

BIOTECHNOLOGY

Patent Prosecution, Licensing, Litigation, and Hatch-Waxman

PART IV: THE ROLE OF PATENT & NON-PATENT EXCLUSIVITY UNDER THE HATCH-WAXMAN ACT

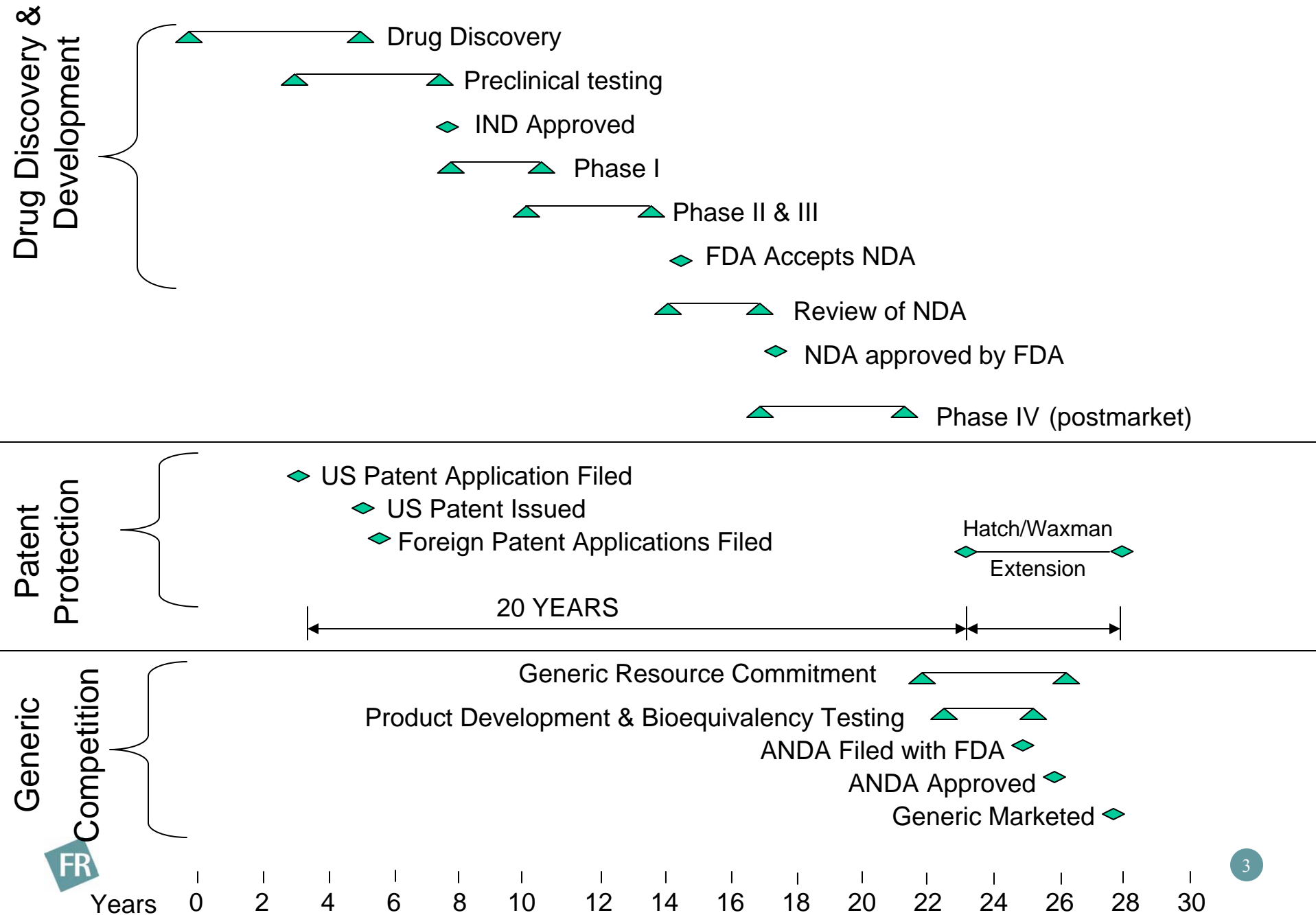
Terry G. Mahn

HATCH-WAXMAN ACT OF 1984

