Notes on the 2004 to 2009 United States Food and Drug Administration
Approval of New Molecular Entities (NMEs)

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Molly Redfield Ward[1]
Knowledge Ecology International

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Introduction

One of the United States Food and Drug Administration (FDA) most important responsibilities is the regulation of prescription medicines, particularly the evaluation of the safety and efficacy of new prescription drugs and vaccines. New prescription drugs or vaccines are regulated under procedures for a New Drug Application (NDA), or a Biologic License Application (BLA).

An NDA consists of the drug's entire history, from formulation ingredients, to the results of animal and human testings, the biological reaction of the body and the manufacturing, as well as processing and packaging systems. It must provide enough evidence of the pharmaceutical product's safety and efficacy to receive marketing

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approval by the FDA.[2] The regulatory approval for an NDA is provided by the FDA's Center for Drug Evaluation and Research (CDER).

The regulatory review of biological drugs, vaccines or recombinant proteins used in medical treatments is similar in some respects to the process for a pharmaceutical drug. The BLA is the request to the FDA to market a biological compound, providing a detailed history of the fundamental chemistry, medicinal effects, pharmacology as well as the manufacturing process. The regulatory approval of a BLA, however, is provided by the FDA's Center for Biologics Evaluation and Research (CBER).[3]

Each year hundreds of regulatory applications concerning prescription drugs and biological compounds are considered by the FDA, including those seeking approval for new formulations or uses of existing compounds, as well as the approval of completely new compounds, called new molecular entities (NME)s. A NME is defined by the FDA as follows:

> ...an active ingredient that has never before been marketed in the United States in any form.[4]

This classification is a particularly important category of new medicines. Tracking the number and nature of such products is an important measure of the benefits of public and private sector investments in biomedical research and development, and their impact on health outcomes. The review process of the NME is important to providing additional insight into the nature of the compound relative to existing drugs on the market.

The purpose of this document is to gain a better understanding of the nature of the new molecular entities that were approved between 2004 and 2009. The NMEs were described in terms of the following characteristics:

- FDA Review Classification, including designation under the Orphan Drug Act
- Indications for specific diseases and conditions
- Prevalence of indicated disease in high and low income countries

FDA Review Classification

The FDA defines a Priority Review (P) as:

> drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A Priority Review means that the time it takes FDA to review a new drug application is reduced. The goal for completing a Priority Review is six months.[5]

Advances worthy of a Priority Review are demonstrated by:

> evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of patient willingness or ability to take the drug according to the required schedule and dose; or evidence of safety and effectiveness in a new sub-population, such as children.[6]

The FDA defines a Standard Review (S) as:

2 Drugs@FDA Glossary of Terms
3 Ibid
4 Drugs@FDA Glossary of Terms
5 Ibid
6 Ibid

a drug that offers at most, only minor improvement over existing marketed therapies[7]

Orphan classification (O) is defined as an entity that treats less than 200,000 Americans, as defined under the Orphan Drug Act of 1983.[8] The orphan designation does not indicate what FDA review classification the NME will receive.

This data was collected from FDA's New Molecular Entity Drug and New Biologic Approvals report.[9]

Indications for specific diseases, conditions or treatment function

All of the NMEs were further classified into 27 different categories based on the function or structure of the compound, listed here:

Table 1: Category for Product Disease or Function

1. Addiction	15. Growth Hormone
2. AIDS	16. Heart Disease
3. Anti-fungal	17. Hepatitis B
4. Antibiotic	18. Immunosuppressants
5. Antihemorrhagics	19. Kidney
6. Arthritis	20. Malaria
7. Cancer	21. Miscellaneous
8. Diabetes	22 Over Active Bladder
9. Diagnostic Aid	23. Pain
10. Dispersing Enhancement	24. Parkinson's Disease
11. Diuretics	25. Psychological
12. Eye	26. Respiratory
13. Gastrointestinal	27. Skin Condition
14. Genetic Condition	

Drugs for specific health problems were focused on initially, such as drugs for AIDS, cancer, diabetes, heart disease, kidney disease, malaria, Parkinson's disease, and psychological conditions, as well as new antibiotics. The remaining classifications emerged from the drugs that did not fall into the above categories. A dispersing enhancement is a drug that aids in the absorption and distribution of another agent. Diagnostic aids are used with imaging machines to improve the visualization of lesions, tumors or other abnormal formations on internal structures. Three drugs were classified twice, as they treated conditions for both heart disease and kidney disease. The duplicates in classification are noted in the title of the graphs (N=145 or N=148).

