1.

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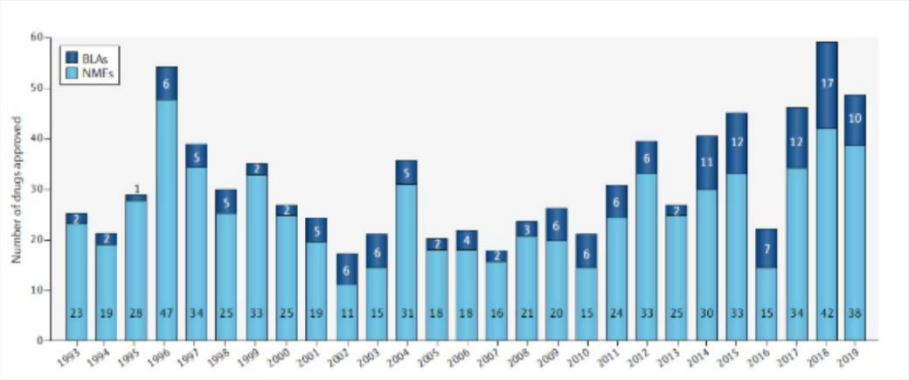
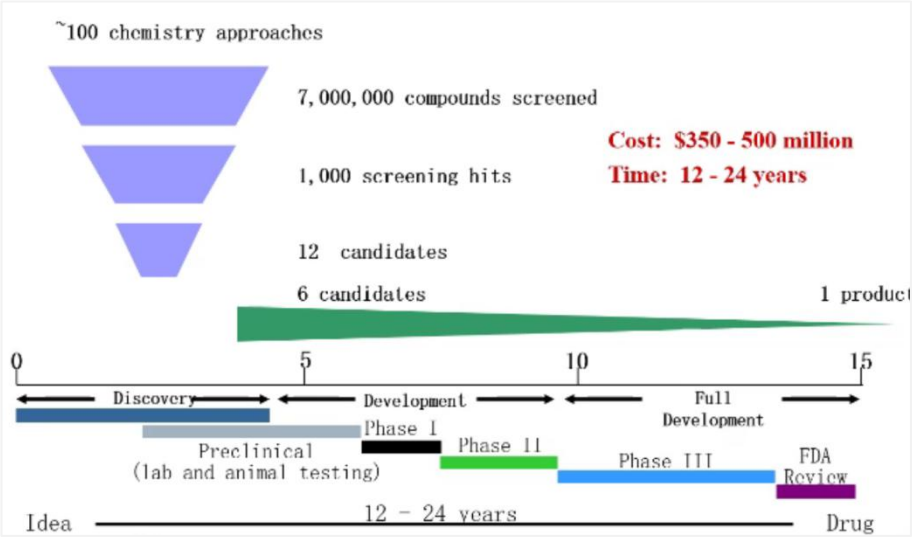
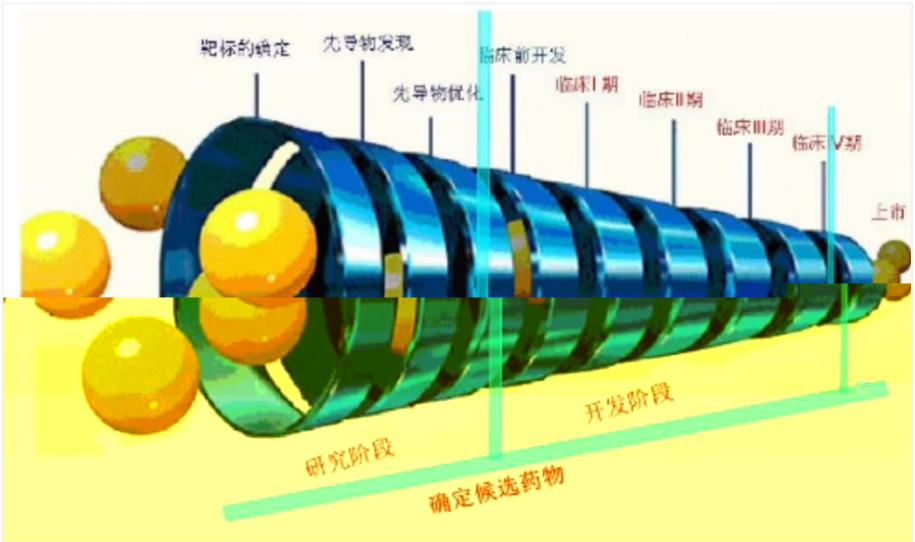

