Regulatory Considerations for Seamless Oncology Drug Development – Expansion Cohorts

National Cancer Policy Forum - The Drug Development Paradigm in Oncology: Managing Benefit and Risk in Seamless Cancer Drug Development Session

December 13, 2016

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Outline

- **Background - Changing Drug Development Paradigm in Oncology**
- **Example of Seamless Expansion Cohort Trial**
- **Regulatory Considerations for Expansion Cohort Trials**

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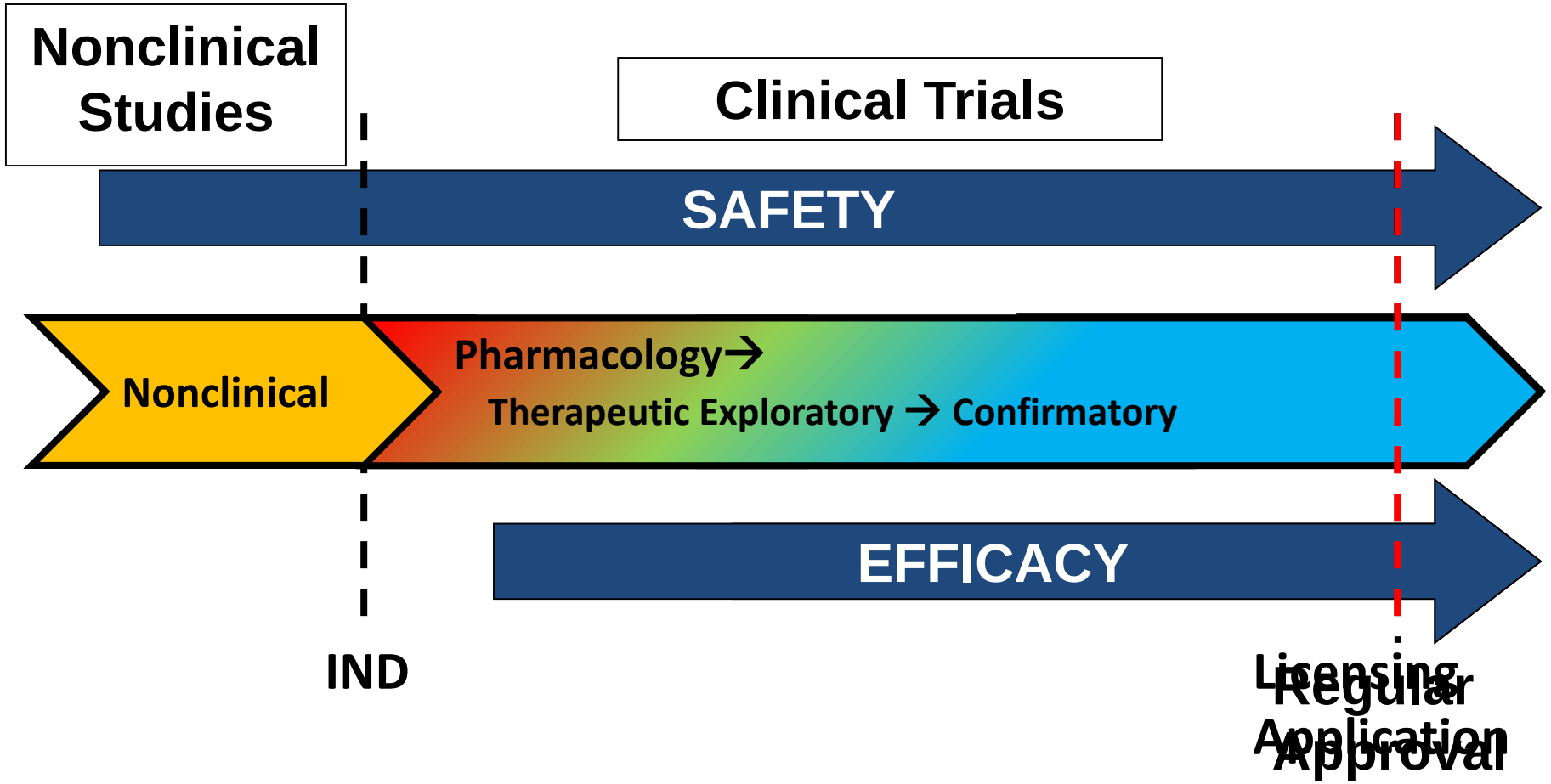
"Shaped" Oncology Drug Development Paradigm



Theoret et. al., Clinical Cancer Research, 2015

Regular Approval

- **Substantial Evidence of Safety And Efficacy**
  - **Adequate and Well-controlled Clinical Trials**
- **Direct Evidence of Clinical Benefit**
  - **Improvement in survival, physical functioning, tumor-related symptoms**
- **Established Surrogate for Clinical Benefit**
- **No Comparative Efficacy Requirement for Regular Approval**

Accelerated Approval

- One of Four FDA Expedited Programs for Serious or Life-Threatening Illnesses
- Meaningful Therapeutic Benefit "Over Existing Treatments"
- Based on "Surrogate" or Intermediate Endpoint Reasonably Likely to Predict Clinical Benefit
- Confirmatory Trials to Verify and Describe Clinical Benefit

FDA Expedited Programs for Serious Conditions - Drugs & Biologics

- **Accelerated Approval**
- **Priority Review Designation**
- **Breakthrough Therapy Designation**
- **Fast Track Designation**

All consider the available therapies to treat the serious condition for the disease context to determine whether there is an unmet medical need, or if the new therapy appears to provide an improvement or advantage over available therapies.

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

FDA Expedited Programs – ORR

- **Breakthrough Therapy Designation Requests**
  - CDER Analysis of BTDR from 9/2012 to 12/2014*
  - Hematology/Oncology – 86 (42%) of the 203 requests
    - 27 (31%) Grant; 18 (21%) Withdrawn; 41 (48%) Denied
    - 18 (67%) of 27 Granted Based on ORR
- **NME Approvals (Oncology) in OHOP 2014-5**
  - Of the 24 NME Approvals, 12 were Accelerated Approvals
  - ORR → Primary Endpoint in 9 of the 12 Accelerated Approvals

