Streamlining Development and Approval Processes for 505(B)(2) NDAs

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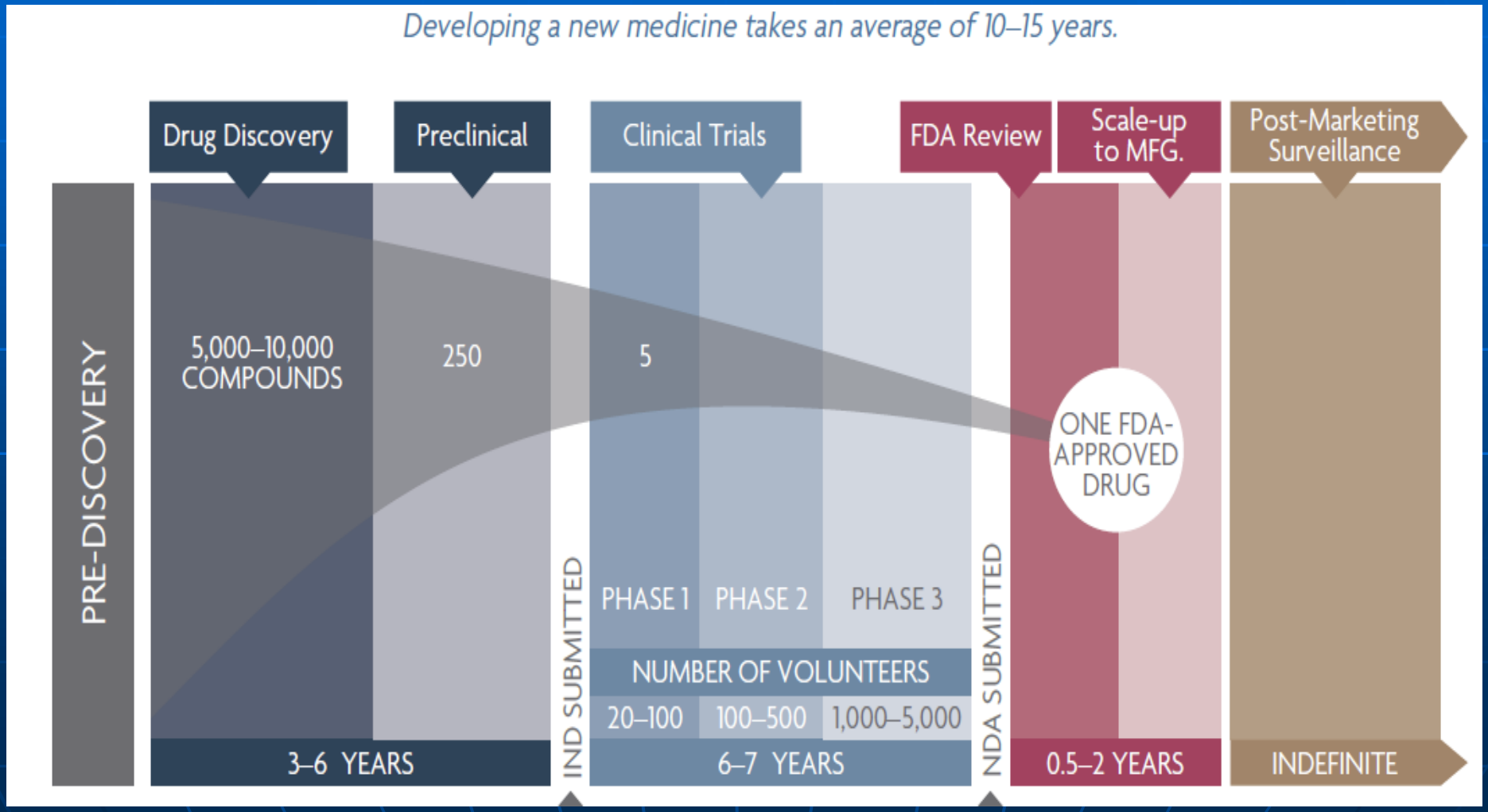
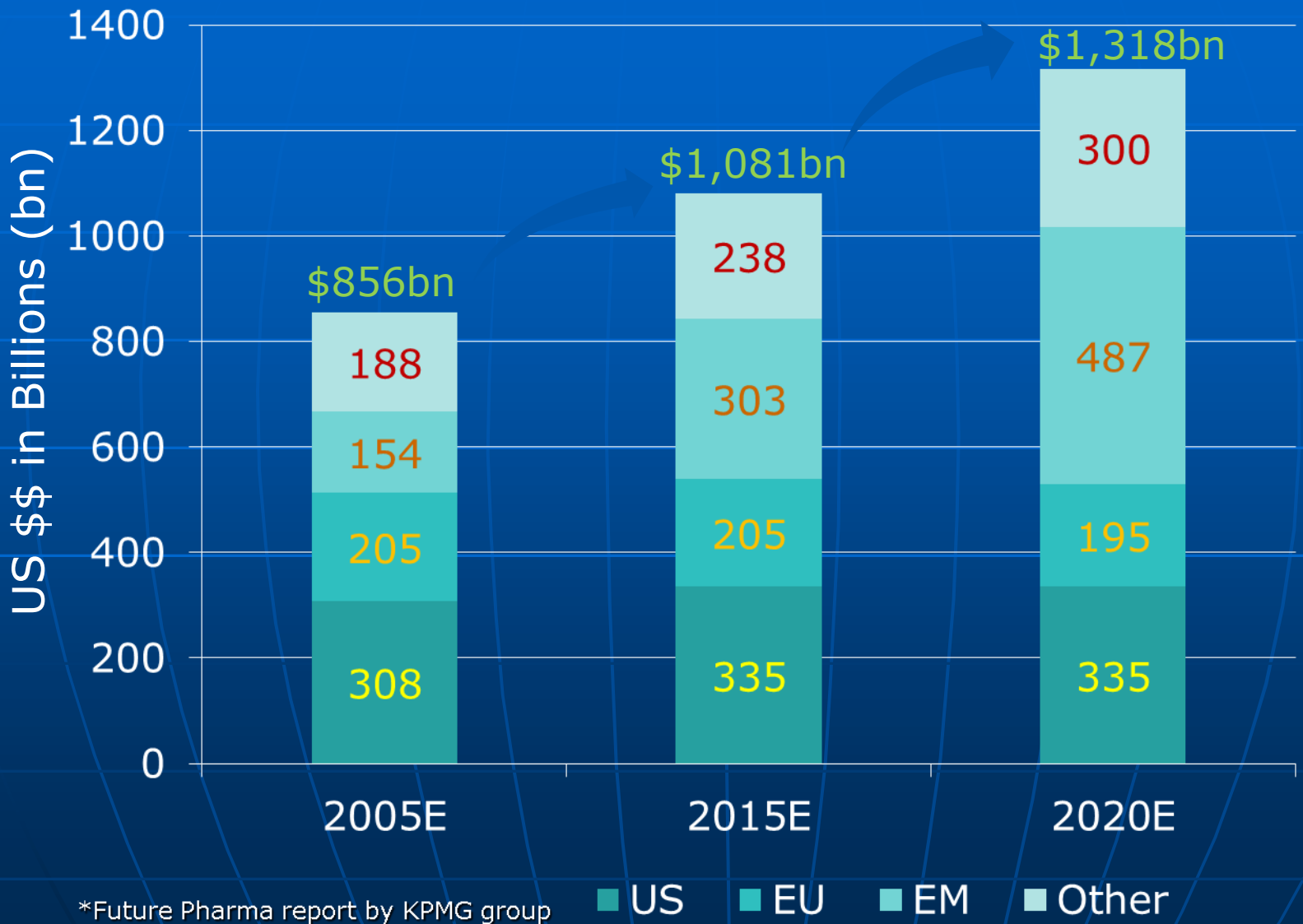
Drug Development, Review and Approval Processes