Distribution of indicated disease in high and low income countries

The NMEs were also assigned a value based on the prevalence of the disease in lower income countries, using the WHO's Type I, Type II and Type III classification, quoting here from the WHO CIPIH:

- **Type I disease.** Diseases that are incident in both rich and poor countries, with large numbers of vulnerable population in each. Examples of communicable diseases include measles, hepatitis B, and

7 Ibid
8 Ibid
9 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121136.htm

Haemophilus influenzae type b (Hib), and examples of noncommunicable diseases abound (e.g. diabetes, cardiovascular diseases, and tobacco-related illnesses).

- **Type II disease.** Diseases that are incident in both rich and poor countries, but with a majority of cases in poor countries. Type II diseases are often termed neglected diseases.

- **Type III disease.** Diseases that are those that are overwhelmingly or exclusively incident in the developing countries, such as African sleeping sickness (trypanosomiasis) and African river blindness (onchocerciasis). Type III diseases are often termed "very neglected diseases."[10]

Results

For the six year period of 2004 to 2009, there were a total of 145 NMEs approved by the FDA, of which 123 (86%) were pharmaceuticals and 22 (14%) were biologics.

The annual average of NMEs was 24.2, including 11.8 (49%) that received priority review status, and 7.3 (30%) that received designation as orphan products.

The percentage of orphan designations remained fairly stable throughout the years, ranging from 23% to 35%.

The percentage of priority reviews was high earlier in this time period, peaking at 75% in 2005 and dropping to 32% in 2009.

80% of the orphan reviews received priority reviews. Of the priority reviews, approximately 49% were for orphan drugs. Of the stand reviews, only 12% were for orphan drugs.

There is a downward trend in the number of priority approvals, and an upward trend for products receiving a standard review status applications continue to rise. The shift from priority to standard review status is an indication of a decrease in productivity.

FDA Review Classification

Table 2: NMEs by Year and FDA Review Classification

	2004	2005	2006	2007	2008	2009	Total	Average
Standard Review	15	5	12	10	15	17	74	12.3
Priority Review	21	15	10	8	9	8	71	11.8
Total NMEs	36	20	22	18	24	25	145	24.2
Orphan Designation	10	7	5	6	8	8	44	7.3
% priority	58%	75%	45%	44%	38%	32%		49%
% orphan	28%	35%	23%	33%	33%	32%		30%
% NDAs	86%	90%	82%	89%	88%	76%		85%
% BLAs	14%	10%	18%	11%	13%	24%		15%

10 *Public health, innovation and intellectual property rights: report of the Commission on Intellectual Property Rights, Innovation and Public Health.* Geneva, World Health Organization, 2006. The definitions are based upon this earlier report: *Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health*. Geneva, World Health Organization, 2001.

