An Integrated Approach to Medical Countermeasure Development

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Responding to the threat

- Understand the threat
- Anticipate the threat
- Develop countermeasures
  - Prophylactic
  - Therapeutic
- Establish logistics
- Detect the threat
- Mitigate the threat

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Biological threats

- Naturally-occurring organisms used offensively
  - Anthrax (*Bacillus anthracis*)
  - Plague (*Yersinia pestis*)

TRADITIONAL

- Acquisition of enhanced pathology by organisms
  - Naturally-occuring
  - "Assisted"

ENHANCED

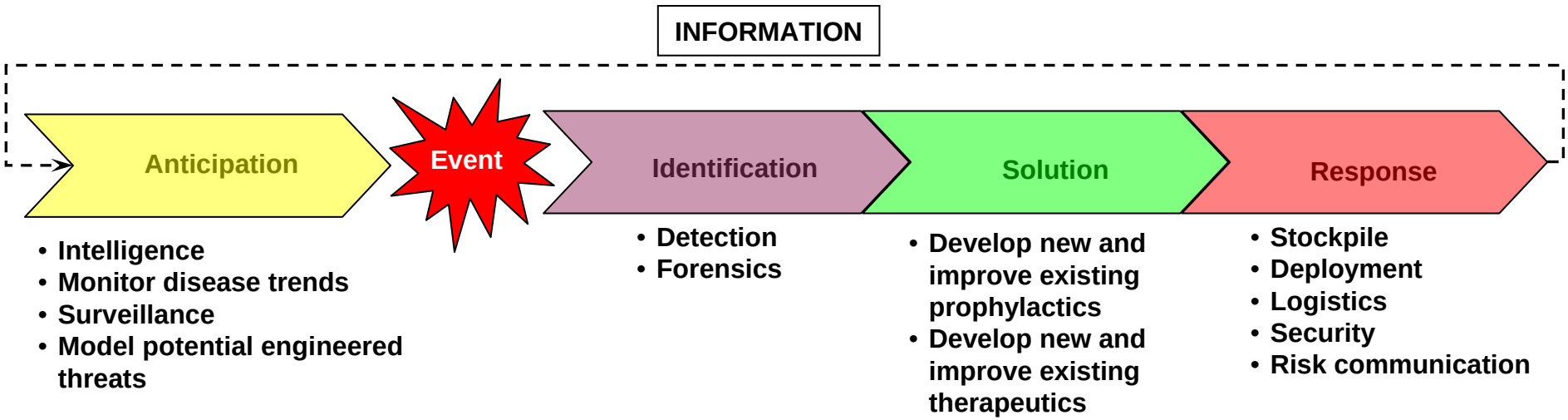
- Zoonoses
- Recurring pandemics (influenza)

EMERGING

- Accidental/intentional release of engineered or synthetic organisms
- Bioregulators and immunological weapons

ADVANCED

Continuum of biodefense



- Assumptions:
  - The term “biodefense” is not strictly limited to manmade events (warfare or terrorism)
  - Many (most?) of the approaches are applicable to chemical, nuclear and radiological countermeasures as well

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It all starts with the requirements…

- We need to know:
  - Nature and identity of threat
  - Level of protection required
  - Onset vs duration of protection
  - Administration strategy
  - Storage conditions
  - Initial delivery amount
  - Ongoing requirements
  - Regulatory strategy
- Because:
  - Specificity of the response
  - Preclinical and clinical study design
  - Administration and testing paradigm
  - Clinical strategy
  - Formulation, stability and format
  - Manufacturing strategy
  - Manufacturing strategy
  - Overall program design (licensed vs. unlicensed)

Deviations from the plan <u>always</u> result in significant cost and schedule ramifications. A clear plan for development of the product is necessary in advance, and modifications should be made only when absolutely necessary.