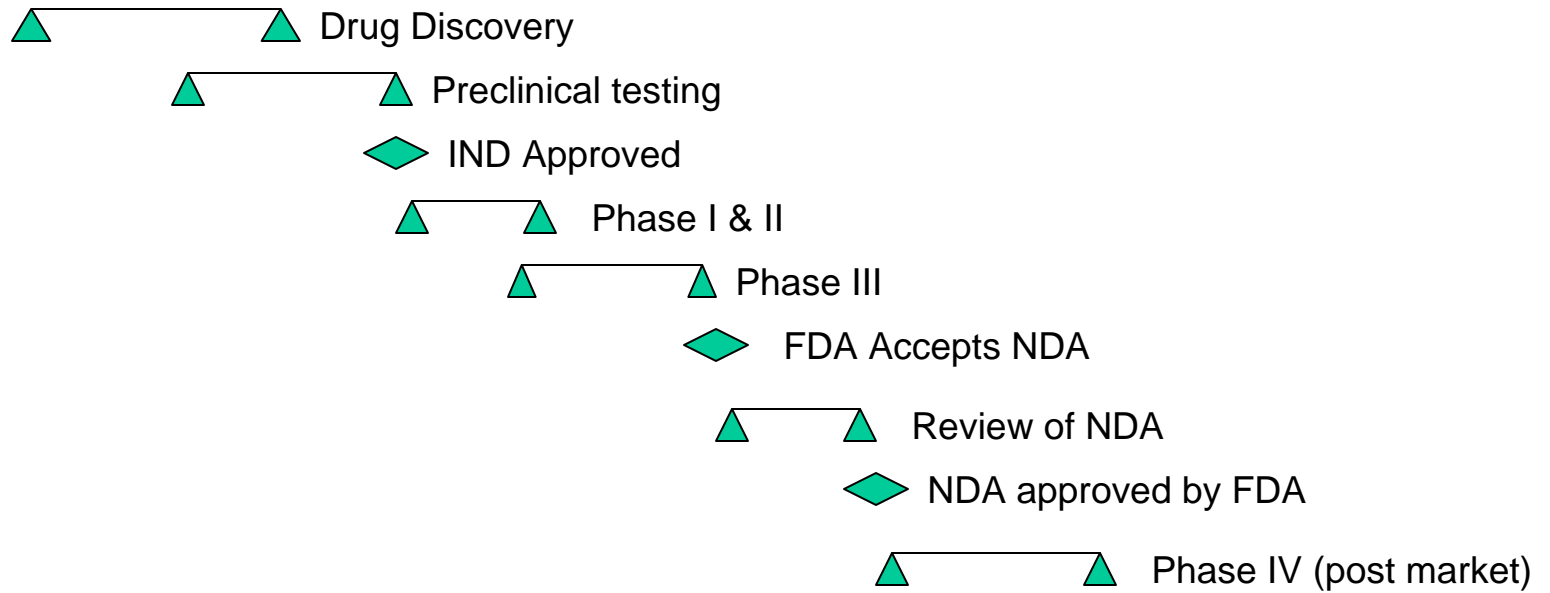
A. Overview

- Political Compromise: Pioneers v. Generics
- New Drug Approvals and Exclusivity Rights
- Patent Term Extensions
- Orange Book Practice and Infringement under § 271(e)(2)
- Safe Harbor from Infringement under § 271(e)(1)

