approval**
- **All drug products still subject to inspection and compliance requirements**
- **Many monographs finished, but not all**
- **Final monographs are published in the Code of Federal Regulations: 21 CFR parts 331-358**
- **Drug products that don't meet the conditions of the monograph can apply for approval under the NDA path**

OTC Drug Regulatory Pathways

New Drug Application

- Product specific (including formulation)
- Confidential filing
- Clinical development required
- Application submitted for approval
- Application fees (PDUFA)
- Mandated timelines
- Potential for marketing exclusivity
- Reporting requirements
- Comply with good manufacturing practices

Monograph Process

- Ingredient and therapeutic category specific regulations (CFR 330-358)
- Public process - no data confidentiality
- Generally no clinical development
- Relies upon adequate data being submitted
- No user fees
- No mandated timelines
- Currently no potential for marketing exclusivity
- Limited reporting requirements (serious adverse events only)
- Comply with good manufacturing practices

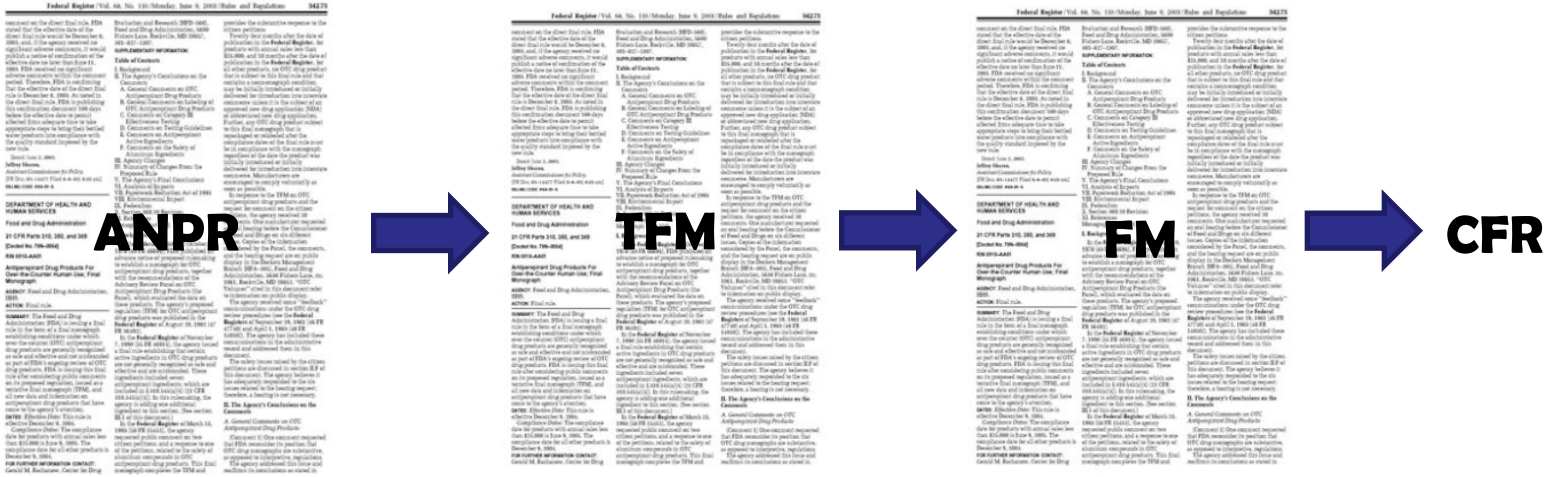
Examples of OTC Monograph Drug Categories

- Antacids
- Antidiarrheal products
- Antiemetics
- Antiperspirants
- Cough and cold products
- Wart removers
- Sleep aids
- Ophthalmic products
- Hemorrhoidal products
- Dandruff products
- Anticaries products
- Otic products
- Analgesics

Current OTC Monograph Rulemaking Process

Requires a three-step public notice and comment rulemaking process

- Advance Notice of Proposed Rulemaking
- Tentative Final Monograph
- Final Monograph



Status of OTC Monograph

- **Remains one of the largest and most complex regulatory programs ever undertaken at FDA**
- **Approximately 88 simultaneous rulemakings in 26 broad therapeutic categories encompassing over 100,000 OTC drug products**
- **Some 800 active ingredients for over 1,400 different uses**
- **Additional resources needed to continue this massive effort**
- **The OTC monograph is a living document; science continues to evolve**

Challenges for Monograph Review

- **Despite scope of responsibilities, the monograph review program is very small**
- **Current resources often consumed by external mandates, for example:**
  - **Special statutes (e.g. the Sunscreen Innovation Act)**
  - **Consent decrees (e.g. for antiseptic rulemaking)**
- **Even without current external mandates, and even with desired monograph reforms, it would take many decades to finalize GRASE determinations for pending monographs, if resources remain at current levels**

Challenges for Monograph Review (cont.)

