Regulatory Process for the Review of Drugs for Rare Diseases

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Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the presenter and should not be construed to represent FDA's views or policies

Outline

- Definition of a rare disease and orphan products
- Regulatory framework for drug evaluation
- Benefit-Risk Framework
- Advisory Committee
- Pathways for approval
- Conclusion

Definition of a Rare Disease

- Section 526(a)(2)(A) of the Federal food, drug, and cosmetic act defines a rare disease, in part, as a disease or condition that “affects less than 200,000 persons in the United States".

- An **orphan drug** is a drug or biological product used for the prevention, diagnosis, or treatment of a rare disease in US

Challenges in Rare Disease Drug Development

- **Natural history** is often poorly understood
- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs**
- **Small populations** often restrict study design options
- **Phenotypic and genotypic** diversity within a disorder
- **Development programs often lack solid translational background**
- **Drug development tools** - **outcome measures** and **biomarkers** often **lacking**
- Lack of **precedent**, including **clinically meaningful endpoints**, for drug development in many rare diseases

U.S. Evidentiary Standard for Drug Approval

- Effectiveness established "substantial evidence" (FD&C Act, 1962 amendments)
  - Minimum of 2 adequate and well-controlled studies, each persuasive on its own

- Adequate & Well-Controlled Studies
  - Studies designed well enough to be able "to distinguish the effect of a drug from other influences, such as spontaneous change, placebo effect, or biased observation" (21 CFR 314.126)

- Complimentary statutory standard (FDAMA, 1997)
  - One adequate and well-controlled study and "confirmatory" evidence

- Also requires demonstration that the benefit of the drug outweighs the risk for the intended use

Confirmatory Evidence

- One adequate and well-controlled clinical study
- Plus Confirmatory Evidence (independent confirmation of benefit):
  - Clinical evidence from a related indication
  - Mechanistic or pharmacodynamic evidence
  - Evidence from a relevant animal model
  - Evidence from other members of the same pharmacological class
  - Natural history evidence
  - Real-world data/evidence
  - Evidence from expanded access use

Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence Guidance for Industry
https://www.fda.gov/media/172166/download

Benefit-Risk Framework

To be approved for marketing, FDA must determine that the drug is safe and effective

- "effective" is codified in statute:
  - Demonstrates "substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use" (21CFR 314.125, 21CFR 314.126)

- "safe" is not explicitly defined in statute or regulations
  - Because all drugs can have risks, the demonstration of safety is interpreted as a determination that drug's benefit outweighs its risks

Benefit-risk assessment is an integral part of FDA's review of a drug application

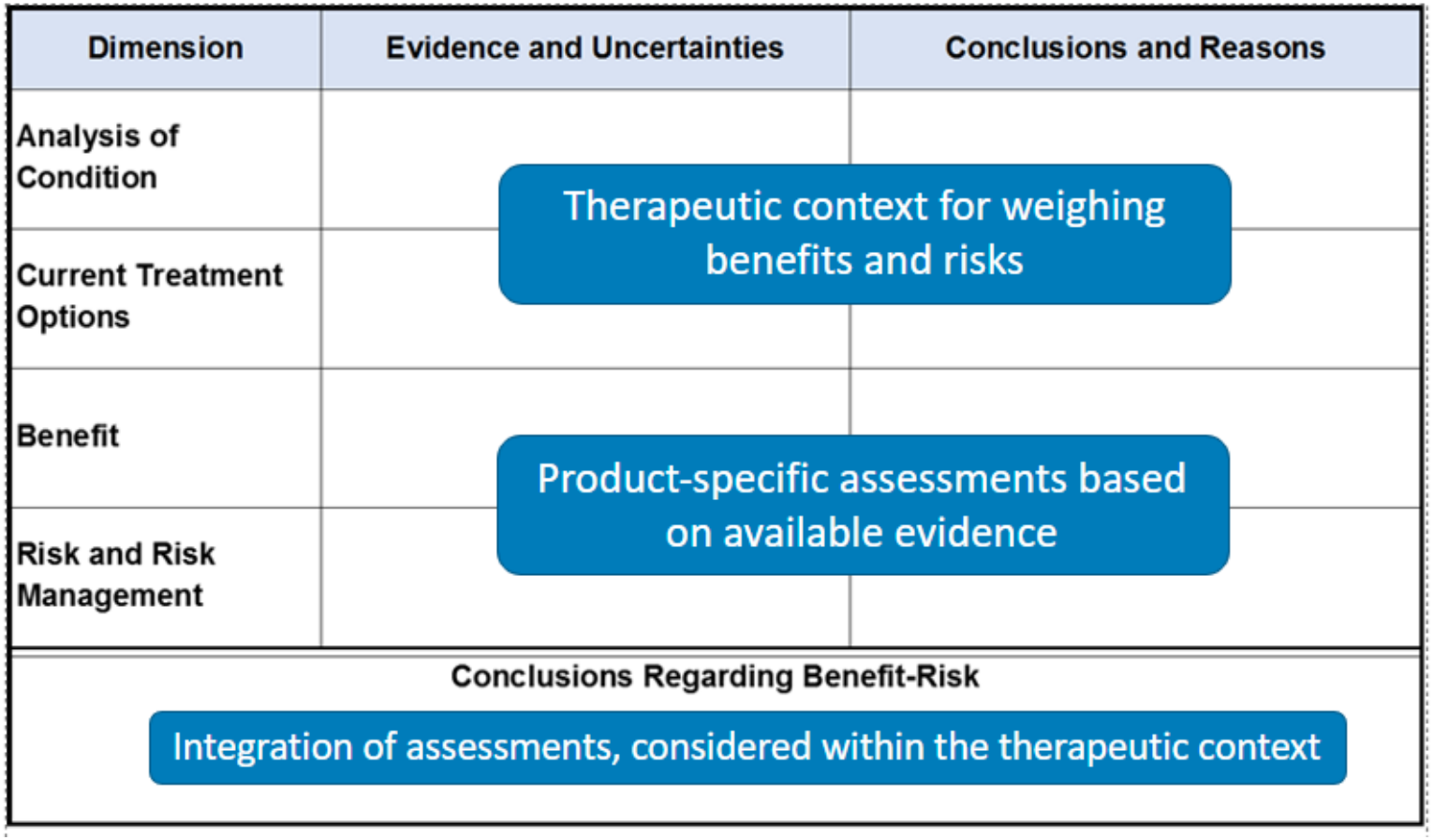
- Broadly speaking, benefit-risk assessment in FDA's drug regulatory context is making an informed judgement as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to managing risks) under the conditions of use described in the approved product labeling