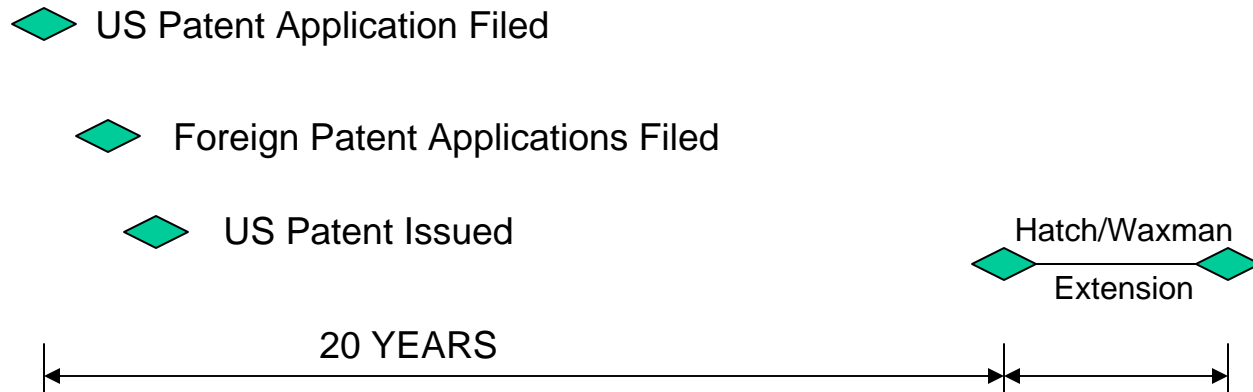
Drug Development Time Line



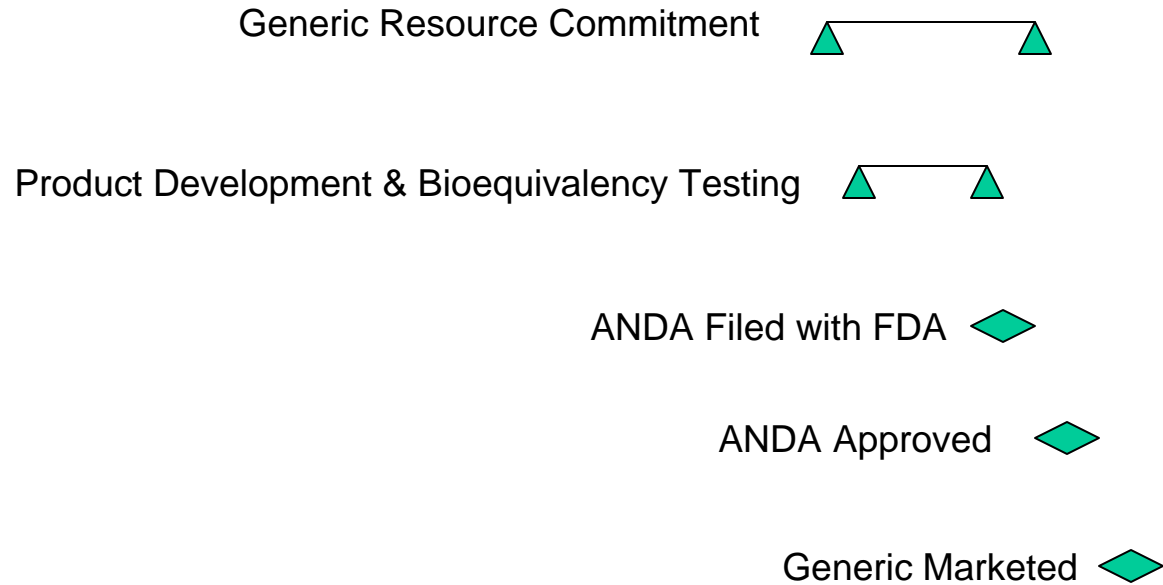
Drug Development Time Line



Drug Development Time Line



Drug Development Time Line



B. Drug Approvals and Exclusivity (21 USC § 355)

1. New Routes to Drug Approval

- 505(b)(1) or NDA – full clinicals, patent declaration
- 505(b)(2) or “paper NDA”
 - new drugs
 - generic drugs
- 505 (j) or ANDA – true generic
 - can petition for changes in active ingredient, route, dosage or strength
 - patent certification required

2. Exclusivity Rights

- Scope: drugs, biologics regulated as drugs, combinations regulated as drugs, antibiotics (since 1997)
- 5 year exclusivity
 - new active moieties only
 - no generic or 505(b)(2) application can be filed
 - 4 year exclusivity if listed patent
- 3 Year exclusivity
 - clinicals required
 - change in dosage, indications, or from Rx to OTC
 - no generic or 505(b)(2) can be approved

- 180 day exclusivity
 - protects first generic to challenge listed patent
 - can be shared
 - triggering necessary for other generic approvals
 - forfeitures under Medicare Modernization Act of 2003

3. Non Hatch-Waxman Exclusivities

- Orphan Drugs (1983)
 - scope: population <200,000 or no expectation of cost recovery
 - drugs and biologics
 - 7 years protection
 - no FDA approval for same product for same indication
 - “sameness” – active moiety or macromolecule; clinical superiority
 - OD exclusivity stops NDAs as well as generics
 - designation must be made before NDA/BLA submission
 - tax credits, fee waivers, grants

