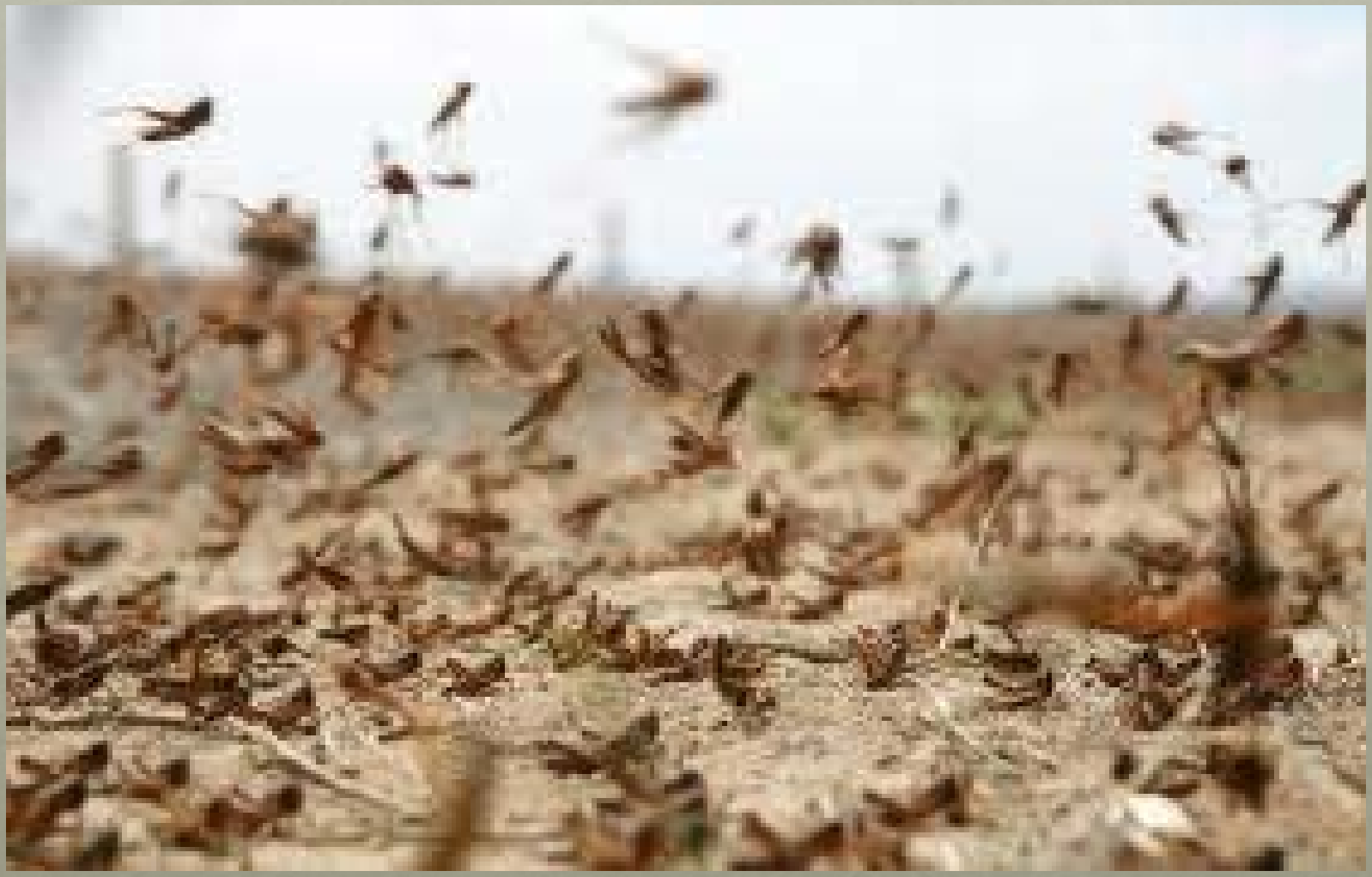
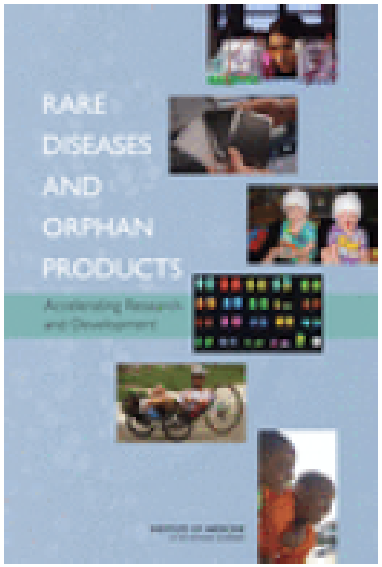
FDA Policies and Procedures Relevant to Individuals with Rare Heritable Disorders