Figure 1: Distribution of New Molecular Entities

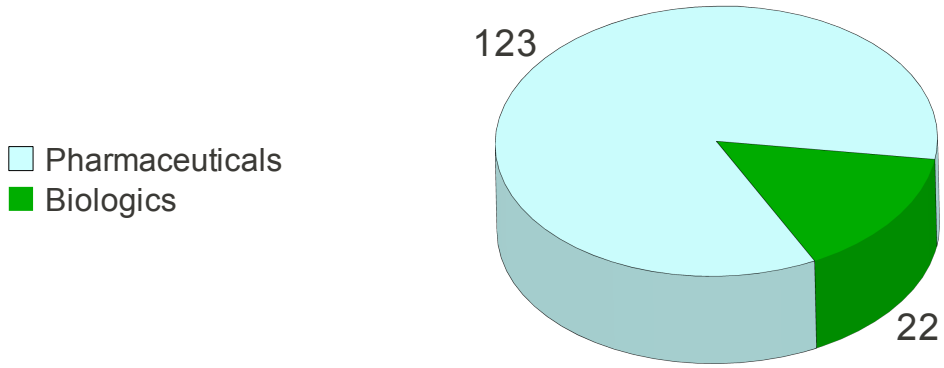


Figure 2: Priority and Orphan Reviews of New Molecular Entities

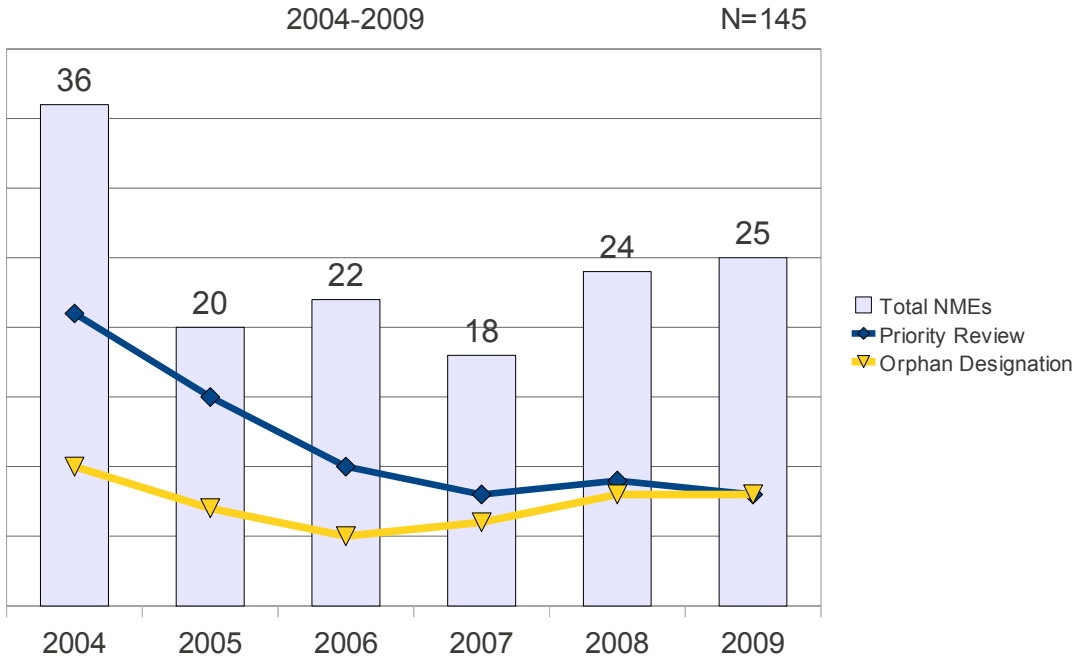
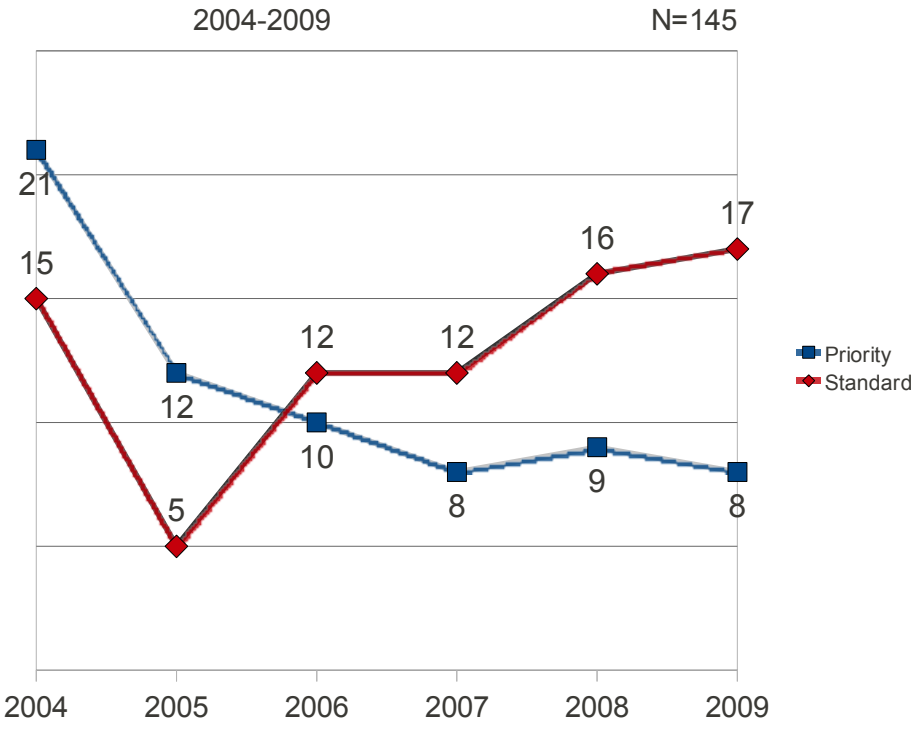


Figure 3: Review Classification by Year



Of the pharmaceuticals drug applications approved, 45% received priority reviews and 28% received orphan designation.

The highest percentage of priority reviews came in 2005 with 72% and the lowest came in 2009 with 26%, showing a downward trend similar to all priority reviews.

The percentages of drugs with orphan designations remained fairly stable, ranging from 17% to 33% throughout this period.

An average of 20.5 drugs were approved per year, of which 9.2 were priority review and 5.7 received orphan designation.