Patient Input

- FDA recognizes the importance of enabling meaningful patient input to inform drug development and regulatory decision-making
- Patient experience data can inform benefit-risk assessment:
  - Therapeutic context
  - Potential benefits are meaningful
  - Acceptability of risk and uncertainty
  - Value and burden of risk minimization efforts
- FDA must balance the perspectives of patients with the judgements it must make regarding overall benefit-risk of a product for the patient population

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

Benefit-Risk Framework



Case Study: olipudase alfa-rpcp

- approved in 2022 for treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients

- ASMD: autosomal recessive lysosomal disease that results in deficient activity of acid sphingomyelinase (ASM), an enzyme that metabolizes sphingomyelin into ceramide and phosphocholine.
  - Type A: most severe form with profound CNS involvement, hepatosplenomegaly, interstitial lung disease (ILD) and rarely survive beyond two to three years of age
  - Type B: no CNS involvement, hepatosplenomegaly, ILD, survive to adulthood
  - Type A/B: intermediate form with some CNS symptoms, hepatosplenomegaly, ILD

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disease that results in deficient activity of acid sphingomyelinase (ASM), an enzyme that metabolizes sphingomyelin into ceramide and phosphocholine. ASMD encompasses Neiman-Pick type A, type B, and type A/B. • ASM deficiency leads to the accumulation of sphingomyelin affecting organ systems such as the central nervous system (CNS), liver, spleen, lymph nodes, adrenal cortex, lung airways, and bone marrow. • Patients with ASMD type A have the most severe form of the disease, exhibit hepatosplenomegaly, pathologic alterations in the lungs in infancy, and profound CNS involvement, and rarely survive beyond two to three years of age. • Patients with ASMD type B have less severe disease, but also have hepatosplenomegaly and pathologic alterations of their lungs, however, there is no CNS involvement. Most patients can survive into adulthood. • Patients with ASMD type A/B have symptoms that are intermediate between type A and type B. The disease presentation and progression rate vary greatly in type A/B patients, but all are characterized by the presence of some CNS manifestations • Patients have noted that organ enlargement can cause pain, vomiting, feeding difficulties and falls. (Section 4) • The estimated incidence is 0.4 to 0.6 per 100,000 births.	• ASMD is a rare and serious disease manifested by deterioration in liver function, splenomegaly, and interstitial lung disease caused by storage of sphingomyelin in pulmonary macrophages that results in frequent respiratory infections and eventual respiratory failure.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no approved therapies for the treatment of ASMD; the mainstay of therapy is supportive care. • Hematopoietic stem cell transplantation has been evaluated with variable results.	• There is an unmet need for the treatment of ASMD as there are no approved therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	an open-label single arm trial DFI13803 (ASCEND-Peds). Subjects received 64 weeks of olipudase alfa (dose escalation to the target dose of 3 mg/kg). • The mean percentage reduction in spleen and liver volumes from baseline to Week 52 was 46.7% and 37.3% (n=8 for both), respectively. The mean percentage increase in % predicted DL_{CO} from baseline to Week 52 was 50.6% (n=3) • Only one patient less than 2 years of age was enrolled in the pediatric trial. • No patients with ASMD type A were enrolled in the clinical trials	• The key drivers of disease burden in ASMD are expected to be similar across age groups. Mechanistically, olipudase alfa would be expected to have a similar effect in patients regardless of the age group. Therefore, the clinical response of olipudase alfa in patients <2 years of age would be expected to be similar to those >2 years of age. • While the neurological manifestations differ among ASMD type A, B, and A/B, similar somatic manifestations are observed in all these disease phenotypes. Due to the mechanism of action of olipudase alfa, similar improvements in lung function and liver volume are expected across phenotypes. This therapy is expected to provide non-CNSclinical benefit to patients with ASMD type A as no other treatment currently is available in this devastating disease.