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The integrator concept

- Expert core team supported by functional area experts
- Primary focus is information creation and management
- Model is product-agnostic
  - Independent of intellectual property
  - Service-based model
- Physical activities (manufacture, testing, etc.) are outsourced
  - Allows maximal optimization of available resources
  - Promotes flexibility in subsystem management
- Addresses high-risk enterprise of countermeasure development by project manager and risk mitigation

“Subsystems” to be integrated

DISCOVERY

TECHNOLOGY TRANSFER

PROOF-OF-CONCEPT

MANUFACTURE AND TESTING

SPECIFICATIONS

SAFETY (ANIMAL → HUMAN)

MONITORING/ANTICIPATION

CLINICAL ASSESSMENT

BRIDGING (ANIMAL RULE)

DEMONSTRATION OF HUMAN EFFICACY

STRATEGY AND COMPLIANCE

PROJECT MANAGEMENT (COST/SCHEDULE/RISK/PERFORMANCE)

LOGISTICS (SHIPPING/STORAGE/CONTROL)

DATA AND INFORMATION MANAGEMENT

RISKS/RESOURCES

FIELDED PRODUCT

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Responsibilities of an integrator

- Develop and implement strategies for the advanced development and production of medical countermeasures
- Manage cost, schedule, risk and technical performance of countermeasure development
- Ensure governmental regulatory compliance
- Serve as the interface with regulatory authorities
- Maintain due diligence
  - Secure and maintain best-of-class resources
  - Monitor, adopt and adapt new technologies as appropriate
  - Apply best practices and lessons-learned

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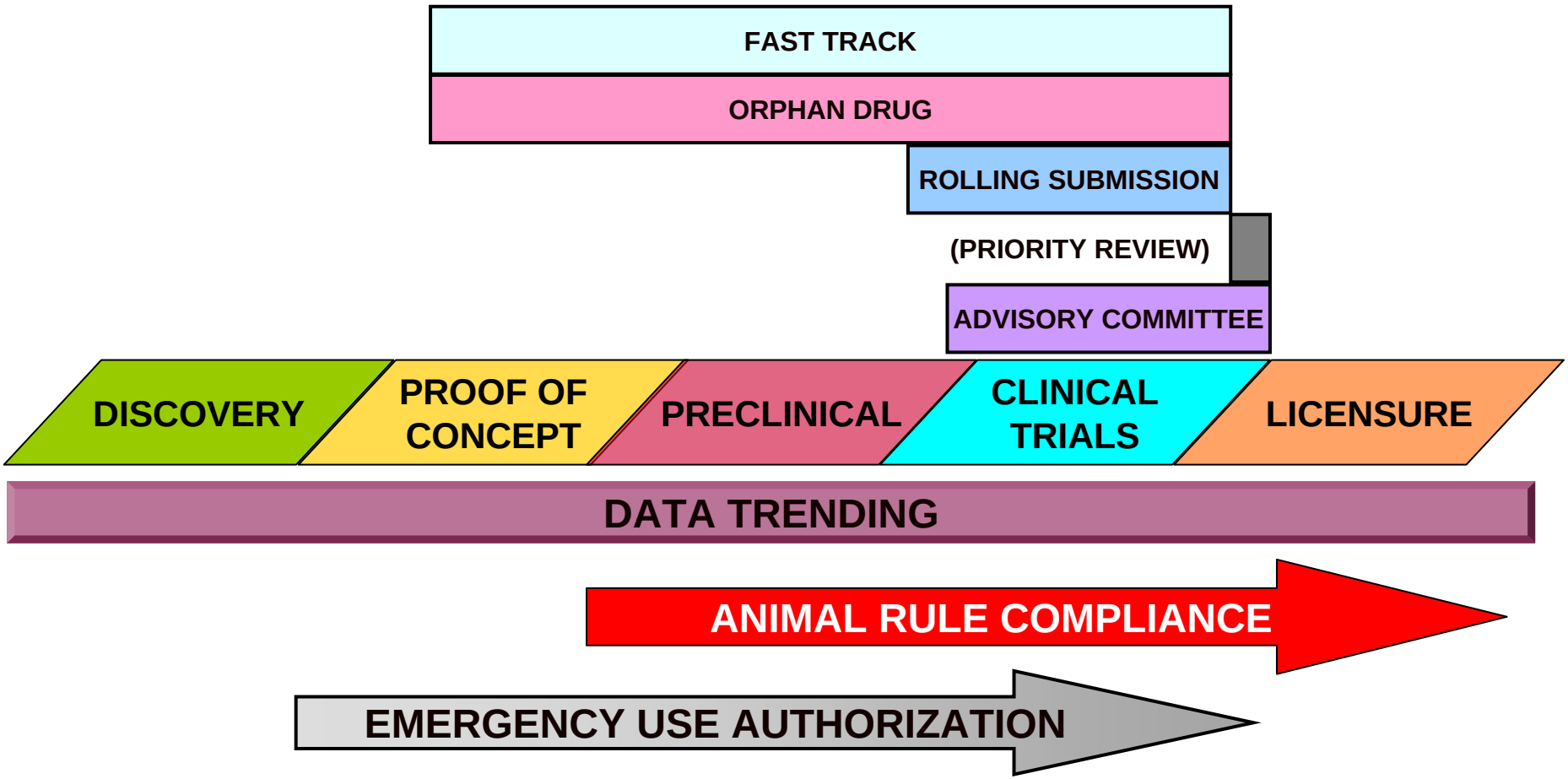
Regulatory strategy for countermeasure development