Table 3: New Drug Application Approvals by Year and FDA Review Class

	2004	2005	2006	2007	2008	2009	Total	Average
Standard Review	14	5	12	9	14	14	68	11.3
Priority Review	17	13	6	7	7	5	55	9.2
Total NDAs	31	18	18	16	21	19	123	20.5
Orphan Designation	10	6	3	5	6	4	34	5.7
% priority	55%	72%	33%	44%	33%	26%	45%	
% orphan	32%	33%	17%	31%	29%	21%	28%	

Of the biological license applications, 73% received priority review and 45% received orphan designation.

The percentages of biologics that received priority reviews was high, consistently above 50% and reaching 100% in 2005 and 2006.

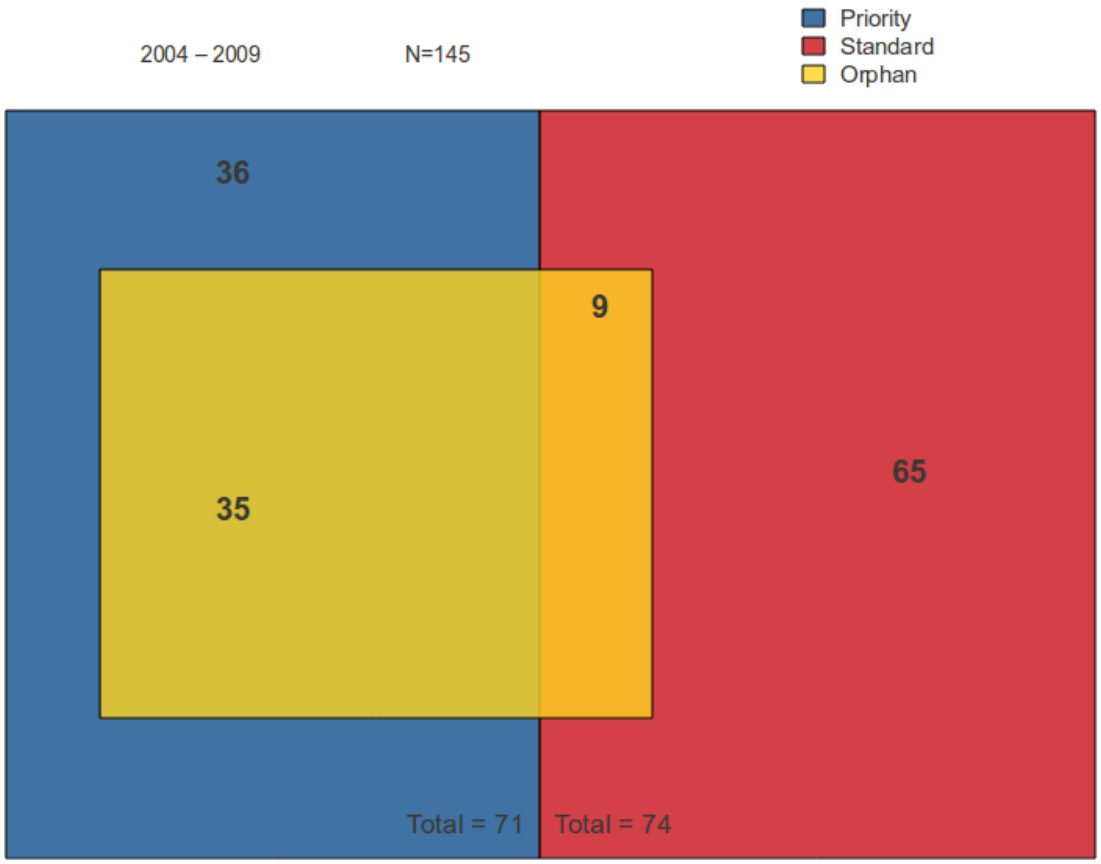
The percentage of orphan designations each year was additionally strong at either 50% or 67% for four of the six years. There was only one year with no orphan designations.

An average of 3.7 biologics were approved each year, of which 2.7 were priority reviewed and 1.7 were orphan designations.

Table 4: Biologic License Application Approvals by Year and FDA Review Class

	2004	2005	2006	2007	2008	2009	Total	Average
Standard Review	1	0	0	1	1	3	6	1.0
Priority Review	4	2	4	1	2	3	16	2.7
Total BLAs	5	2	4	2	3	6	22	3.7
Orphan Designation	0	1	2	1	2	4	10	1.7
% priority	80%	100%	100%	50%	67%	50%	73%	
% orphan	0%	50%	50%	50%	67%	67%	45%	