*Breakthrough Therapy Designation: Exploring the Qualifying Criteria; 4/24/15

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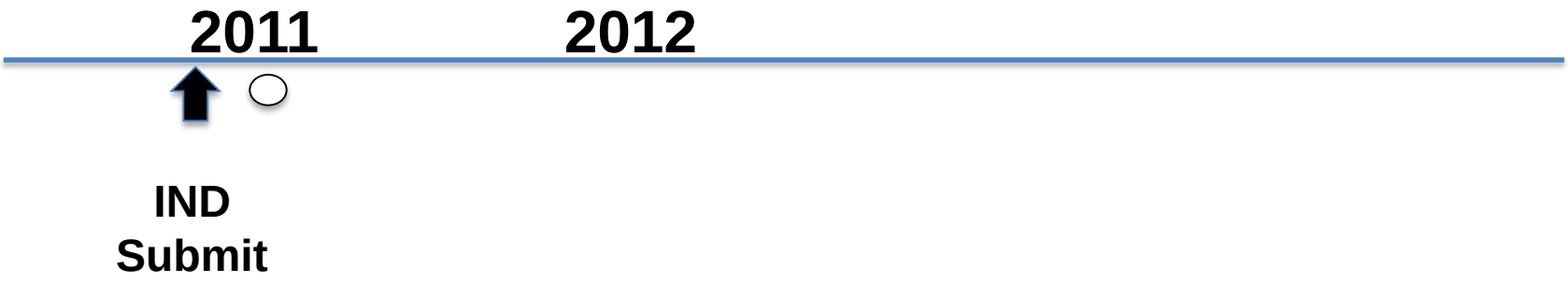
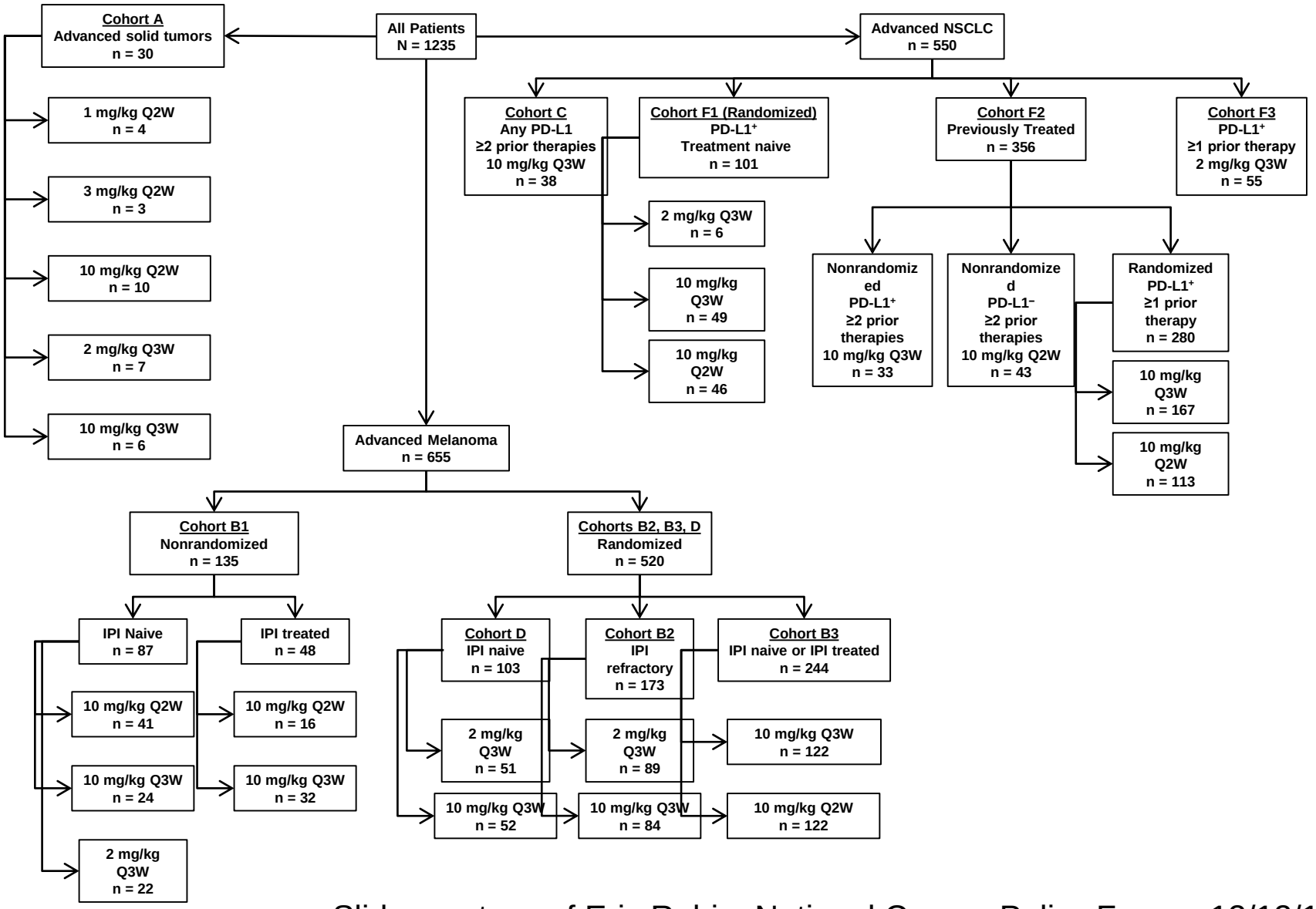
MK-3475: PN001 Trial



KN-001 Treatment Cohorts



Slide courtesy of Eric Rubin, National Cancer Policy Forum, 12/12/16

MK-3475: PN001 Trial

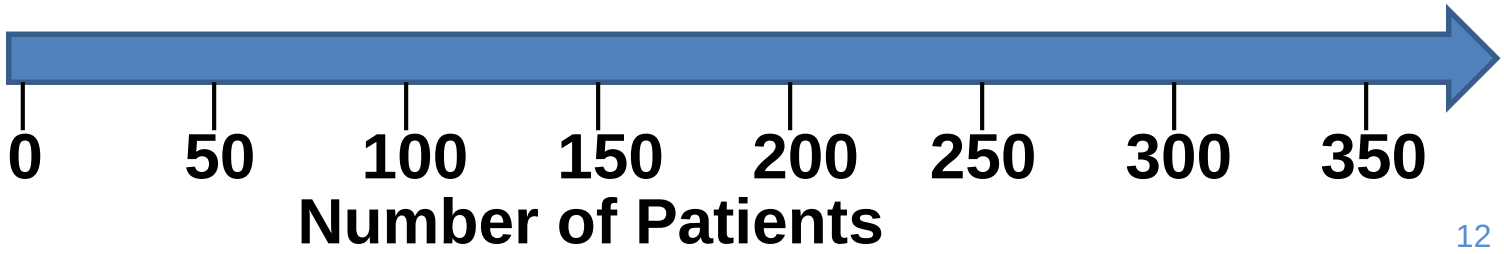
Amendment

1

Part A

Part B

32



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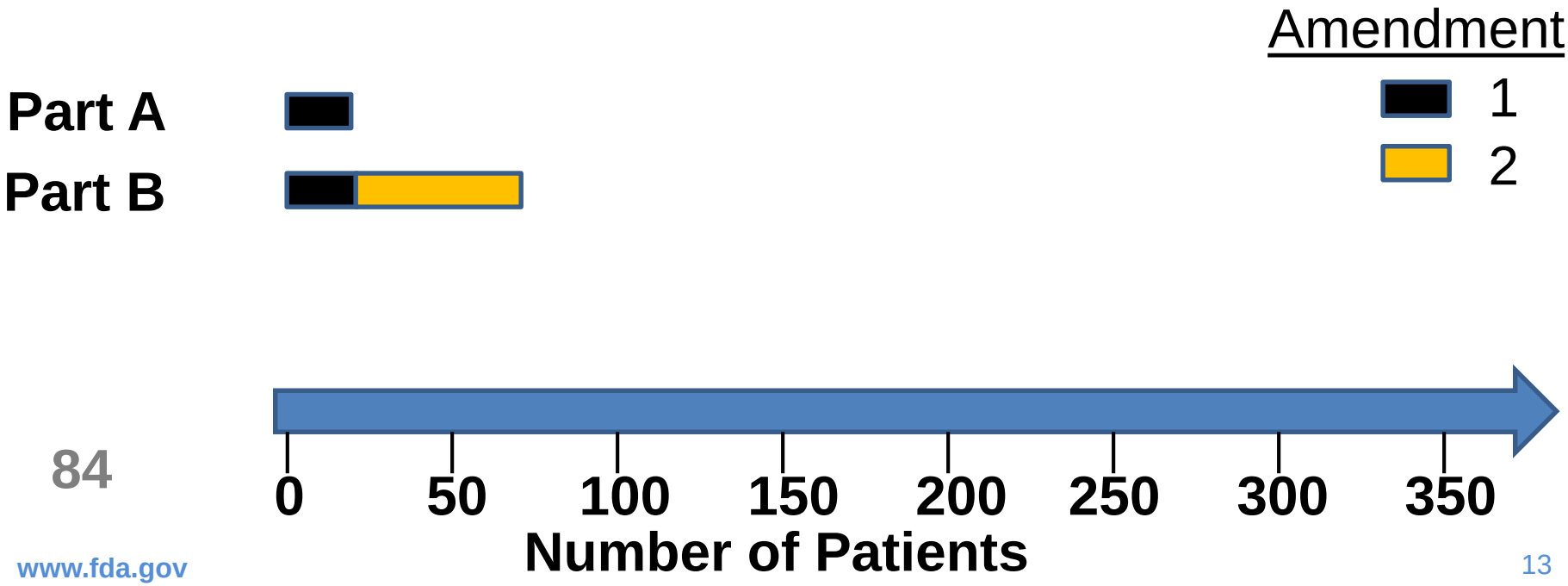