Pharma Industry Revenue Growth by Major Geographies* (2010 to 2020)



*Future Pharma report by KPMG group

505(j) Abbreviated NDA

- 505(j) – Abbreviated NDA (ANDA): ANDAs are submitted for drug products in which the approval of a **generic** drug is based on demonstrating comparability to an innovator drug (RLD) in the US:
  - Identical in active ingredients(s)
  - Identical in dosage form
  - Identical in strength
  - Identical in route of administration
  - Identical in conditions of use, labeling, performance

- Applications are "abbreviated" as they generally do not include preclinical or clinical data to establish safety and efficacy. Instead, they need to demonstrate BE to innovator product.

505(b)(1) NDA

- 505(b)(1) - Full NDA: An application that contains complete reports of investigations of safety, effectiveness, quality of drug product:
  - Used for new chemical entities
  - Studies conducted by the innovator
  - Requires complete reporting of
    - Non-clinical pharmacology/toxicology
    - Clinical pharmacology
    - Clinical investigations proving safety and efficacy
    - Quality (Chemistry, manufacturing, and controls)

505(b)(2) NDA

- 505(b)(2): Intended to encourage innovation in drug development without requiring duplicative studies (safety, efficacy) of previously known information (21CFR314.54)

- Applicant must include reports of safety and effectiveness where at least some of the information required for approval is from studies "not conducted by or for the applicant/ sponsor, and for which the applicant has not obtained a right of reference"
  - *Not a completely new product*
  - BE to a previously approved product not relevant/required
  - Documents previously reported non-clinical and clinical data
  - Approval requires clinical data to support difference(s) and/or changes to approved products.

505(b)(2) Business Drivers

- Losses in patent protection in major western markets
- $120 billion loss in product revenue during 2010-2015 due to losses in patent protection
- Significant competition and growth in generic pharmaceutical sales
- Higher regulatory hurdles, greater uncertainty for product approval
- Declining new (505b1) product approvals
- Growing safety and AE reporting requirements by regulatory agencies

505(b)(2) NDA Applications

- Change(s) that support submission of a 505(b)(2) NDA can include:
  - Dosage form (e.g. tablets to transdermal patches)
  - Strengths – higher or lower
  - Route of administration
    - oral to transdermal or iontophoretic delivery
    - Oral to IV
    - Immediate release to extended release
    - Lotion to foam, etc
  - Dosing regimen
    - Twice daily to once a day
  - API switch (new salt, ester, complex, racemate, enantiomer, combinations, etc)

505(b)(2) NDA Applications

- Change(s) that support submission of a 505(b)(2) NDA can include (cont'd):
  - Formulation changes excluding 505(j)
  - Substitution of an active ingredient in a combo product
  - Different active ingredient (such as a different salt)
  - Indications – adding new indications
  - Rx/OTC indication switches
  - New combination – combining two or more actives approved individually
  - Drug-device combination products
  - Naturally derived or recombinant active ingredient
  - Bioinequivalence.

Market Exclusivity - 505(b)(2)

- 505(b)(2) applications may be granted *exclusivity* under certain conditions:
  - ✓ 3 years *Waxman-Hatch* exclusivity if one or more of the clinical investigation(s), other than BA/BE studies, were conducted or sponsored by the applicant - blocks approval of other pending 505b2 NDAs regardless of filing date
  - ✓ 5 years exclusivity if the 505b2 NDA is for a new chemical entity - blocks filing of competing 505b2 NDAs.
- Orphan drug exclusivity possible
- Pediatric exclusivity possible.