Risk and Risk Management	• Safety was assessed in a total of 38 treatment naïve subjects with ASMD type B or type A/B. This included 30 adult subjects with a median (range) olipudase alfa exposure of 3.0 (1.4 – 4.7) years and 8 pediatric subjects with a median expousure of 2.7 (2.5 – 3.1) years. • Treatment emergent serious adverse events (SAEs) were reported in 33.3% (10/30) adult subjects and in 50% (4/8) pediatric subjects. Treatment related SAEs included anaphylactic reaction; these SAEs were reported in pediatric subjects. • The most common adverse events (AEs) occuring in ≥10% adults that were considered related to olipudase alfa included headache, cough, diarrhea, hypotension, and ocular hyperemia. Common AEs occuring in ≥25% of pediatric subjects included pyrexia, cough, diarrhea, rhinitis, vomiting, abdominal pain, headache, urticaria, nausea rash, arthralgia, pruritus, fatigue, and pharyngitis. • Mild to moderate treatment related hypersensitivity AEs were reported in 33% (10/30) of adult and in 50% (4/8) of pediatric subjects. Hypersensitivity reactions occurred in adults were pruritus, urticaria, erythema, rash, rash erythematous, eczema, angioedema, and erythema	• The safety database was adequate for the safety assessment of olipudase for the proposed indication, patient population, dosage regimen, and duration. • Safety risks of hypersensitivity, including anaphylaxis and infusion-associated reactions, are known risks to enzyme replacement therapies (ERT). These risks can be addressed through labeling with a boxed warning specifically for hypersensitivity including anaphylaxis. • As the IARs were considered mild to moderate with no discontinuations, they can be addressed within warnings and precautions and does not require a boxed warning. • The dose-escalation regimen provides a gradual debulking of sphingomyelin and gradual release of ceramide decreasing the inflammatory response. • However, there are minimal safety data in patients with Type A ASMD and those under the age of 2, therefore a PMR is advised to further evaluate safety in those patients. • Due to the elevation of ceramide seen during the dose escalation phase, the labeling will advise that dosage initiation or escalation, at anytime during pregancy, should not occur as it may lead to elevated metabolite levels that

Drugs@FDA

- Drugs@FDA: FDA-Approved Drugs

- Listing of products approved for human use in the United States
  - Prescribing information
  - FDA staff reviews that evaluated the safety and effectiveness of the product

