Rare Disease and Clinical Trials

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Outline

- Background
- Flexibility
  - Case examples
- General IND considerations
- Expanded Access
- Key points
- Additional Resources

Rare Diseases

- Rare disease aka "Orphan" disease defined as:

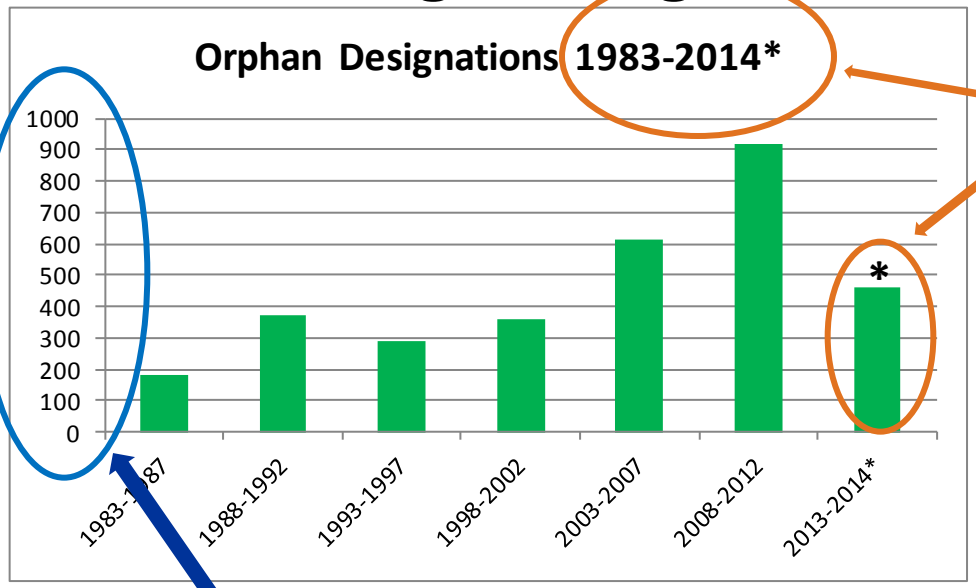
  "A disease or condition affecting less than 200,000 persons in the United States"[1]

  - In reality though, most rare diseases are far less prevalent than this
  - Large public health concern
    - ~7,000 different diseases
    - affect ~25 million Americans
- Orphan Drug Act
  - Mainly provides incentives intended to make the development of drugs to treat small populations financially viable
  - Does not provide for separate regulatory standards for Orphan drugs
  - Intention: Patients with rare diseases are as entitled to safe and effective medications as those with common diseases

[1]Orphan Drug Act Pub L 97-414, as amended 1984

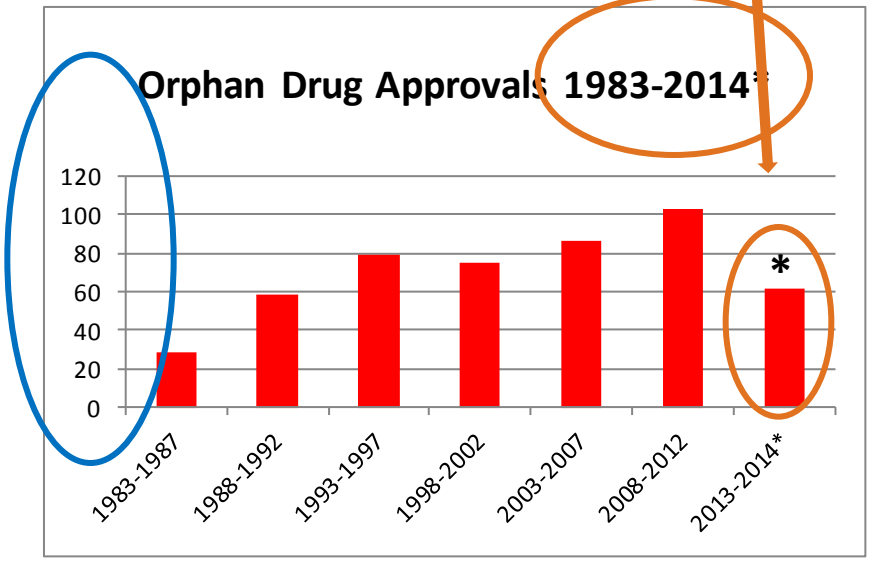
Rare Diseases (R)Evolution

- Fastest growing area of drug development[2]