Figure 4: NMEs by FDA Classification



Categories for Diseases, Conditions and Treatments

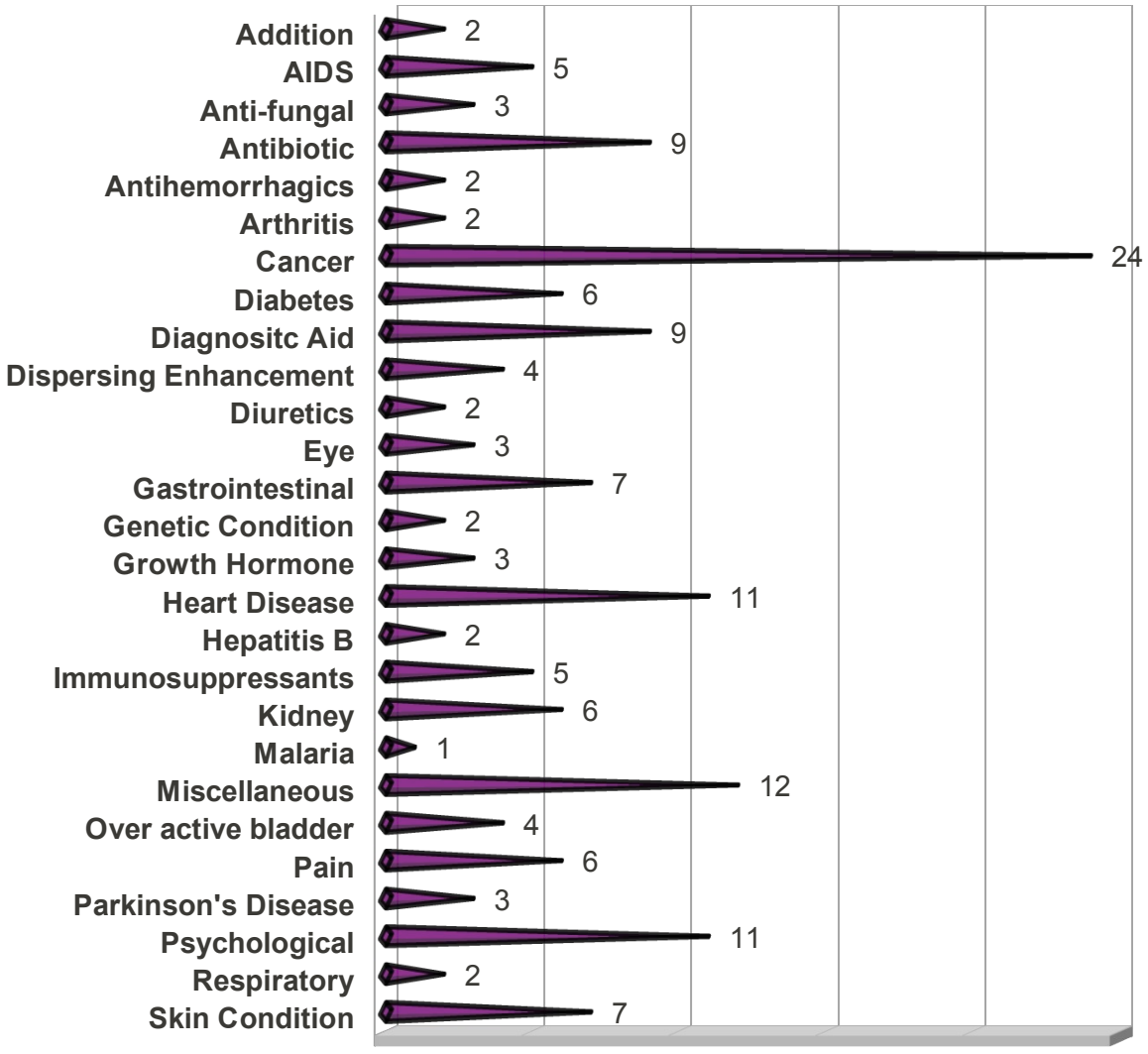
The greatest number of drugs approved under these classifications were for cancer, with 24 drugs approved during these six years. Drugs for psychological conditions and heart disease were also quite prominent with 11 drugs approved each. Drugs for neglected tropical diseases were disappointingly although not entirely unexpectedly low, as only one drug was approved during this time period – a product for malaria that had already been on the international market for several years.[11] The number of AIDS drugs was significant, with almost one new drug approved each year. The high number of new antibiotics approved is also notable, as it is an area of major concern in recent years due to the increasing resistance to existing antibiotics.