- **FDA does not have adequate resources to consider proposed innovations to the monograph, or even to address pressing safety issues**
- **The monograph review program needs sufficient resources to give priority to matters of high public health importance, while still meeting other mandates**

1992: The Prescription Drug User Fee Act

- Allows FDA to collect fees from drug manufacturers
- Fees support a portion of the cost of the drug review process
- Significantly shortened review times
- Number of innovative drugs coming to market increased
- Drugs became more likely to become available in the US first (before becoming available in other countries)

PDUFA and Other FDA User Fee Programs

- Subsequent user fee programs established for generic drugs (GDUFA), biosimilar drugs (BsUFA), and medical devices (MDUFA)
- Re-authorized every 5 years, based on negotiated agreements between FDA and industry
- User fees do not affect approvability of drugs and devices; all decisions based on science
- Funds from PDUFA and other user fee programs cannot be used for review of OTC monograph drug products; the limited funds for OTC monograph review still come entirely from budget authority

Potential Benefits of Additional Monograph Review Resources

- **Ability to address safety issues in a timely manner**
- **Timely determination on safety and efficacy of thousands of marketed monograph drug products**
- **Ability to consider certain monograph product innovations proposed by industry**
- **Streamlined ability to update monographs to allow modern testing methods, potentially reducing the need for animal testing, and simplifying and speeding product development**

Potential Benefits of Additional Monograph Review Resources (cont.)

- **Development of information technology infrastructure for submission, review and archiving**
- **Development of modern, useful, transparent Web interface**
- **Ability to hold more public meetings on important monograph issues**
- **Increased ability to respond to monograph-related concerns from the public and industry**
- **Establishment of additional infrastructure for efficient continued conduct of monograph activities in the longer term**

User Fee Considerations in the Context of Over-the-Counter Monograph Drugs

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June 10, 2016

Outline

- Current Monograph Resourcing
- What is a User Fee?
- How Does a User Fee Program Work?
- What kind of input do we need from you today?

Which of these costs the most?

- **Wastewater treatment for Concord, NH** **$7.4 million**
- **The animal welfare department of Albuquerque, NM**

  $11.1 million
- **Production of the "Blackwater" episode of the hit TV series *Game of Thrones***

  $8.0 million
- **Oversight of the nation's over-the-counter drug supply**

  $8.2 million

OTC Monograph Resourcing

In recent years, the Agency has dedicated just under 30 FTEs per year to the OTC monograph program:

Fiscal Year	FTE	Cost
2014	27.3	$ 7,901,157
2015	27.7	$ 7,415,645
2016	30.1	$ 8,233,296

What does this expenditure cover? It covers FDA oversight of hundreds of thousands of products consumed - in many cases, on a daily basis - by millions of Americans.

What is a User Fee?

- **Not a tax**
- **The payor of a user fee receives a benefit for having paid the fee**
- **There is a direct relationship between the amount of total fee revenue and FDA's total cost of providing the service**
- **The fee *defrays* the cost of a government service; the government does not make a profit**

Examples of Other User Fee Programs

- **From the FDA**
  - Prescription Drug User Fee Amendments (PDUFA)
  - Generic Drug User Fee Amendments (GDUFA)
  - Biosimilar User Fee Act (BsUFA)
  - Medical Device User Fee Act (MDUFA)
- **Elsewhere in the Government:**
  - Entrance fees to national parks
  - Security fees for airline travel
  - Crop insurance
  - Tipping fees at your local transfer station or dump