Please note: 2013-2014 <2-year increment, as of Sept 25, 2014

Please note: different scales

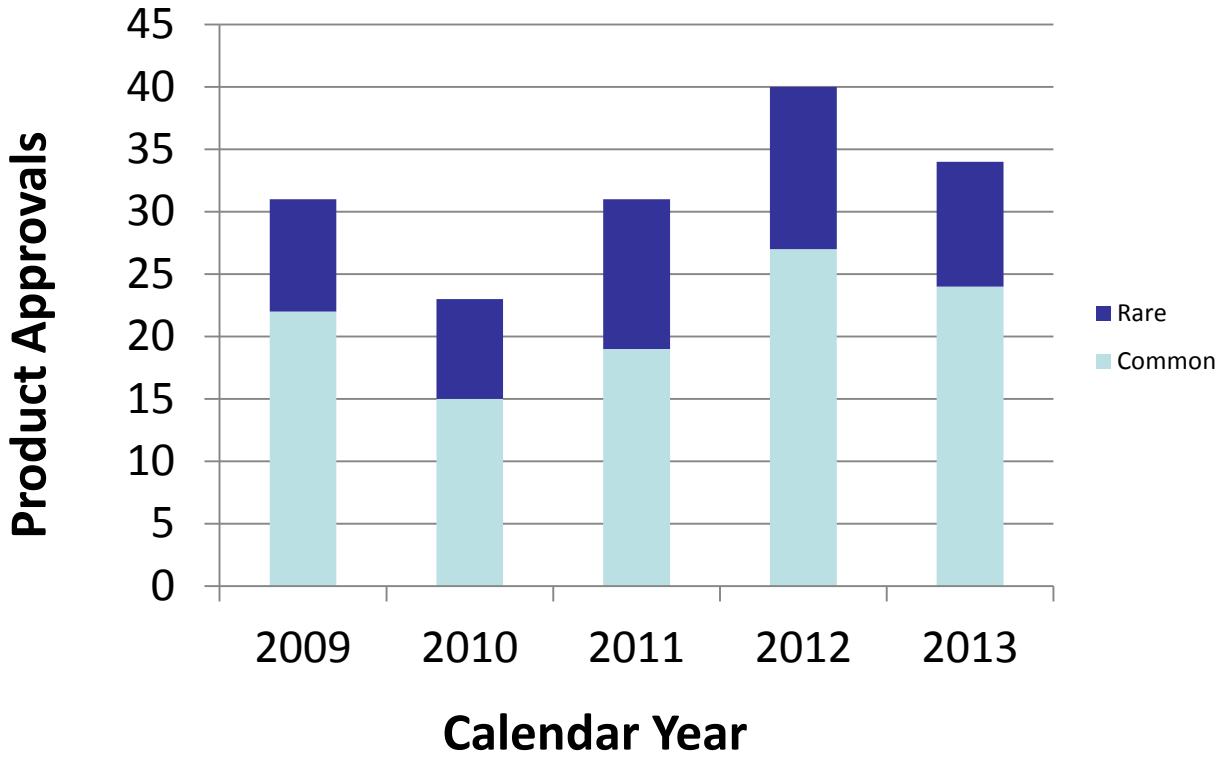


[2]Source FDA Office of Orphan Products Development, Search Orphan Drug Designations and Approvals, available at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/

Rare Diseases and New Drugs

- ~1/3 of new drugs at CDER each year are for rare diseases

Table 2: CDER New Molecular Entities/Original Biologic Approvals 2009-2013[3]