Table 5: Number of NMEs by Category of Disease or Function

Disease or Function	Number of NMEs
Malaria	1
Skin condition	2
Respiratory	2
Diuretics	2
Antihemorrhagics	2
Hepatitis B	2
Genetic condition	2
Arthritis	2
Addiction	2
Parkinson's disease	3
Growth hormone	3
Eye	3
Anti-fungal	3
Over active bladder	4
Dispersing enhancement	4
Immunosuppressants	5
AIDS	5
Pain	6
Kidney	6
Diabetes	6
Gastrointestinal	7
Diagnostic Aid	9
Antibiotic	9
Psychological	11
Heart disease	11
Miscellaneous	12
Cancer	24

11 The US registration of the malaria drug Coartem (Artemether; Lumefantrine 120) by Novartis was motivated by the new Priority Review Voucher (PRV) program. The PRV rewards the registration of neglected diseasses with a voucher that grants an expeedited regulatorty review to a separate product choosen by the holder of the voucher, that would otherwise have a standard review time.

Figure 5: New Molecular Entities by Categories of Disease or Function



There are important differences between the treatment categories with regard to FDA review classification. In looking at the percentage of approvals that received priority status:

- All 21 products approved for diabetes, diuretics, psychological or respiratory illnesses received a **standard review.**
- All 21 products approved for addiction, AIDS, antihemorrhagics, dispersing enhancements, genetic conditions, immunosuppressants and malaria received a **priority review.**
- Despite the often discussed need for new antibiotics, only 11% of the NMEs that were classified as antibiotics received a priority review classification, meaning the majority of new antibiotics provide only marginal benefits over existing regimens.
- Ten treatment categories had 33 percent or lower priority reviews.
- Twelve treatment categories had 67 percent or higher priority reviews.

Table 6: FDA Review Classification by Category of Disease or Function

Categories	Priority	Standard	Percentage of Priority Review	Orphan
Diabetes	0	6	0%	0
Diuretics	0	2	0%	0
Over active bladder	0	4	0%	0
Psychological	0	11	0%	2
Respiratory	0	2	0%	0
Antibiotic	1	8	11%	1
Kidney	1	5	17%	1
Gastrointestinal	2	5	29%	3
Diagnostic Aid	3	6	33%	1
Parkinson's disease	1	2	33%	1
Miscellaneous	5	7	42%	5
Heart disease	5	6	45%	3
Arthritis	1	1	50%	0
Hepatitis B	1	1	50%	0
Skin condition	1	1	50%	1
Anti-fungal	2	1	67%	0
Eye	2	1	67%	0
Growth hormone	2	1	67%	3
Pain	4	2	67%	0
Cancer	19	5	79%	14
AIDS	5	0	100%	0
Addiction	2	0	100%	0
Antihemorrhagics	2	0	100%	2
Dispersing enhancement	4	0	100%	0
Genetic condition	2	0	100%	2
Immunosuppressants	5	0	100%	4
Malaria	1	0	100%	1

Figure 6: Percentage of Approvals Receiving Priority Status, by Disease or Function Category