IOM REPORT



Rare Diseases and Orphan Products: Accelerating Research and Development

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ACCELERATE RESEARCH

- Active involvement and collaboration by a wide range of public and private interests, including government agencies, commercial companies, academic institutions and investigators, and advocacy groups
- Timely application of advances in science and technology that can make rare diseases research and product development faster, easier, and less expensive
- Creative strategies for sharing research resources and infrastructure to make good and efficient use of scarce funding, expertise, data, biological specimens, and participation in research by people with rare diseases
- Appropriate use and further development of trial design and analytic methods tailored to the special challenges of conducting research on small populations
- Reasonable rewards and incentives for private-sector innovation and prudent use of public resources for product development when the latter appears a faster or less costly way to respond to important unmet needs
- Adequate organizations and resources, including staff with expertise on rare diseases research and product development, for the public agencies that fund biomedical research and regulate drugs and medical devices
- Mechanisms for weighing priorities for rare diseases research and product development, establishing collaborative as well as organization-specific goals, and assessing progress toward these goals

FDA ISSUES ADDRESSED

- Insufficient resources for timely meetings and guidance for sponsors
- Inconsistency in reviews of applications for orphan drug approvals across CDER divisions
- Inadequate resources for the orphan products grants program

SPONSOR ISSUES

- Delayed toxicology studies
- Inadequate characterization of chemical compounds
- Lack of natural history studies to characterize the disease process
- Poor use of early phase studies (e.g., safety, dosing) to guide the design of phase III studies
- Inadequate trial design with lack of
  - Formal protocol
  - Well-defined question
  - Adequate controls
  - Validated biomarkers
  - Appropriate surrogate measures
- Lack of advance communication with FDA about the adequacy of clinical trial plans

RECOMMENDATIONS

- Assessment of staff reviews of applications for the approval of orphan drugs
- Evaluate the extent to which studies submitted in support of orphan drugs are consistent with advances in the science of small clinical trials
- Ensure that NIH-funded product development studies involving rare diseases are designed to fulfill requirements for FDA approval
- FDA should expand its Critical Path Initiative to define criteria for the evaluation of surrogate endpoints for use in trials of products for rare conditions
- FDA and NIH should collaborate on an assessment of unmet device needs and priorities relevant to rare diseases
- FDA should take steps to reduce the burdens on potential sponsors of Humanitarian Use Devices

THREE ISSUES

- Compassionate use protocols
- Alternative (emergency) supplies for single source medications
- Process for approval for new technologies for diagnosing rare diseases

COMPASSIONATE USE

- Confusion abounds
- Asked not to include specific examples
  - Risk/benefit in rare diseases is inherently different
  - Regulation to death
- Frequent questions
  - What are advantages and disadvantages to use of compassionate use protocol?
  - Does this differ from “emergency approval”?
  - What constitutes appropriate toxicity data?
  - When a company has agreed to supply compound, what else might interfere with approval?

EMERGENCY SUPPLIES

- Many medications used for treatment of IEMs are single source in US
  - Foreign source sometimes available
  - Non-medicinal grade source
  - Not necessarily complicated biomolecules
- Emergency needs cannot be anticipated for every rare disease treatment
- When the need arises, what is the process for urgent approval of alternative source medications?

NEW DEVICE APPROVAL

- Diagnostic kits are devices
- What are the regulations for use of existing kits for new purposes?
- Do single lab reagents/tests require approval?
- Process for approval for rare disease oriented applications

RARE DISEASE CHALLENGES

- Uniform recognition of ability to use discretion when applying regulations to rare diseases
- Considering the risk benefit ratio when the inevitable outcome is poor
- How to protect investigators and patients without making treatment impossible