[3]Source, Drugs@fda

Rare Diseases: What is different

- Small populations, limited opportunity for study and replication in clinical trials
  - Few treating physicians, few treatment centers
- Highly heterogeneous collection of diseases
  - Within and between diseases
  - E.g., genetic disorders often characterized by wide range of severity, clinical presentation and rate of progression
- Diseases are poorly understood
  - Natural histories incompletely described
  - Diagnosis difficult
    - Often years between presentation and diagnosis
- Most are serious or life-threatening, most have unmet medical needs
  - Lack regulatory/drug development precedent
- Endpoints, outcome assessment tools often lacking
- Many affect pediatric patients
  - Additional ethical considerations and constraints

Rare Diseases: What is the same

- Best access for patients to an efficacious treatment is an approved drug
- Statutory standards for approval apply to all drugs – rare and common
  - Requires establishing a drug's effectiveness by "substantial evidence"[4]
- Substantial evidence defined as evidence from adequate and well-controlled (A&WC) trials:

  "on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use"[4]
  - Generally, 2 A&WC trials (affirm and confirm)

[4]PHS Act 505(d)

Adequate and Well-controlled Trials

- A&WC = Trial has been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"[5]
  - RCTs are the gold standard
  - Control can be concurrent or historical
    - Purpose of any control is to measure what *might* have happened without the intervention

[5]Code of Federal Regulations, title 21, section 314.126, Adequate and well-controlled studies

Flexibility

- Statute allows for flexibility and exercise of scientific judgment in kinds and quantity of data required for a particular drug for an indication[6]

[6]21CFR §314.105 Approval of an application and an abbreviated application

Flexibility: Rare vs. Common Diseases

Table 2. CDER NME/NBE Approvals 2009-2013, Level of Evidence[7]

	All	Rare	Common
Approvals	159	52	107
≥2 A&WC Trials	92 (58)	17 (33)	75 (70)
1 A&WC Trial + Supporting Evidence	61 (38)	31 (60)	30 (28)
Other	6 (4)	4 (8)	2 (2)

NME = new molecular entity; NBE = original biologic (new biologic)
A&WC = adequate and well-controlled
159 approvals = 143 drugs for 159 drugs + indication (at time of initial approval, 3 drugs approved for 3 indications each, 10 drugs from 2 indications each)

[7]Source, Drugs@fda

[8]Additional reference: Sasinowski F. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Drug Inf J. 2012;46:238-263.

Flexibility - Approaches

- For example, a single study + supporting evidence, e.g.
  - multiple event measures, pharmacologic/pathophysiologic endpoints,
  - statistically persuasive findings
  - Extrapolation from existing studies
    - Commonly used in pediatrics (e.g., HIV drugs)
    - Bioequivalence
    - Different dosage forms or routes of administration
  - Studies in qualitatively similar populations, other phases of disease or closely related diseases
    - E.g., Commonly used in cancer: one study in refractory population, one to support earlier stage
- Described in Guidance:
  - Providing Clinical Evidence of Effectiveness in Human Drug and Biological Products[9]

[9]Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008

Example #1: Elosulfase (Vimizim)

- Elosulfase (Vimizim)[10]
  - Enzyme replacement therapy (ERT) for the treatment of Morquio Syndrome Type A (Mucopolysaccharidosis (MPS) IVA)
- MPS IVA
  - Rare autosomal recessive enzyme deficiency disorder (lysosomal storage disease (LSD)) results in accumulation of glycosaminoglycans (GAGs) throughout the body
  - Most commonly manifests in early childhood (~18 months of age) with growth deficiency, skeletal and joint development abnormalities, heart problems
    - Wide disease spectrum, attenuated forms may present as late as early adulthood
  - High morbidity, life-limiting, life expectancy 20s-30s years (attenuated forms may be to ~60s)
  - ~500-800 patients in the US (1 in 1-2 million live births)
  - Related disorders: MPS 1-VII