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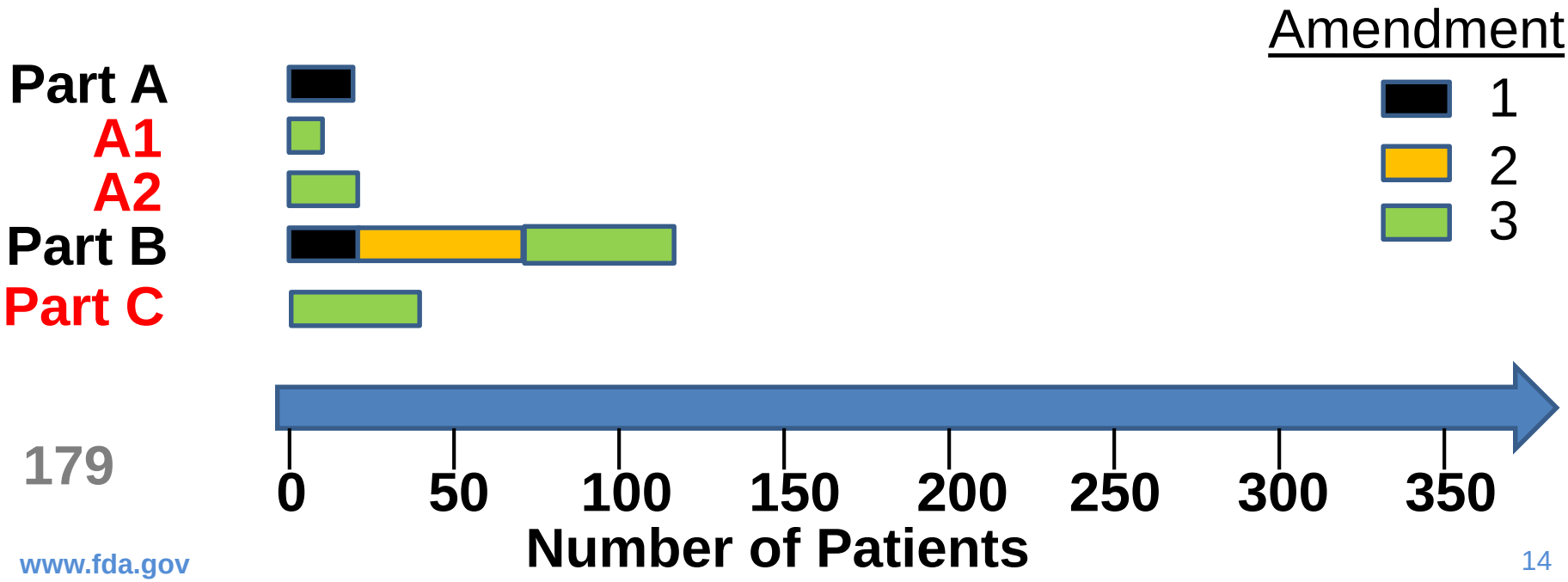

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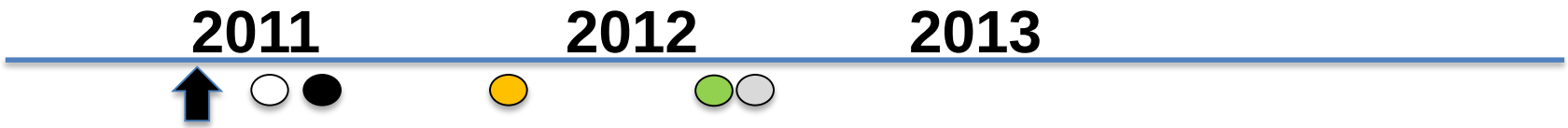

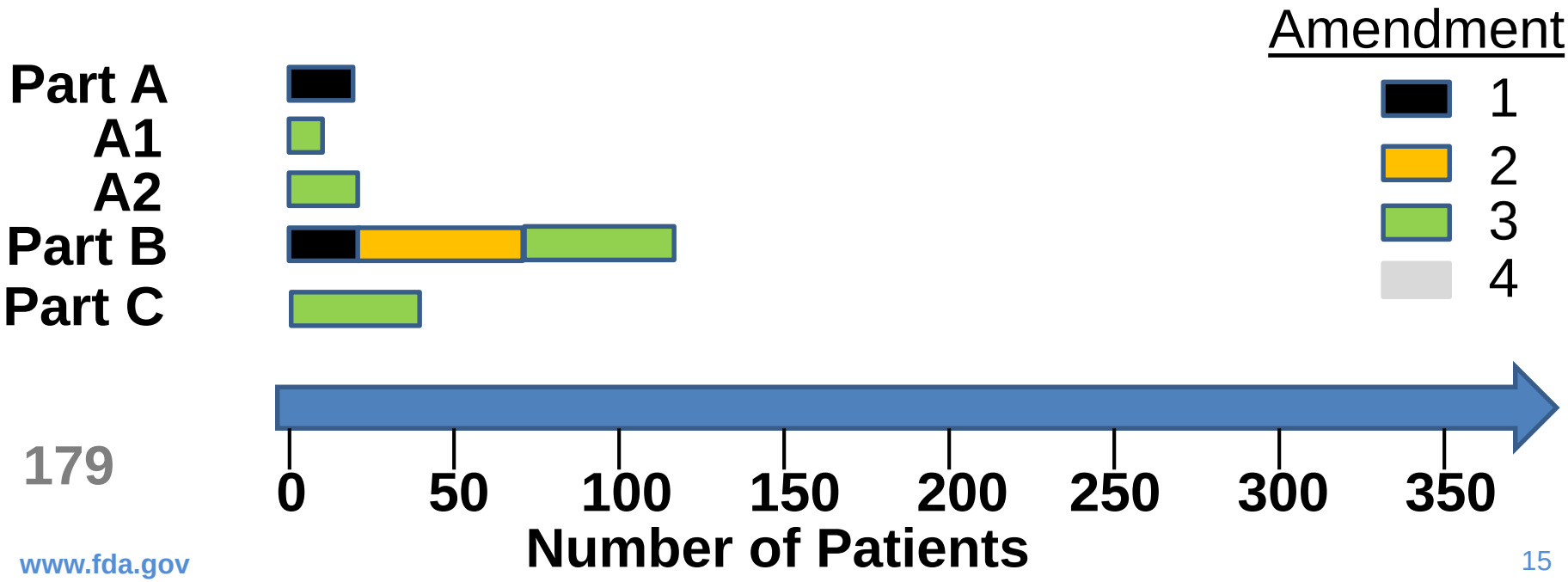

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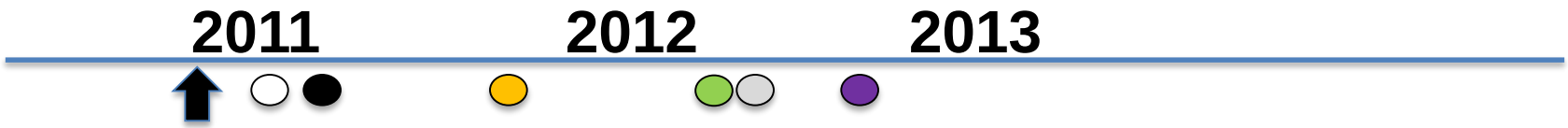

