Balancing Evidence and Speed in COVID-19 Therapeutics and Vaccines

Aaron S. Kesselheim, M.D., J.D., M.P.H.
Professor, Harvard Medical School
Director, Program On Regulation, Therapeutics, And Law (PORTAL)
September 23, 2020
akesselheim@bwh.harvard.edu
FDA oversight of drugs and vaccines

• Statutory standards for drug/vaccine approval
  – Substantial evidence of efficacy from adequate and well-controlled trials
  – Adequate tests by all methods reasonably applicable to show whether or not a drug safe for use

• FDA scientists review data, determine whether benefits appear to outweigh risks

• Why?
  – Protect consumers
  – Advance knowledge
  – Promote well-functioning markets/useful innovation
Important principles

• No minimum efficacy thresholds (other than zero)
• Efficacy can be demonstrated based on changes to surrogate measures or actual clinical endpoints (how a patient feels, functions, or survives)
• Efficacy as measured in clinical trials may not predict effectiveness in routine care, owing to differences in real-world patient characteristics
• Not all adverse reactions can be detected during pre-approval clinical trials, even if the trials are large
  – Phase 4 studies, spontaneous adverse event reports, Sentinel/PRISM systems for prospective monitoring
COVID19 Vaccine Trial Guidance

• Either laboratory-confirmed COVID19 disease or laboratory-confirmed infection is acceptable primary endpoint
  – If use infection, prefer + at least 1 symptom
• Expect approved vaccine would reduce the occurrence or severity of disease in at least 50% of recipients, a standard similar to that for annual influenza vaccines
  – 95% confidence that it is effective in at least 30% of the recipients
  – 2007 FDA guidance: vaccine for pandemic influenza should be supported by evidence showing that the lower bound of the 95% CI of the percent of subjects achieving seroconversion was at least 40%
• Safety considerations
  – Solicited adverse events within 7 days
  – Unsolicited adverse events within 21-28 days
  – Monitor serious events for at least 6 months
  – Expect at least 3,000 patients to get vaccine
Shortcuts Relevant to COVID19

1. Accelerated approval
   - Endpoint: surrogate measure “reasonably related” to actual clinical endpoint
   - Post-approval confirmatory study required

COVID19 guidance: allow “accelerated approval” of a vaccine based only on antibody levels or another biochemical marker rather than actual clinical outcomes. This could occur if “additional understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might be reasonably likely to predict protection against COVID-19, is acquired”
AA confirmatory studies

• 22 drugs (24 indications) marketed via AA pathway 2009-2013
  – 38 post-approval studies required
• By April 2017 (minimum 3 yrs of follow-up), 20 complete and 18 published
  – 10 randomized, 8 single-arm
  – 17 surrogate measures as endpoints
    • Disease response (n=9, 50%), progression-free survival (n=6, 33%), pharmacokinetic measures (n=2, 11%)
  – 15 were positive
Shortcuts Relevant to COVID19

• 1. Accelerated approval

• 2. Expanded access
  – Authorize use of investigational product outside clinical trials
    • Criteria: potential benefit justified the risks AND treating physician determined that probable risk from drug not greater than risk from disease (individual pts) or at least preliminary clinical evidence of effectiveness (larger patient populations)
  – “Right to Try” (2018)
Convalescent Plasma

• National Expanded Access Treatment Protocol run by Mayo Clinic
  – Est 4/20, enrolled >90,000 by 8/13/20
  – Primary goal: provide access in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
Remdesivir

• Expanded access program managed by Gilead
  – Access to >1000 patients before March 2020
  – Switch to group expanded access at 46 sites in US, FR, IT, SP, SW, UK
    • Exceptions for pregnant women and children under 18
• 4/20 (NEJM): Case series of 61 pts with severe Covid19
  – 36 (68%) of 53 patients improved
    • 56% of intubated patients did well
  – 23% of patients had serious adverse events
• What conclude?
  – Unclear how many patients in original denominator
  – Administered median 12 days after symptom onset
  – 8 patients excluded from analysis

Shortcuts Relevant to COVID19

• 1. Accelerated approval
  – Endpoint: surrogate measure “reasonably related” to actual clinical endpoint (feels/functions/survives)
  – Post-approval confirmatory study required

• 2. Expanded access
  – Authorize use of investigational product outside clinical trials
  – “Right to Try” (2018)