This strategy is intended to make the process more efficient, not necessarily faster.

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Clinical trial strategy for countermeasure development

PHASE 1/2

PHASE 2/3

LICENSURE

PHASE 1

PHASE 2

PHASE 3

PHASE 4

ADAPTIVE CLINICAL TRIALS?

ANIMAL RULE COMPLIANCE

MEDICAL INFORMATICS

PHARMACOVIGILANCE

DATA MANAGEMENT/DATA CLEANSING

BIOSTATISTICAL DESIGN AND INTERPRETATION

Long-range regulatory implications of the Animal Rule are unknown at present.

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Risk management

- Identify all conceivable risks and their interconnections and dependencies
- Assess likelihood and impact
- Establish risk severity index
- Determine potential mitigation(s)
- Establish contingency plans
- Review and re-evaluate constantly
- Maintain recovery planning
- Communicate risk to stakeholders

Probability of occurrence
X Impact on:
Performance
Schedule
Cost
= Risk Severity Index

Risk Severity Index guides resource allocation to retire risks early and often.

Risks inherent in countermeasure development

- Time- and finance-intensive nature of biopharmaceutical development
  - Even radical improvements in efficiency only slightly mitigate this
  - Current paradigm not conducive to quick start-up or switching
- Uncertainty of the potential threat
  - Effective countermeasures may drive “second-string” threats
  - Synthetic biology opens the way for nearly limitless threats
- Rapid advances in countermeasure identification not necessarily matched by advanced development paradigm
  - Danger of a loss of focus from too many new ideas
  - Advantage of multiple candidates as risk mitigation for product failure
- Ongoing interest in participation by the commercial sector

Risk assessment and management

- Products may fail at any stage during development
  - Early involvement of integration in the product life cycle
  - Multiple solutions developed with logical down-select
  - Development of complementary countermeasures and approaches
- Subsystem (subcontractor) management
  - Careful selection of subcontractors at the outset, and maintenance of the relationships
  - Incentives and disincentives
  - Develop redundancy in all key systems (nonclinical, clinical, manufacturing) and all suppliers (when practical)
  - Robust technology transfer capability to facilitate quick turnaround of facilities
  - Consortium development and management
  - Communications strategy

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Risks inherent in integration of subsystems

- Communication breakdown
  - Expectations are never made clear enough
  - An active process
- Loss of crucial resources
  - No longer doing business
  - Change of business focus or business model
  - Mergers and acquisitions
  - Expense
  - Loss of confidence (technical/regulatory)
- Loss of access to technology
  - Intellectual property restrictions
  - Technology failure
- Technical setbacks and unintended consequences

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Putting it together

DISCOVERY | PROOF OF CONCEPT | PRECLINICAL | CLINICAL TRIALS | LICENSURE

Candidate Assessment
Discovery Data
'Omics' Target Data
Safety Trending
Pharamacovigilance
Adaptive Trial Design
Patient Records

Project Management

Risk Management
Cost/Schedule Management
Science/Technology Management

Quality Assurance/Regulatory Design and Compliance
Cost/Schedule/Performance Risk Management Systems
Information Management Systems
Electronic Submission
Data Trending/Biostatistics

Future integration concepts

- Prophylaxis still a prime option for those at known risk of exposure:
  - Prevents the window of opportunity for pathogenesis
  - Prevention always better than treatment
- Both prophylaxis and therapeutics will need to be agile, and the technology must evolve quickly
  - "Bundled" solutions of vaccine and therapeutics: seamless protection ideal opportunity for integration
  - Novel mechanisms for bridging innate and adaptive immune responses: the intersection between prophylaxis and treatment
  - Systems integration of detection, protection and treatment
- Movement of countermeasure development toward parallel rather than sequential process.