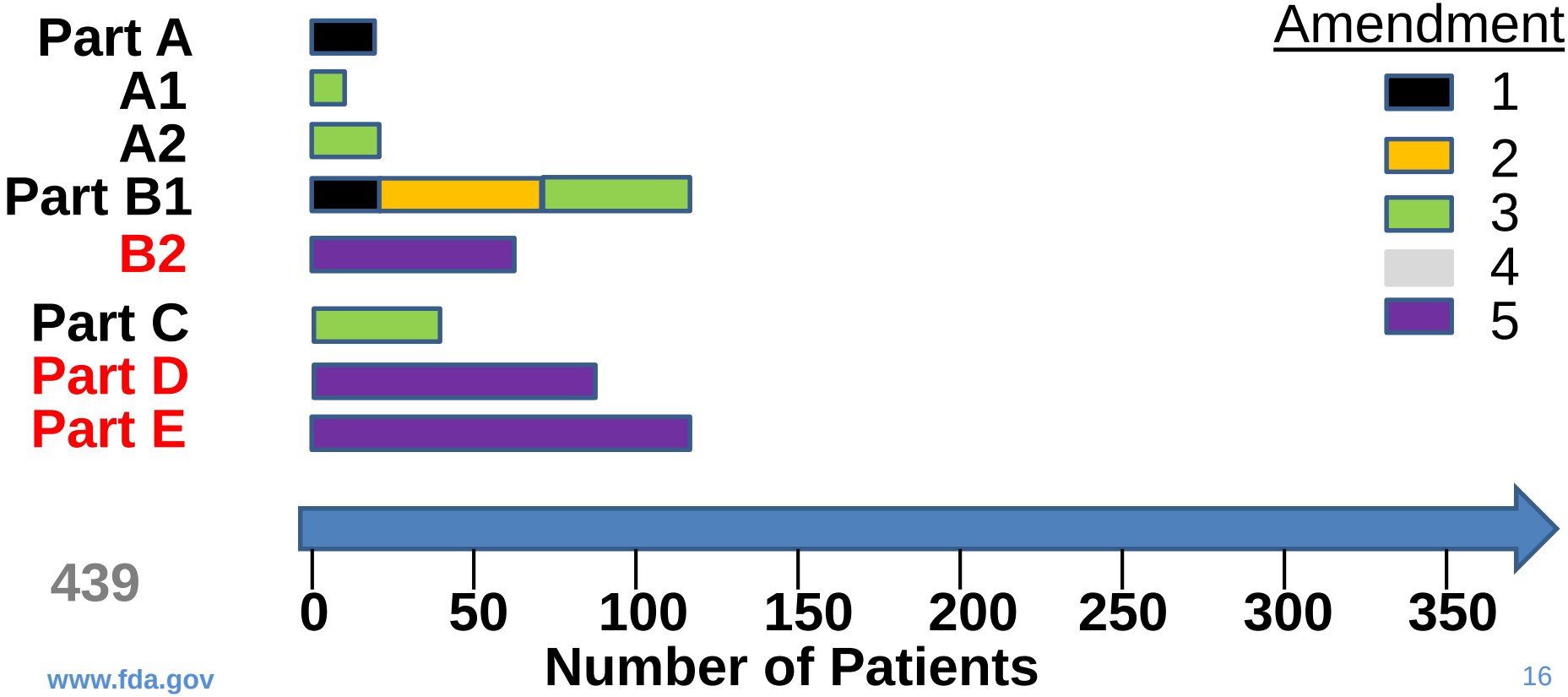

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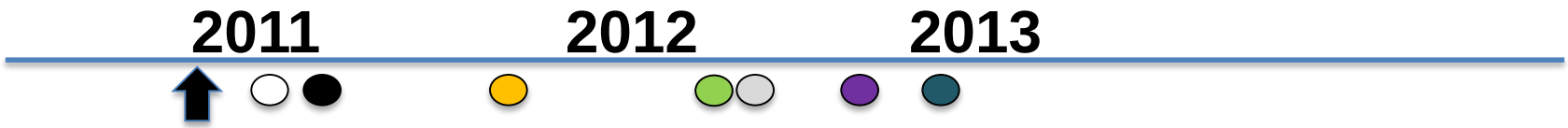