• 3. Emergency Use Authorization
Emergency Use Authorization (EUA)

• Project Bioshield Act of 2004: FDCA §564
  – Secretary of HHS power to authorize emergency use of drugs, devices, and biological products that (a) have not yet been approved, cleared, or licensed by FDA or (b) that have been approved, cleared, or licensed for certain uses but not others
  – FDA can then permit public health authorities, health care providers, and others to distribute and administer products needed to respond to emergency, potentially on a mass scale

• “Medical countermeasures” against CBRN threats
  – Drugs
  – Biologic products (blood plasma, vaccines)
  – Devices (PPE, in vitro diagnostics)

• NOT an approval – cannot claim that product is now FDA-approved for the condition
Criteria for issuing EUA

1. The specified agent can cause a **serious or life-threatening disease or condition**;

2. Based on the **totality of available scientific evidence**, it is reasonable to believe that (a) the product **may be effective** in diagnosing, treating, or preventing the disease or condition, or a serious or life-threatening disease or condition caused by an EUA product or an approved, cleared, or licensed product for diagnosing, treating, or preventing the disease or condition, and (b) the **known and potential benefits of the product outweigh the known and potential risks**; and

3. There is **no adequate, approved, available alternative** to the product for diagnosing, preventing, or treating the disease or condition
First Drug EUA

• Mar 28: Chloroquine and Hydroxychloroquine
  – Already approved for RA, lupus, malaria
• “Limited in-vitro and anecdotal clinical data in case series” = small trial conducted in France available online Mar 20
  – Non-randomized
    • many controls refused treatment
    • Intervention group was from large center in Marseilles while control group was from other centers
    • limited data, big differences on baseline characteristics (no adjustment)
    • Not significant if comparison between azithro group and Hcq/azithro
  – Primary endpoint of unclear relevance: virus clearance at day 6 (clinical endpoints and side effects not reported)
  – Differential loss to follow up: 26 pts in intervention group (6 lost: 3 to ICU, 1 died); 16 controls (none)

• Withdrawn 6 wks later

Rome & Avorn, NEJM, 2020
Second Drug EUA

• May 1: Remdesivir
• 3 studies reviewed and determined that known and potential benefits outweigh known and potential risks and that may be effective for hospitalized patients with COVID-19
• Double-blinded, placebo-controlled NIAID trial
  – 1063 patients randomized
    • Median recovery time 11 vs 15 days for placebo (P<0.001)
    • Non-sig change in HR for death: 0.70 (95% CI: 0.47-1.04)
    • SAE: 21.1% vs 27.0% for placebo

Sarpatwari, Kaltenboeck, Kesselheim, JAMA, 2020
Another drug

• March 2020: RECOVERY RCT initiated to test a range of potential treatments for COVID-19
  – Over 11,500 patients enrolled from over 175 NHS hospitals in UK

• June 8 2020: analysis halted enrollment to the dexamethasone arm
  – “Sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit”

• 2104 pts randomized receive dexamethasone 6 mg qd vs. 4321 randomized to receive usual care
  – 33% of the steroid-treated patients had died, compared to 41% of the patients on usual care or a placebo

• No EUA
Third Drug EUA

- Aug 23: Convalescent plasma
- History, preclinical evidence, other trials, Mayo EAP results
  - Open-label, non-randomized
  - Post-hoc subgroup analysis
    - In patients transfused within 3 days of diagnosis, mortality 8.7% (95% CI 8.3%-0.2%) vs. 11.9% [CI 11.4%-12.2%] in patients transfused 4 or more days after diagnosis (p<0.0001)
- NIH panel: “insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19”
Next steps: Vaccine EUA?

• What will be the efficacy outcome used?
• What are safety outcomes?
  – What kinds of patients are enrolled, how long did the trial last, and how were adverse events ascertained?
• Will government encourage FDA to issue EUA for a product that has antibody data that only seem promising, even over objections of internal FDA scientists?
  – Or even without formal request of manufacturer?
  – Use Defense Production Act to require production?
If EUA issued...

• What is the post-EUA data gathering plan?
  – What are the criteria for revoking EUA or ‘graduating’ to full approval?

• What price will vaccine be made available for?
  – Remdesivir at $3,120 per patient
  – Substantial taxpayer investment in vaccine development

• How will vaccine EUA be received by public given growing patient skepticism about political influence on the process?