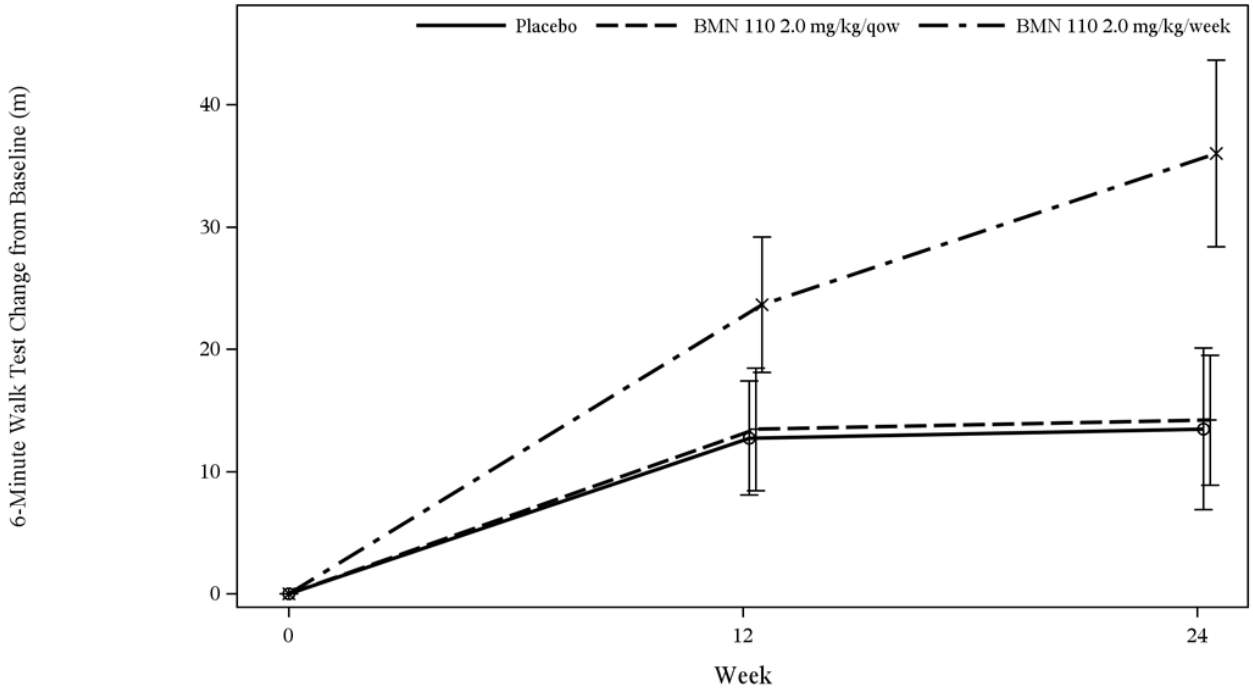
[10]Source, Drugs@fda

Elosulfase Clinical Development

- Elosulfase first AP'd treatment for Morquio
  - 4th ERT approved for an MPS
    - MPS I (Hurler, Hurler-Scheie, Scheie syndromes) laronidase (Aldurazyme) AP'd 2003)
    - MPS VI (Maroteaux-Lamy syndrome) galsufase (Naglazyme) AP'd 2005
    - MPS II (Hunter syndrome) idursulfase (Elaprase) AP'd 2006
- Clinical Program
  - Pivotal trial: 1 A&WC trial: R DB PC trial X 24 weeks, n=176 patients with MPS IVA, ages 5-57 years, randomized 1:1:1 elosulfase qWeek, qoW or PBO
    - Followed by open-label extension where all patients received elosulfase, n=173
  - Primary endpoint: 6MWT
  - Other endpoints: 3- minute stair climb, urinary GAG levels
  - Entire program= 6 clinical trials
    - 1 Phase 3, 1 Phase 1/2 (n=20)
    - 2 on-going extension trial
    - 2 ancillary Phase 2 trials (n~35)

Elosulfase Results

Treatment difference btw Elo qWeek and PBO at Week 24
--22.5 m (p = 0.0174)[11]
Largest effect in patients who walked ≤ 200 m at baseline



[11]Source: Johnson T, Clinical Review. BLA 125460, elosulfase alfa, available at "Drugs@FDA"