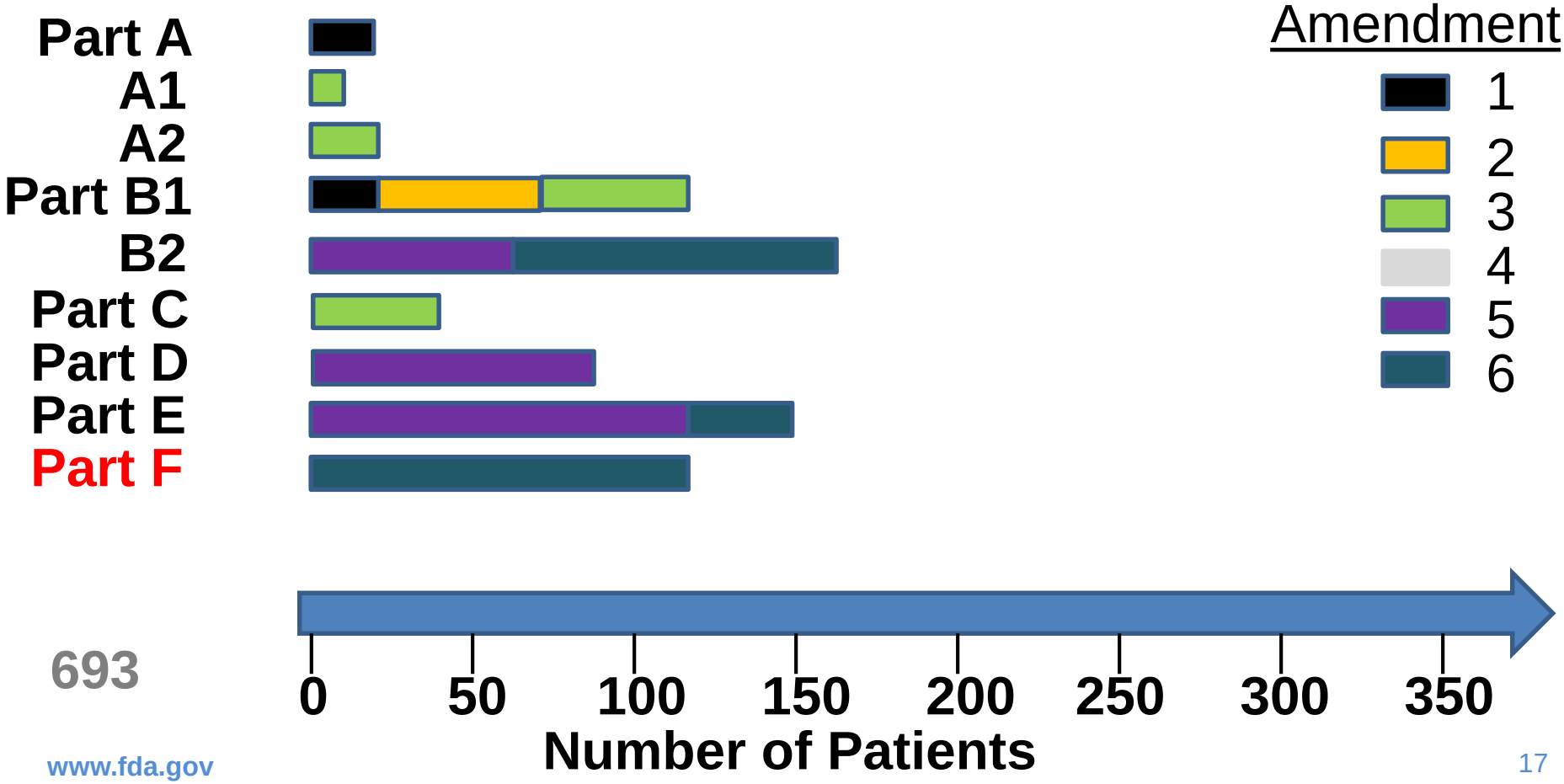

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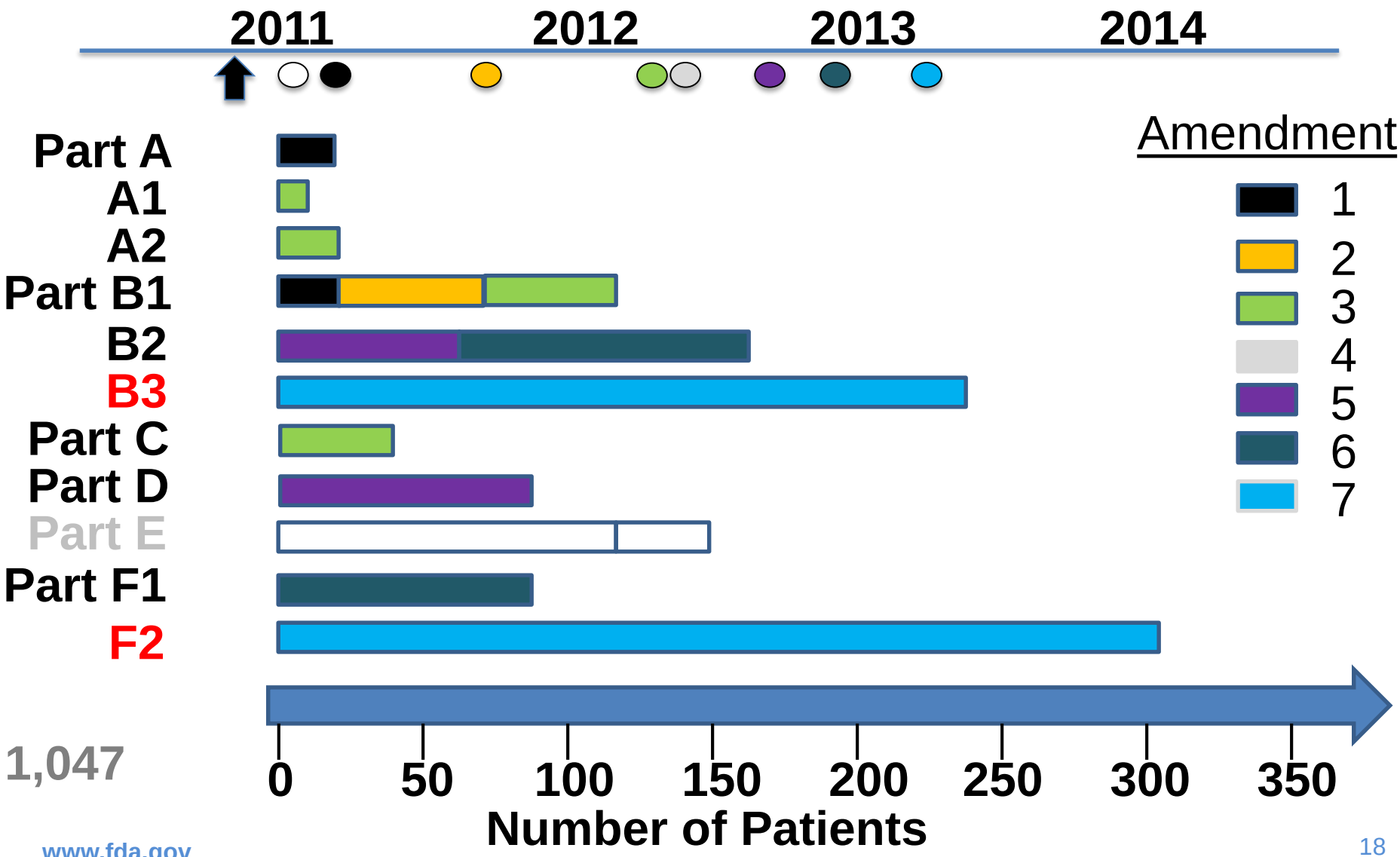

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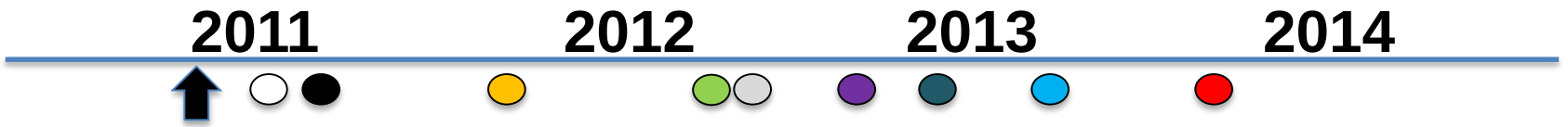