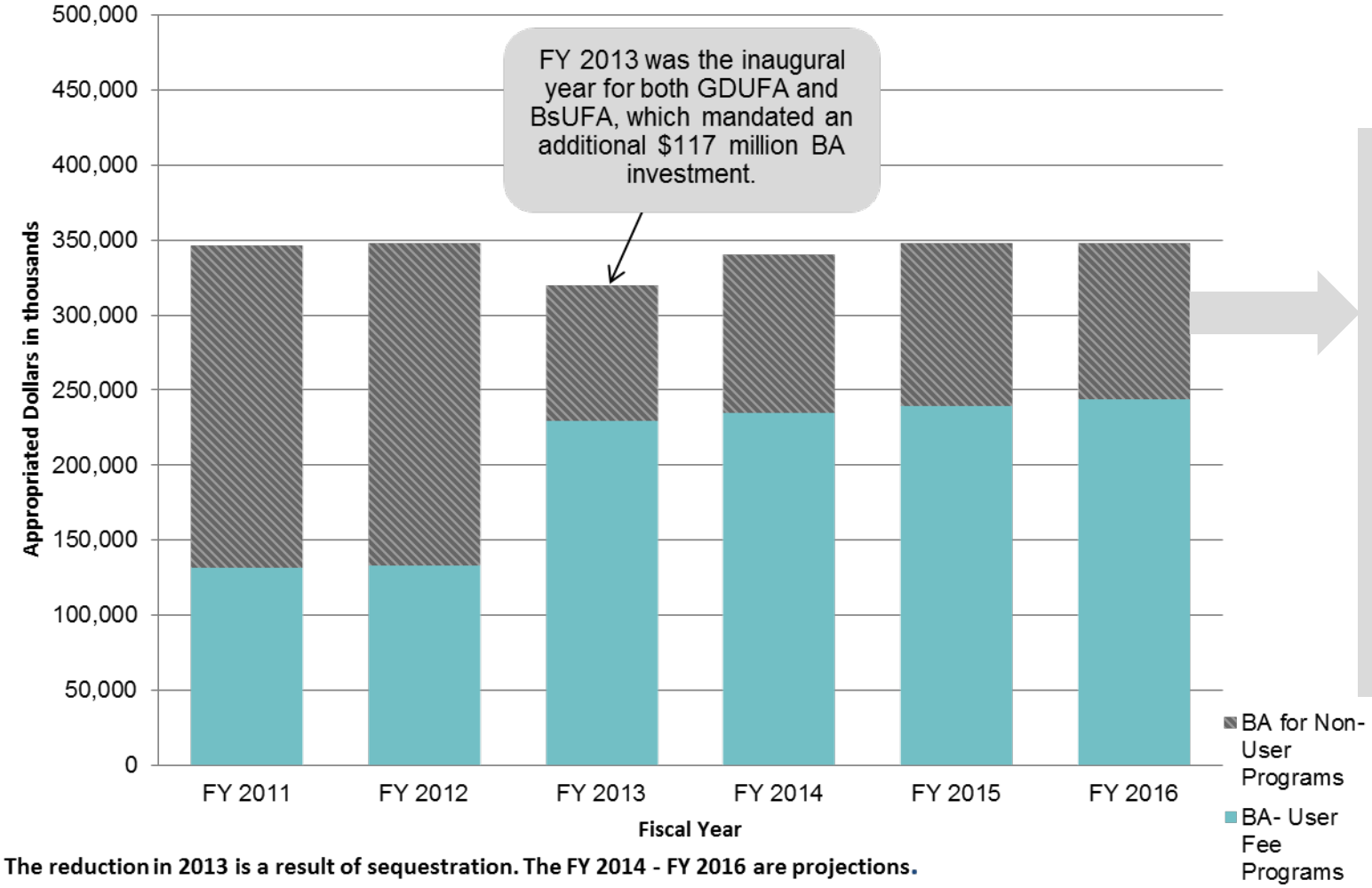
Characteristics of a Good User Fee Program

- Revenue is fairly stable from year to year
- Fees are paid by those who benefit from the program
- Beneficiaries pay a “fair share” of the liabilities
- Fees collected cover enough of the intended service
- The cost of administering the user fee program is not inordinate

CDER Funding Constraints

- **Two types of funding**
  - Budget authority (taxpayer dollars from Congress)
  - User fee funds (paid by industry)
- **Trigger concept**
  - BA dedicated to a user fee program
- **Competition for non-user fee funding**

Why is CDER so limited in how it can spend its non-user fee money?



Examples of Non-User Fee Programs:

- Direct-to-Consumer Programs
- Sentinel
- OTC monograph
- Critical Path
- Drug Safety Contracts
- Legislative Mandates:
  - DQSA
  - FDASIA

The reduction in 2013 is a result of sequestration. The FY 2014 - FY 2016 are projections.

Question: Types of User Fees

What types of user fees (e.g. product listing fees, facility fees, application fees, other types of fees) might be appropriate for a potential monograph user fee program? Consider the following in your answer:

- **For monograph products (unlike for products currently covered by user fee programs), premarket applications are not generally submitted, and thus the approach regarding application-based fees might be expected to be different for a monograph user fee program compared to other user fee programs.**
- **Desirable industry activities or behavior that might be discouraged by the assessment of fees**
- **The stability and predictability of the funding provided by the user fee type**

Question: Types of Performance Goals

In conjunction with receiving user fees, FDA typically commits to certain performance goals related to FDA's activities with respect to the relevant products.

What types of performance goals might be important to consider from a public health and sponsor perspective?

What parameters could be measured to gauge the success of a user fee program?