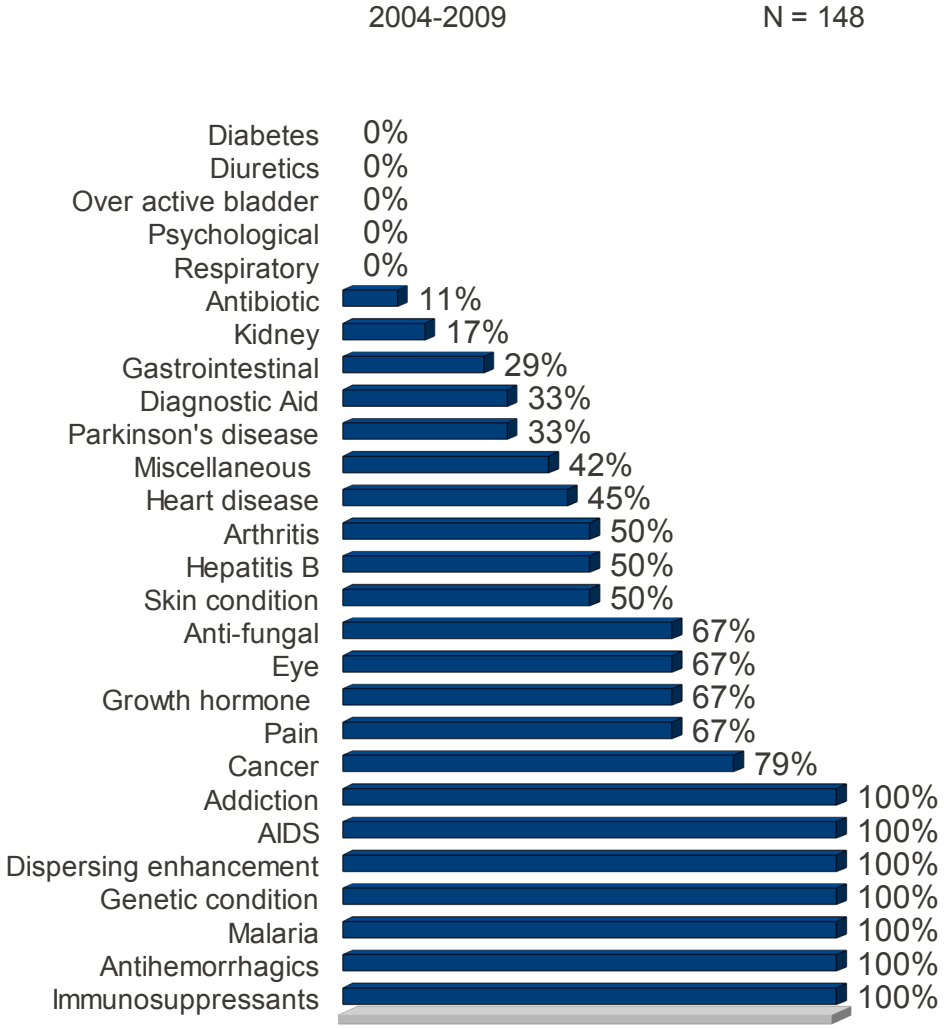
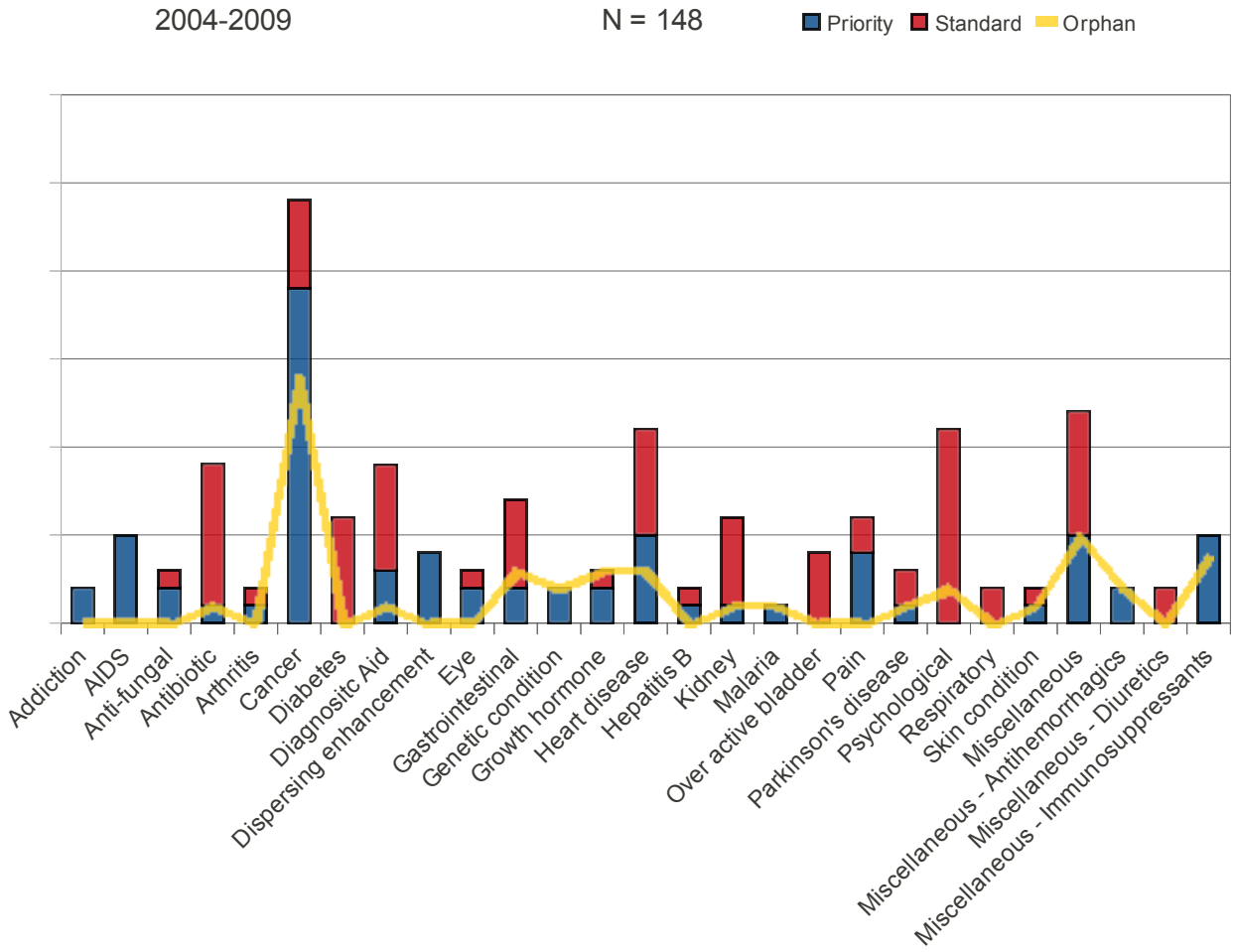