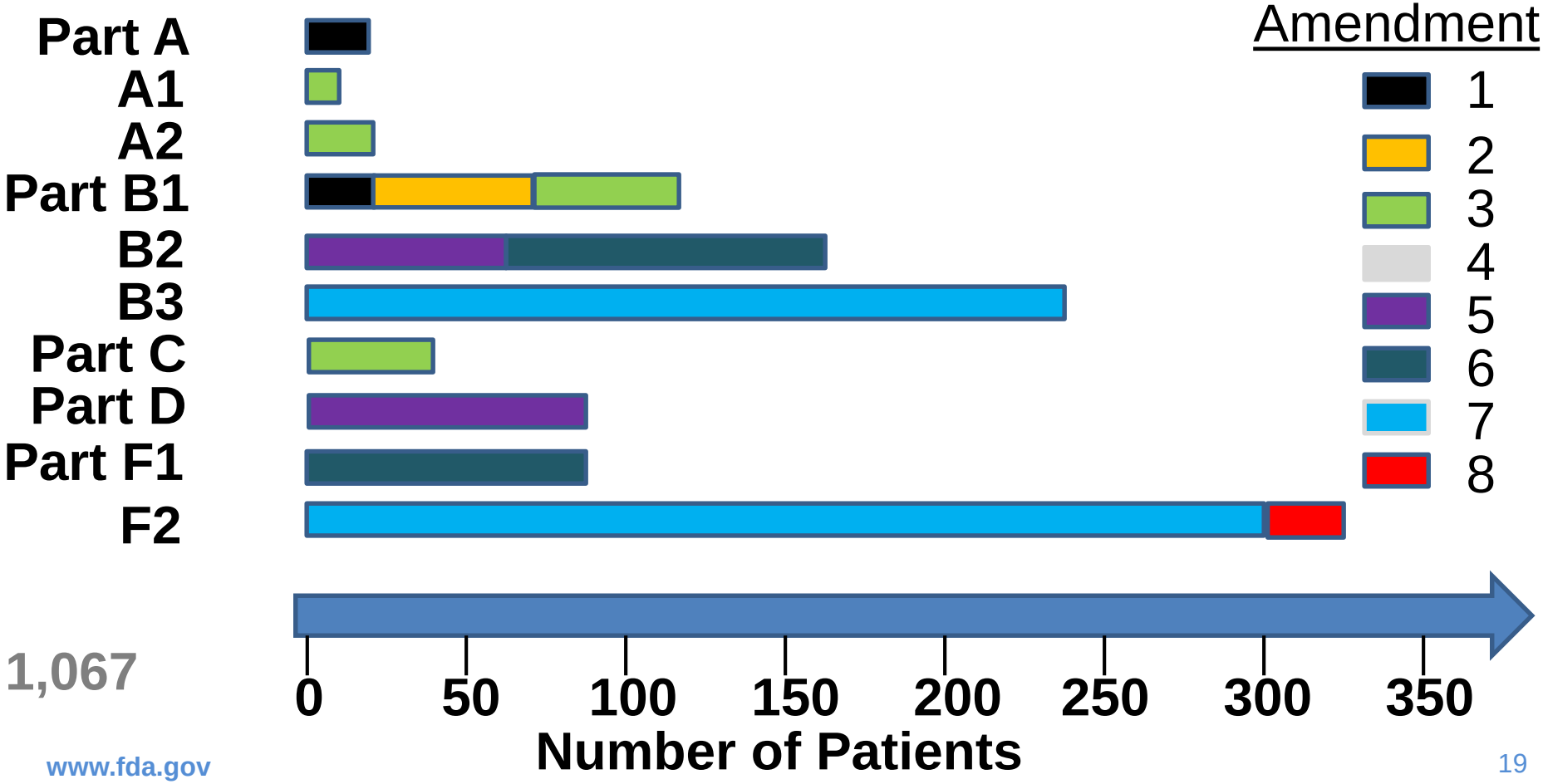

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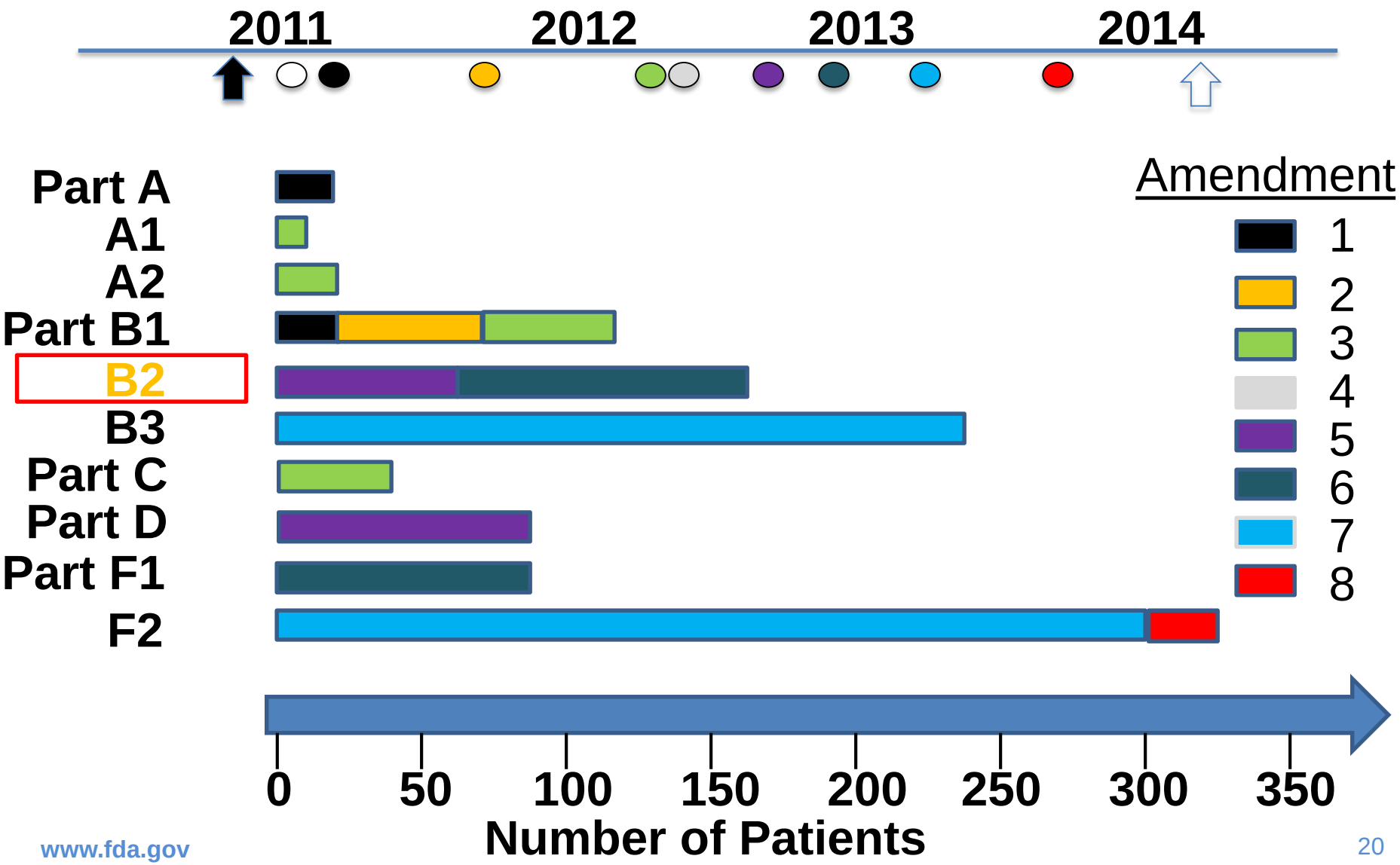