Elosulfase: Key Points

- Disease reasonably well understood and characterized
  - Natural history data
  - Biochemical, pathophysiology described
  - Serious, life-threatening disorder with unmet medical needs
- Close and frequent communication with FDA review division during drug development
- Existing regulatory history from other MPS ERTs (and other LSDs)
  - Relied upon functional endpoints of six- or twelve minute walk tests (6MWT, 12MWT), stair climbs or pulmonary testing PFTs
  - Each relied upon 1 A&WC trial with supporting evidence, small pre-market populations
- Continued evaluation post-approval in a long-term registry
- Use of incentive and expedited programs
  - Orphan drug designation and exclusivity
  - Pediatric Rare Disease Priority Review Voucher
  - Fast Track, Priority Review

Example #2: Glucarpidase[12]

- Indication: Treatment of toxic plasma methotrexate concentrations due to impaired renal function
- Full approval 2012
  - Pharmacodynamic endpoint
    - Proportion of subjects with elevated MTX level who achieved rapid and sustained clinically important reduction (RSCIR) in MTX level $\leq$1 µmol/l

[12]Source, Drugs@fda

Glucarpidase (2)

- Evidence of effectiveness
  - Analysis of subset of patients (n=22) in an NCI-sponsored study who had evaluable MTX levels post-glucarpidase administration
  - NCI trial: prospective, OL, historically-controlled, non-randomized single-arm compassionate use trial in 184 patients with high-dose MTX-induced nephrotoxicity and delayed MTX excretion.
  - "not feasible to prospectively study glucarpidase in a randomized placebo controlled trial for this indication…emergency situation that occurs unpredictably"[13]
  - 10/22 patients (45%) met criteria for RSCIR
  - All 22 patients >95% reduction in MTX for up to 8 days

[13]Dinndorf P, M.D., Clinical Review BLA 125327, available at Drugs@FDA

Glucarpidase (3)

- Historical Information
  - MTX available since 1948
  - Used for higher-dose (e.g., leukemias, sarcomas) as well as lower-dose (e.g., RA) indications
  - Large and long-term clinical experience
    - Effects, mechanism of action, toxicity, excretion and metabolism well understood
    - Adverse effects of toxic MTX levels well understood
      - E.g., MTX excretion curve and correlation with increased risks of toxicity and MTX C_{max} and AUC, and repeated confirmation
- "Given the extensive data… the (MTX) excretion curves are well-characterized and can be used as an historical control against which the results of this trial can be assessed for efficacy and is sufficient to provide a clear assessment of the treatment effect"[14]

[14]Keegan P, M.D., Summary Review BLA 125327, available at Drugs@FDA

Glucarpidase Key Points

- Open-label single-arm historically controlled study design supported by body of existing, good quality information
  - Condition well-understood and well-characterized
  - Used all available information in study design and assessment of results
  - Well-characterized endpoint
  - Results self-evidence and persuasive
- Close communication during drug development
- Use of incentive and expedited programs
  - Orphan drug, priority review, Fast Track

A Few Words on IND Studies

- Study designs expected to vary widely depending on many factors
  - E.g., novelty of drug, previous experience, developmental phase, etc.
- Initial IND, generally will contain, at minimum[15]
  - Animal pharmacology and toxicology studies
  - Manufacturing information
  - Clinical protocols and investigator information adequate for phase of investigation
- Please note, same ethical and safety standards apply to rare and common disease drug IND applications

[15]21CFR 312.23 IND Content and Format

IND Studies: General Approach

- As with all IND trials, medical research in rare diseases must conform to generally accepted scientific principles
  - i.e., Good Clinical Practice[16]
- Generally states:
  - Results must be credible and accurate
  - Rights, safety and well-being of subjects protected
  - Based on through understanding of scientific information from all relevant sources
  - Design and conduct of each study must be clearly described in the submission
    - E.g., detailed protocol
  - Before trial is initiated, a careful assessment of foreseeable risks to subjects should be weighed against anticipated benefits for subjects
  - And more…

[16]Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance. Available at: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf.