Figure 7: FDA Review Classification by Category of Disease or Function



WHO Disease Types for high and low income countries

Of the 145 NMEs approved by the FDA between 2004 and 2009, 139 were for Type I diseases – more than 90% for approvals in every year.

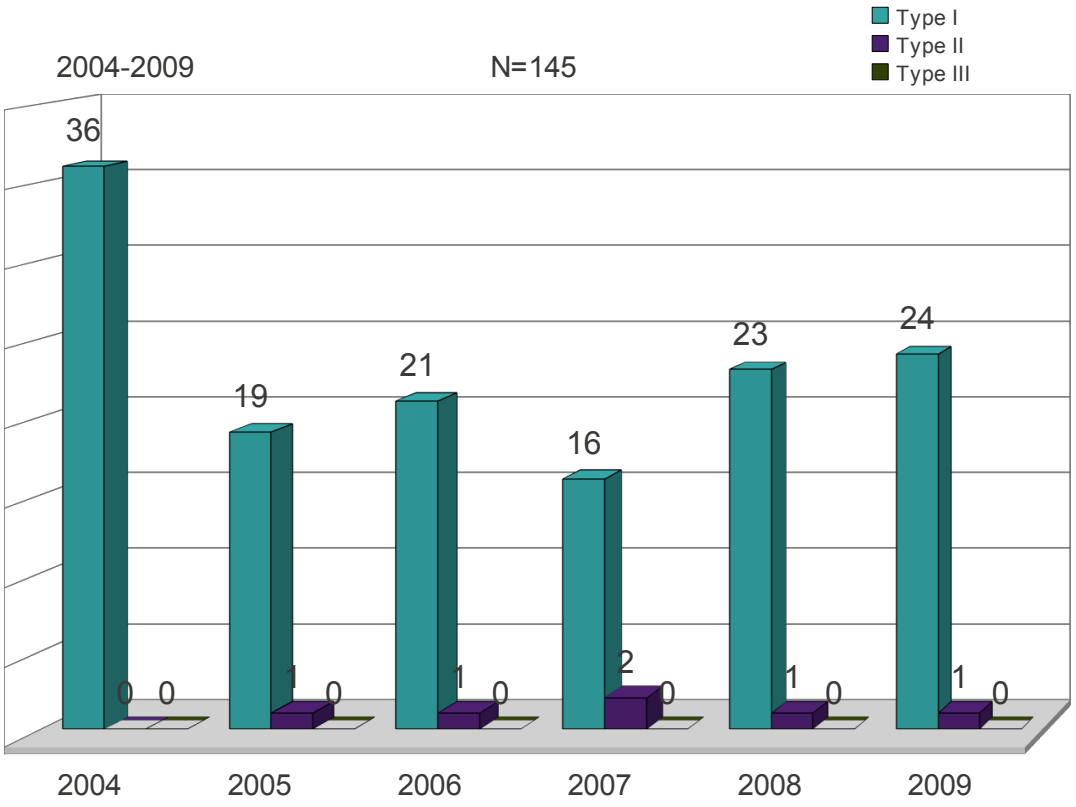
Just six Type II disease products were approved over all, one each year in 2005, 2006, 2008 and 2009, none in 2004 and two in 2007.

There were no Type III drugs approved.

Table 7: FDA NME approvals by WHO Disease Type, by Year

Year	Type I	Type II	Type III
2004	36	0	0
2005	19	1	0
2006	21	1	0
2007	16	2	0
2008	23	1	0
2009	24	1	0

Figure 8: FDA NME Approvals by WHO Disease Type, by Year



Of the Type I diseases, 65 were priority reviews and 74 were standard review. There were a total of 43 orphan drugs for Type I diseases.

Of the Type II diseases, all 6 were priority review. Only 1 was an orphan drug.

There were no Type III diseases.

Table 8: FDA Review Classification by WHO Type I-III Disease Category

Disease Type	Priority	Standard	Orphan
Type I	65	74	43
Type II	6	0	1
Type III	0	0	0

Figure 9: FDA Review Class by WHO Disease Type