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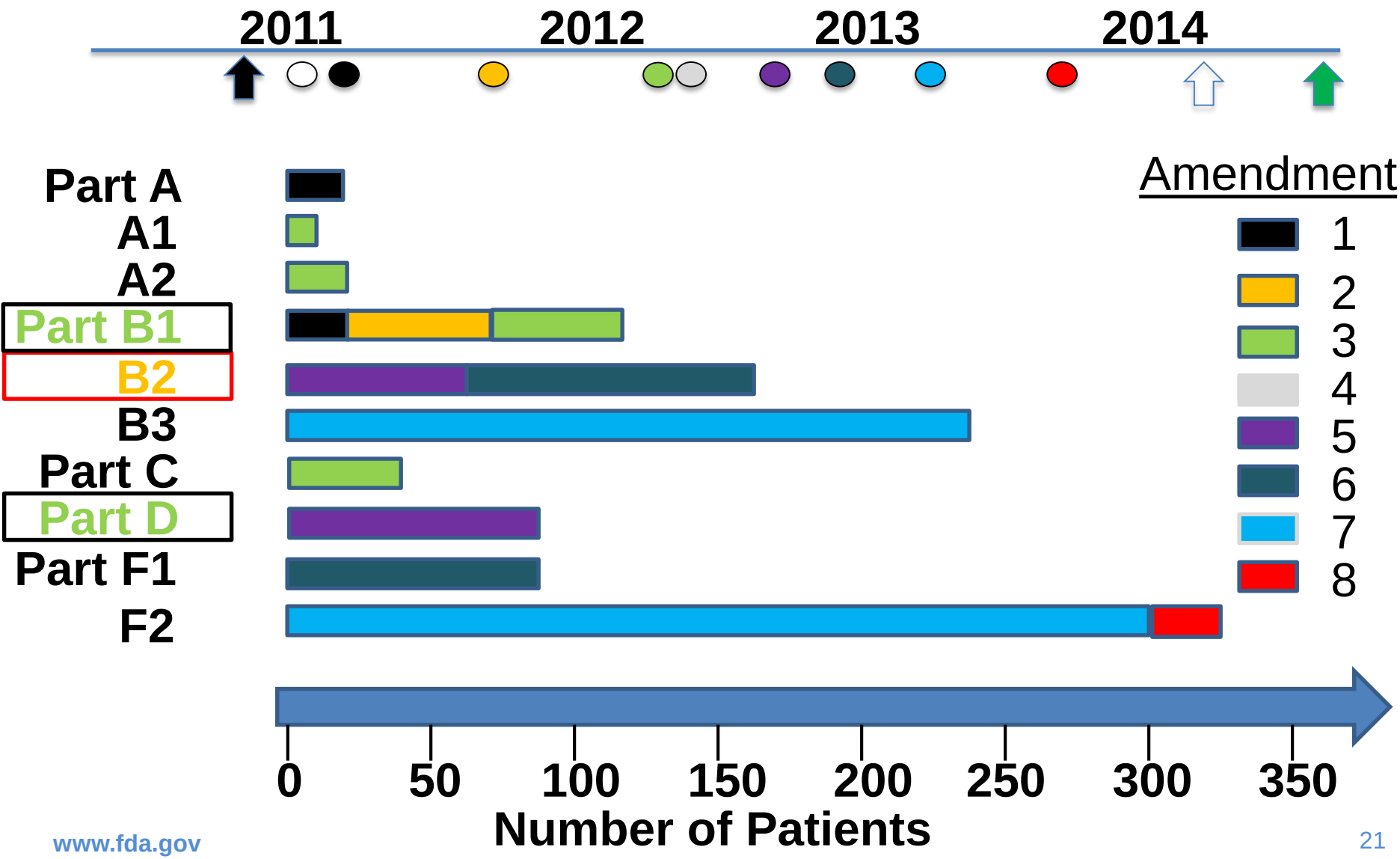

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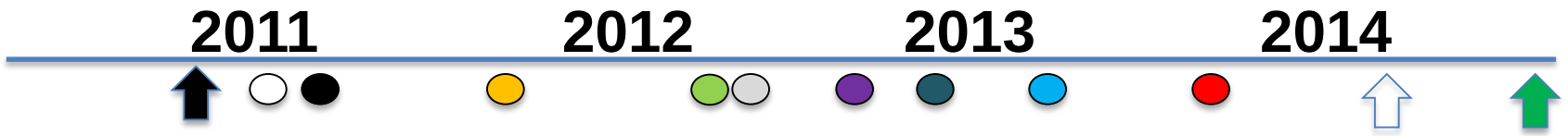
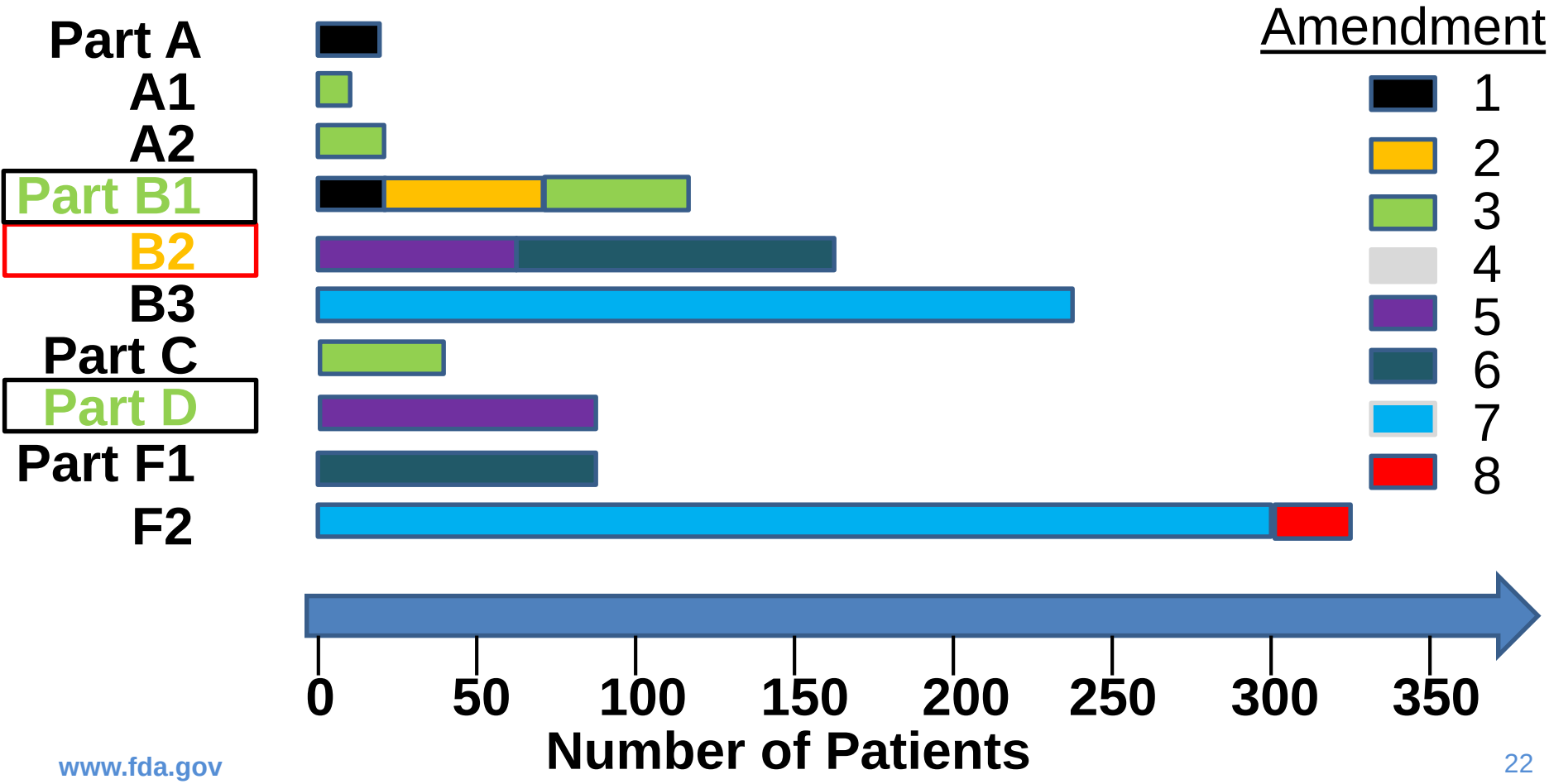
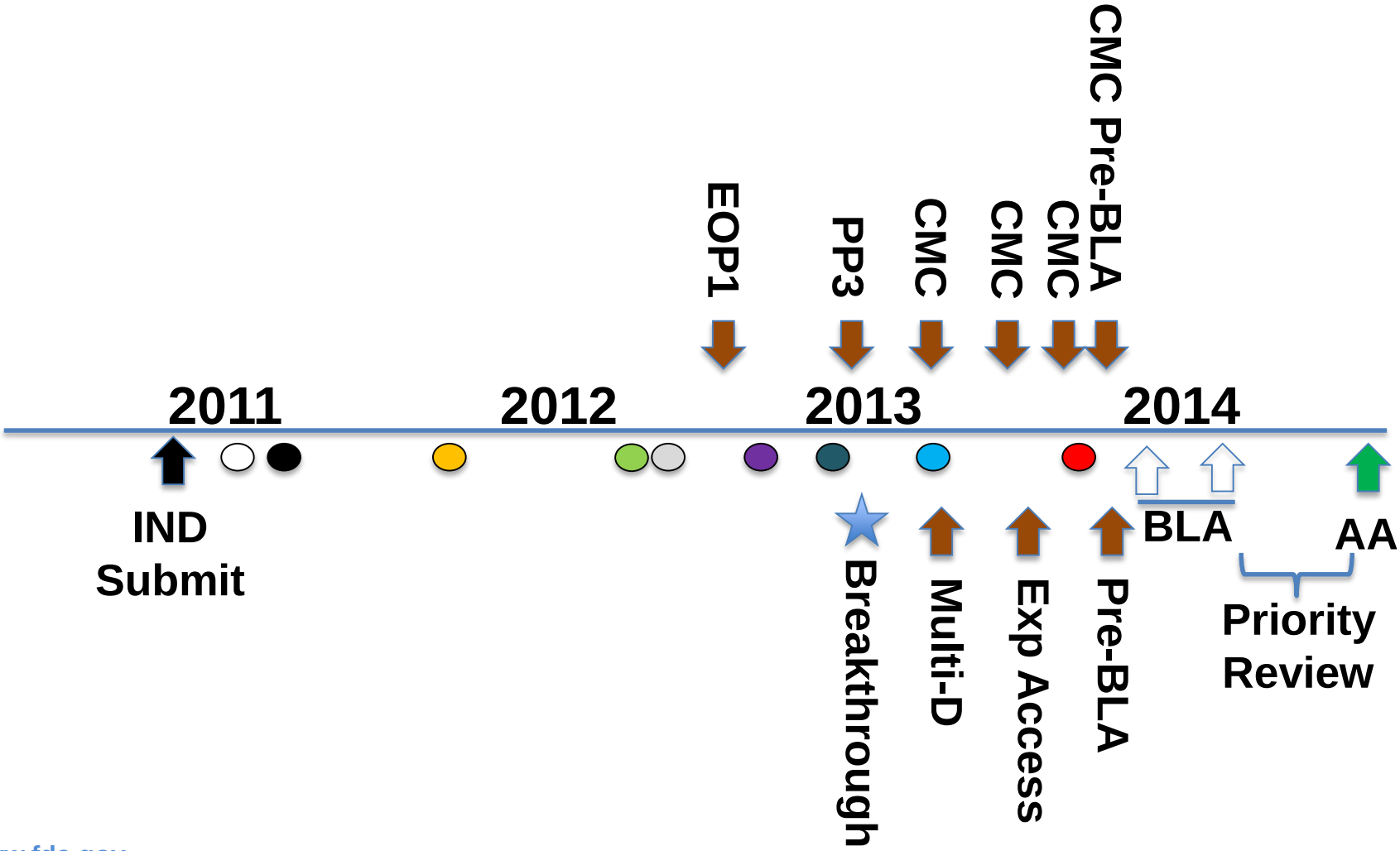