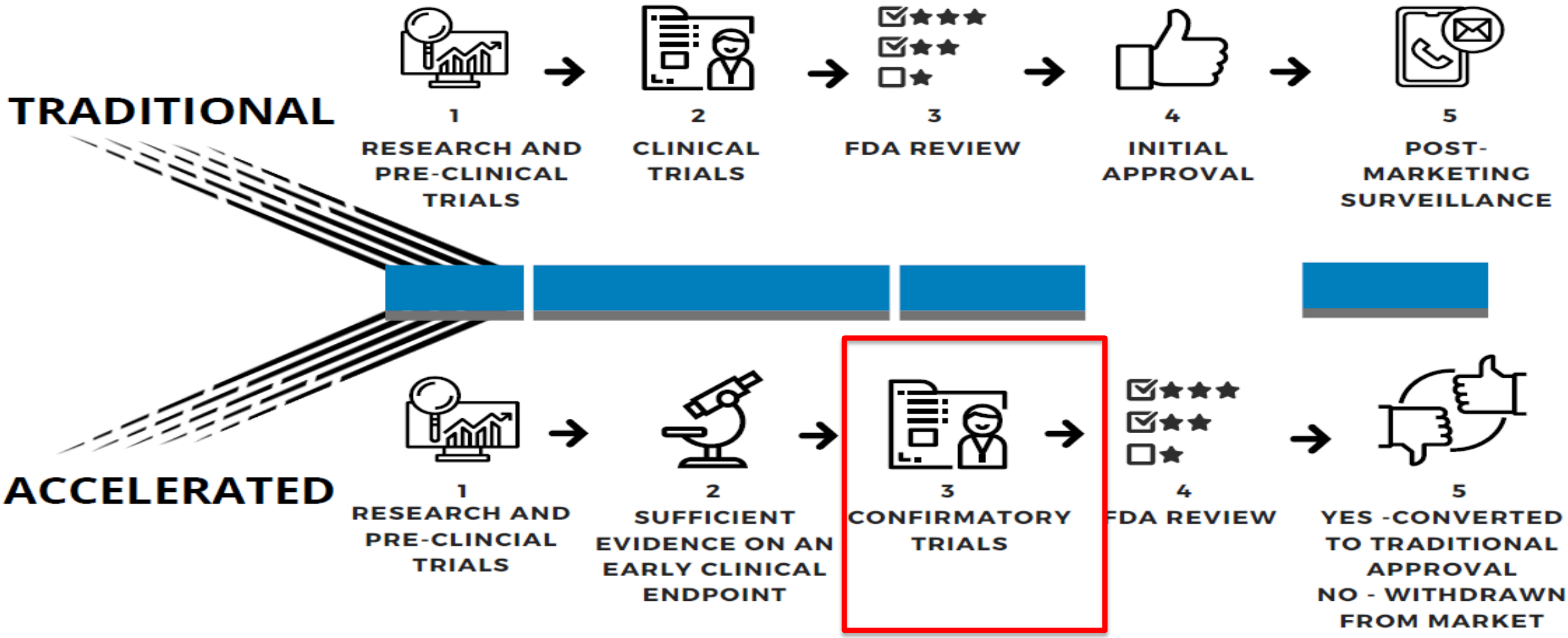
Advisory Committees

- Allow the FDA to receive input from subject matter experts, patients, academia, and other external stakeholders when evaluating the potential benefits and risks of a new therapy
- Evaluate and discuss summary information from a marketing application under review and the FDA's and analyses
- Provide an independent opinion and recommendations
- Allow for a public hearing regarding the product under discussion

Genetics Metabolic Diseases Advisory Committee (GeMDAC)

- **Purpose:** provide a forum for discussion of experts knowledgeable in the fields of medical genetics, inborn errors of metabolism, small population trial design, translational science, pediatrics, epidemiology, statistics and related specialties
- **Core membership:** nine voting members (permanent and temporary), including the committee chairperson
- Individuals nominated as scientific members must be technically qualified experts in their relevant fields and have experience interpreting complex data
- Genetic Metabolic Diseases Advisory Committee | FDA

Approval Pathways for Drugs and Biologics



Approval Pathways

- Traditional Approval

1. Endpoint measures survival or how a person feels/functions or the effect on a validated endpoint that is known to predict clinical benefit
2. No postmarketing studies to confirm efficacy are required

- Accelerated Approval

1. Endpoint measures a marker that is reasonably likely to predict clinical benefit (usually a biomarker)
2. Requires a postmarketing confirmatory trial to confirm clinical benefit

Accelerated Approval Definition

- . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on:
  - a surrogate endpoint that is reasonably likely to predict clinical benefit, or
  - on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit,
- taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

Section 506 (c) of the Food Drug and Cosmetic Act (21 U.S.C. 356(c))

Accelerated Approval Requirements

- Serious Condition
- Meaningful Advantage over Available Therapy
- Demonstrates an effect on an endpoint that is reasonably likely to predict clinical benefit
  - Surrogate endpoint (not a measure of clinical benefit itself)
  - Intermediate clinical endpoint
- Post Approval Confirmatory Trial
  - Verify clinical benefit
  - Evaluates a clinical endpoint that directly measures clinical benefit

Examples of Approval Pathways for Different Products

Traditional Approval

- Velmanase alfa-tycv (Lamzede) - enzyme replacement therapy approved for the treatment of non-central nervous system manifestations in adult and pediatric patients

- Efficacy assessed 3-minute stair climbing test, 6-minute walking test and forced vital capacity

Accelerated Approval

- Migalastat (Galafold) – pharmacological chaperone approved for the treatment of adults with Fabry disease and amenable galactosidase alpha gene variants based on in vitro assay data
- Efficacy based on reduction of GL-3 substrate in the kidney interstitial capillaries
- Post approval trial to confirm clinical benefit pending

Conclusions

- Approval Considerations for Drugs/Biologics:
  - Substantial evidence of effectiveness
  - Demonstration that benefit outweighs risk
  - Scientific opinion of the advisory committee if applicable

- Different approval pathways but same statutory standards for safety and effectiveness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