IND Studies: General Approach (2)

- Careful planning even more important for rare diseases than common diseases.
- General plan:
  1. Understand the disease (e.g., disease natural history)
  2. Understand the target/intervention and expected outcomes
     -- Assays, tests, biomarkers
  3. Develop clinical outcome assessment tools
     -- Can pilot in, for example, natural history trials
  4. Plan/conduct IND-enabling studies in a timely manner (e.g., animal toxicology)
  5. Use all available information (e.g., related diseases, prior studies)
  6. Use 1→5 to define efficacy and safety (i.e., design and conduct pivotal trial(s))
  7. Feedback loops: additional study in post-marketing period, e.g., registries

IND Studies: Common Concerns

- Clinical plan should be supported by information in the IND submission.
- Clinical Hold issues:
  - Early/Pre-IND Phase
    - Usually safety related
    - Hold criteria – two most common[17]
      - Subjects would be exposed to an unreasonable and significant risk of illness or injury
      - Insufficient information to assess risks to subjects
  - Later phase - hold criteria
    - Safety concerns (as above), and
    - Plan/protocol for the investigation is clearly deficient in design to meet its stated objectives

[17]§312.42 Clinical holds and requests for modification

A Few Words on Expanded Access (EA)[18]

- Aka "compassionate use"
  - Purpose:
    - Provide access to investigational drugs outside of a clinical trial
    - Patients with serious or life-threatening conditions
    - No comparable or satisfactory alternative treatment options
    - Enables these patients to access products that are still in development for treatment purposes
  - Includes
    - Emergency INDs (E-IND)
    - Single-patient investigational new drug applications (IND)
    - Small or medium-sized group INDs
    - Treatment INDs

[18]Guidance for Industry, Expanded access to investigational drugs for treatment use -- Qs & As

Expanded Access (2)[19]

- Intended to provide access to investigational drugs to patients with serious or life-threatening conditions with no satisfactory alternatives
  - EA INDs ***NOT*** likely to describe effectiveness
  - EA INDs ***NOT*** likely to provide evidence for marketing applications
- EA use **cannot "interfere with** the initiation, conduct or completion of clinical investigations that could support marketing approval… or otherwise compromise the potential development" of the product
- ***Manufacturer must be willing to supply the drug***
  - Contact the manufacturer prior to contacting FDA
  - FDA ***cannot*** compel the manufacturer to supply the drug

[19]Physician request for an individual patients IND under Expanded Access for Non-emergency or emergency use, available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm

Key Point #1

- Best access for patients to effective, safe, quality products is through approved drugs
  - Investigational agents do not yet have safety and effectiveness described
  - Demonstrate evidence through well-designed appropriate clinical trials
  - Ideally, clinical investigations proceed in a stepwise manner toward defining benefit-risk

Key Point #2

- For rare diseases (and many serious or life-threatening conditions)
  - Opportunity for study and replication will be limited
  - "Getting it right" from the start is critical
  - Careful planning, frequent and quality communication (especially early communication) between FDA and drug developer is strongly recommended
    - Take advantage of all opportunities for formal meetings[20]
      - come in early, come in often

→ and bring your data

[20]Guidance for Industry, Formal meetings between the FDA and sponsors or applicants. Available at: http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf.

Key Point #3

- IND-enabling and foundational science (e.g., translational research, disease natural history)
  - Critical to designing, initiating and conducting successful clinical trials
  - Proposed clinical plan needs to be supported by information in the IND submission

Key Point #4 – Incentives

- Orphan Drug Act
  - Provides incentives intended to make the development of drugs to treat small populations financially viable
    - Waiver of PDUFA fees (~$2 million)
  - Does not define standard for approval; does not define lower or different standards for development nor approval for orphan drugs
  - Orphan drug designation
    - Separate process and considerations from IND/NDA submissions
    - Need to specifically apply for Orphan Designation prior to NDA filing
- For more information, please contact the Office of Orphan Products Development

http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

Additional Resources

- FDA CDER Office of New Drugs, Rare Diseases Program

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm221248.htm

- Expedited Programs for Serious Diseases

  - Fast track, Breakthrough, Priority Review designations and Accelerated Approval pathway

  - Guidance available at:

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