Approved 505(b)(2) – 100s; Examples

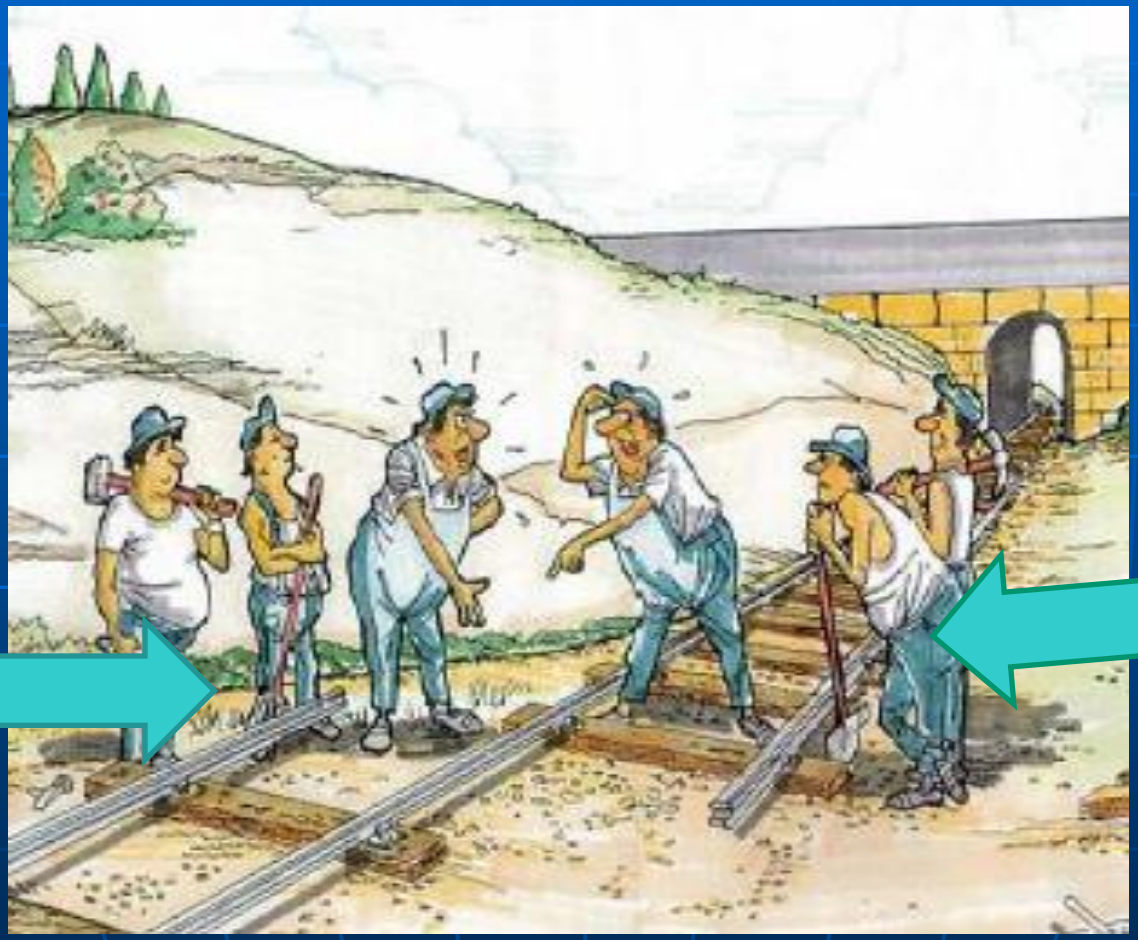
- Zyrtec D (cetrizine and pseudoephedrine combo) – new combination product
- Zecuity (sumatriptan iontophoretic transdermal system) – new drug-device combination product
- Duraclin (clonoidine) – new formulation and route
- Sclerosol (sterile talc) – new molecular entity
- Children's Advil Cold Suspension – new formulation
- Methylphenidate Oral Solution – new dosage form
- Methylphenidate Chewable Tablets – new dosage form
- Doxil (doxorubicin) Liposomal Injection – new dosage form
- Altocor (lovastatin) ER Tablets – new dosage form
- Vandazole (metronidazole) Vaginal Gel
- Forticol (calcitonin-salmon) Nasal Spray
- Luxiq Foam (betamethasone) – new delivery tech
- Canasa (mesalamine) Suppositories – new delivery tech.

	505(b)(1)	505(b)(2)	505(b)(2) combo*
Phases 1-3 development time	5–10 years	2-4 years	2–4 years
Estimated development costs	$800M-$2B	~$10M-$100M	
Preclinical/tox data – single and repeat dose tox data (1 mo, 6 mo, 9 mo)	Always	Usually	
Carcinogenicity studies – short, medium and long term (to 2 yrs)	Always	Usually	
Chronic and reproductive tox (6-9 mo), genotox, local irritation, tolerance studies	Always	Usually	
BA and comparative BA data	Always	Always	
Pharmacokinetic data – PK, PD data	Always	Always	
Clinical trials (Ph I-III) safety and efficacy data, bridging studies as necessary	Always	Always	
API characterization, stability, stress-studies, photo-stability, MLT data	Always	Usually	
Drug product stability, stress-studies, photo-stability, MLT data	Always	Always	
FDA Meetings (preIND, EOPII, preNDA)	Always	Usually helpful	
Approval time period	10 mo / 6 mo	10 mo (std); 6 mo (priority)	
Exclusivity *additional requirements for drug-devices	Always	3 or 5 years	

Streamlining 505(b)(2) Review and Approval Processes

- Nonclinical summary (Mod 2) and nonclin study reports (Mod 4) including the following information be reevaluated/eliminated:
  - Preclinical/tox data - single and repeat dose (1, 6, 9 mo)
  - Carcinogenicity data: short, medium, long term (2 yrs)
  - Chronic dermal tox data
  - Chronic repeat dermal tox data
  - Carcinogenicity potential and local tolerance data
  - Reproductive tox data (6-9 mo), genotox data
- API data requirements when an identical API has been approved previously:
  - characterization, stress-studies, photo-stability, MLT data
  - API stability data, impurities characterization, etc
- Hold EOPII and pre-NDA/BLA meetings with FDA to align on submission data, bridging studies, stability data etc.
- Given the duplication of information, FDA should consider shortening the review periods to 6 months for standard and priority reviews.

Goal Is To Avoid This At All Costs



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