- Pediatric Exclusivity (1997; 2002)
 - scope: clinical studies in pediatric populations
 - drugs only
 - protects active moiety
 - adds 6 months protection to all other exclusivities
 - all indications, dosages, strengths
 - listed patents also get 6 months of protection
 - protects combination drugs containing active moiety
 - second exclusivity for new pediatric patient population; no patent protection
 - Best Pharmaceuticals for Children Act (2002) allows generic approvals despite protected labeling

C. Patent Term Extension (35 USC § 156)

1. Theory and Scope

- Distortion of term by agency review
- FDA and USDA only
- Products, methods of using a product, methods of manufacturing a product

2. Products

- Active ingredient of drug, antibiotic or human biological products regulated under PHS Act
 - including any salt or ester of the AI
 - as a single entity or in combination with another AI
- Animal drug or veterinary biologic (exception for GE biologic)
- Class III medical devices
- Color and food additives

3. Conditions for Term Extension

- Patent not expired before agency approval
- Patent not previously extended
- Agency approval must be “first permitted commercial marketing or use of product”
 - drug product: active ingredient including salt or ester
 - Glaxo v. Quigg (Fed Cir. 1990)
 - Merck v. Teva (Fed Cir. 2003)
 - Pfizer v. Dr. Reddy’s (Fed Cir. 2004)
 - device: each PMA is a separate permitted marketing
 - Pacemakers v. St. Jude (S.D. IN 2001)

- method of manufacturing using rDNA: first marketing or use of any product made by method
- animal drugs: first administration to a food producing animal not first approval
- Extension cannot exceed 5 years
- Total remaining term cannot exceed 14 years
- Extended rights limited to –
 - product/composition: any use approved for product
 - method of use: use claimed in patent and approved for product
 - method of manufacturing: any method used to make the “approved product” or a “product subject to regulatory review period”

- Only one patent per regulatory review period
- Patentee or agent must be directly/indirectly involved in agency review

4. Computing the Regulatory Review Period

- One-half of clinical trial period (IND)
- All of agency review period (NDA/BLA)
- Less time for failing to act with due diligence

- Example:

IND accepted: 1/1995

NDA filed: 1/2001

NDA issued: 1/2002

Potential term extension: $(6 \div 2) + 1 = 4$ years

5. USPTO Procedures

- Interim extensions
- 60 day bar date after agency approval
- PTO decides initial eligibility within 60 days
- FDA computes RPR 30 days later
- FR publication: 180 days for public comment
- Multiple petitions for extension
- Failure to update OB

6. Prosecution Strategies

- Forseeability
 - small % of patents that “make it to market”
 - FDA review/approval cycle
 - cost/benefit for blockbuster drugs
- Related discoveries
 - general rule: separate NCEs should be claimed in separate patents
 - metabolites and pro-drugs
 - sameness issue: isoforms, homologs, racemics
 - sameness issue: genus and species claims
 - active moiety rule for salts and esters: Dr. Reddy’s case

- Bundling of Claims

- general rule: bundle as many claims as possible
- PTO restriction requirements and rejoinder
- composition vs. method claims: “penny wise ...”
- multiple uses and separate NDAs

- One patent per RRP

- general rule: longest and strongest – scope, term, ownership
- composition v. method
- joint ventures and multiple petitions
 - PTO rules on multiple petitions

- Special situations

- Orphan indications v. “first permitted commercial marketing” rule

- metabolites drafted as method claims

- bootstrapping of claims

- combination products: Class I/II device claims with new drug

- new veterinary use of old drug

D. Orange Book Practice and 271(e)(2) Litigation

1. Stakes are high - \$60 Billion in drug sales coming off patent between 2004 and 2008
2. OB listing of patents (drugs only)
 - Purpose is to provide notice to generics
 - NDA applicant shall file patent which claims a method of using the drug and with respect to which a claim of infringement could reasonably be asserted...
 - FDA listing is ministerial but it cannot act arbitrarily

3. 271e2: Filing of ANDA or 505(b)(2) is an (artificial act) of infringement “ if the purpose is to obtain approval ... to engage in the commercial manufacture, use or sale of a drug ... before the expiration of such patent.”