MK-3475: PN001 Trial and Selected Melanoma Development Program Milestones



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Expansion Cohorts

Opportunities

- Adaptable – single protocol
  - IND in effect
  - IRB(s) in place
- Earlier evaluation of efficacy endpoints
- Standardized data collection
- Existing trial networks

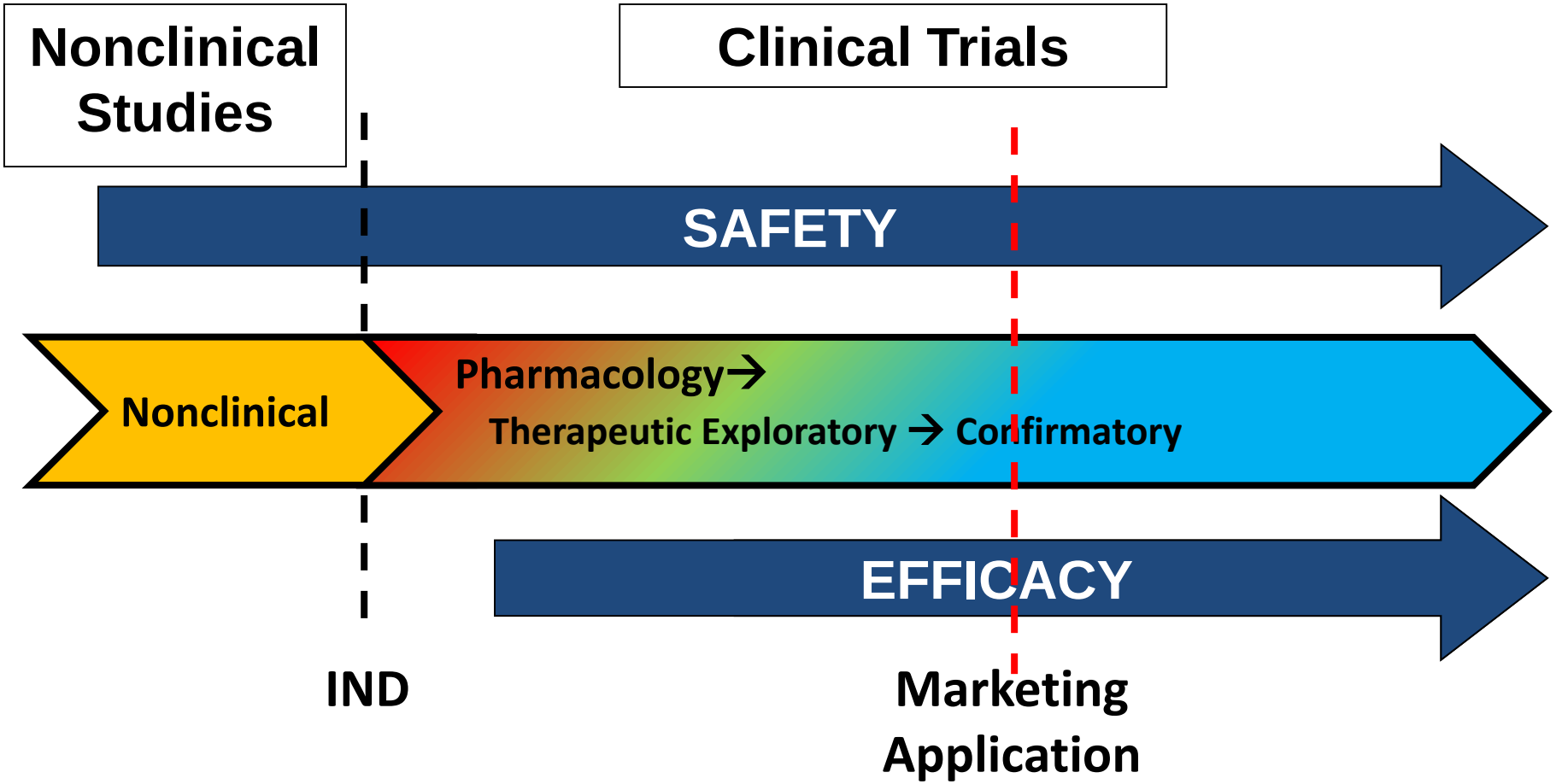
Challenges

- Safety
- Heterogeneous populations
- Adequate statistical plan
- No pre-defined milestone meetings with FDA
- Adequate data collection
- Independent oversight
- Products appropriate for expansion cohort designs

Theoret et. al., Clin Cancer Res, 2015

Prowell et. al., N Engl J Med, 2016

Seamless Oncology Drug Development Paradigm



Thank you

ACKNOWLEDGEMENTS:

PATRICIA KEEGAN, M.D.

RICHARD PAZDUR, M.D.


FDA
U.S. FOOD & DRUG
ADMINISTRATION