4. Generic certification requirements to FDA; Notice to NDA holder and patentee
 - Paragraph I – patent information has not been filed
 - Paragraph II – patent has expired
 - Paragraph III – date patent will expire
 - Paragraph IV – such patent is invalid or will not be infringed by the manufacture use or sale of the drug for which the application is submitted

5. “Section viii” statement for patented uses not sought by generic

- Notice to NDA holder and patentee not required
- For single indication drugs FDA cannot act arbitrarily under APA

6. Procedures following Paragraph IV notice

- NDA holder and/or patentee have 45 days to file suit under 271(e)(2)
- Automatic 30 month stay of FDA approval

7. “Gaming” the Orange Book

- Evergreening and off label patents

- Inducement cannot be brought under 271(e)(2)
 - WL v. Apotex (Fed Cir. 2003); Allergan v. Alcon (Fed Cir. 2003)

8. FDA OB reforms (8/18/2003)

- Listing reforms
 - polymorphs
 - product by process patents
 - packaging patents
 - metabolites
 - intermediates
 - MOU patents
- 30 Month Stay rules – one per NDA per generic drug only for patents filed prior to generic filing
- Patent submission requirements

9. Medicare Modernization Act (2003)

- Court decision for lifting 30 month stay is district court
- DJ available if no suit in 45 days after Paragraph IV notice
- Counterclaims allowed for OB delisting
- 180 day generic exclusivity forfeitures

10. OB litigation in general

- Duty of good faith in filing Paragraph IV notice and willful infringement
- Duty to inform patentee of changes in ANDA
- FTC actions – patent misuse (Buspar, Paxil); OB misuse (Tiazac); pioneer collusion with first generic to file

E. Safe Harbor

1. Statutory requirements

It shall not be an act of infringement to make, use, offer to sell within the US or import into the US a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal Law which regulates the manufacture, use or sale of drugs or veterinary biological products.

2. Legislative purpose – generic testing of drugs for bioequivalence

- Lilly v. Medtronic (S. Ct. 1990) – § 271(e)(1) in symmetry with § 156
- Abtox (Fed Cir. 1997) – symmetry not required

3. Current test used by court (Intermedics (N.D. Cal 1991))

It is reasonable, objectively, ... to believe there was a decent prospect that the use in question, would contribute (relatively directly) to the kinds of information that was likely to be relevant in the process by which the FDA would decide whether to approve the product? If the answer is yes, it should not matter whether ... FDA approval could be secured ... without the information in question.

4. Case law – focus on “reasonably related” – activities within safe harbor

- Using clinical trial data to raise investment capital
- Displaying products at trade shows

- Conducting consumer response studies
- Selling to foreign clinical investigators
- Demonstrations of product at conferences
- Disseminating data to journalist and inventors
- Publishing articles
- Arranging for overseas manufacture and importation
- Manufacturing sufficient quantities for an inventory
- Sales at cost to IND/IDE holder

5. Case Law – activities outside Safe Harbor

- Performances of an agreement to develop product on a commercial scale
- Substantial stockpiling in preparation to market when FDA approves drug
- Preparation of a foreign application
- Activities related to foreign marketing
- Shipment of product abroad to regulatory agencies
- Shipments to foreign investigators
- Sham INDs
- Activities related to drug discovery – *Integra v. Merck* (Fed Cir . 2003)

6. *Integra v. Merck* (Fed Cir. 2003)

- How far “upstream”- does safe harbor extend?
- The invention – basic RGD sequence (polypeptide) that binds to a cell receptor
- Infringing activity – search for derivative polypeptide that binds to certain receptor to inhibit angiogenesis (tumor growth)
- District Court – no safe harbor; \$15 million in damages
- Federal Circuit – safe harbor does not cover research tools and screening patents used to discover/investigate new drugs.

- Issues raised
 - pioneer drugs v. generics
 - preclinical v. clinical activities
 - drug discovery v. development
- Safe Harbor test post – Integra
 - good faith drug development
 - activity likely to generate information related to “safety and effectiveness approval processes”
- Reach through royalties – problem areas
 - reasonableness standard before infringement occurs
- Hatch-Lieberman
 - PTE for biodefense countermeasures