BLAs
NMFs
Number of drugs approved
0
10
20
30
40
50
60
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
23 19 28 47 34 25 33 25 19 11 15 31 18 18 16 21 20 15 24 33 25 30 33 15 34 42 38
2 2 1 6 5 5 2 2 5 6 6 5 2 4 2 3 6 6 6 6 2 11 12 7 12 17 10


~100 chemistry approaches
7,000,000 compounds screened
Cost: $350 - 500 million
1,000 screening hits
Time: 12 - 24 years
12 candidates
6 candidates
1 product
0
5
10
15
Discovery
Development
Full Development
Phase I
Preclinical
(lab and animal testing)
Phase II
Phase III
FDA Review
Idea
12 - 24 years
Drug


靶标的确定
先导物发现
先导物优化
临床前开发
临床I期
临床II期
临床III期
临床IV期
上市
研究阶段
开发阶段
确定候选药物

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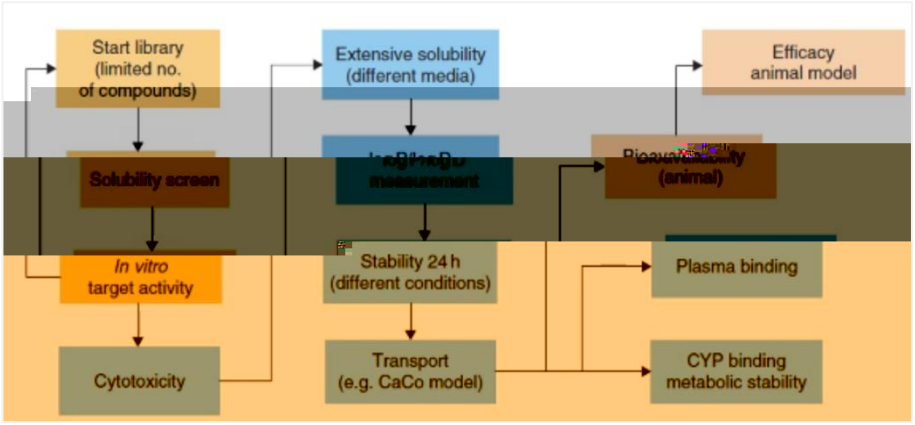
Start library
(limited no.
of compounds)
Extensive solubility
(different media)
Efficacy
animal model
Solubility screen
measurement
(animal)
In vitro
target activity
Stability 24 h
(different conditions)
Plasma binding
Cytotoxicity
Transport
(e.g. CaCo model)
CYP binding
metabolic stability

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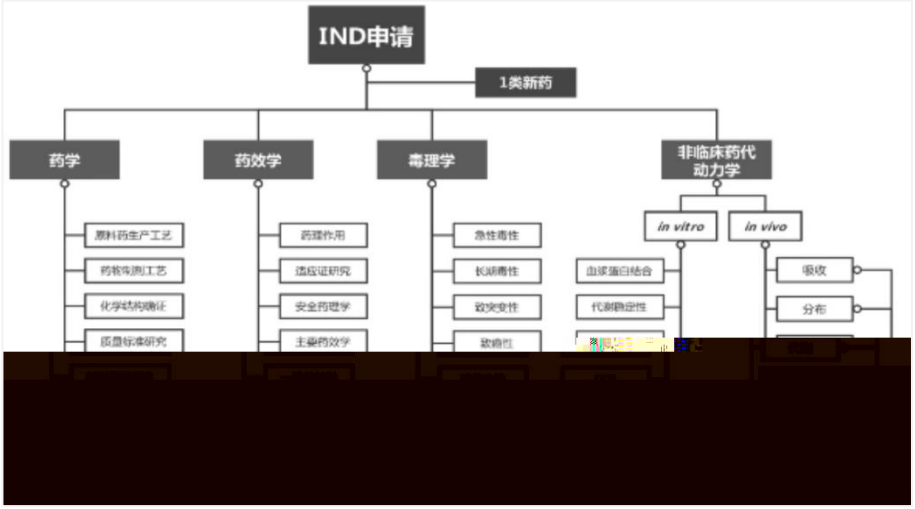
IND申请
1类新药
药学
药效学
毒理学
非临床药代动力学
原料药生产工艺
药物检测工艺
化学结构确证
质量标准研究
药理作用
适应证研究
安全药理学
主要药效学
急性毒性
长期毒性
致突变性
致癌性
in vitro
in vivo
血浆蛋白结合
代谢稳定性
吸收
分布

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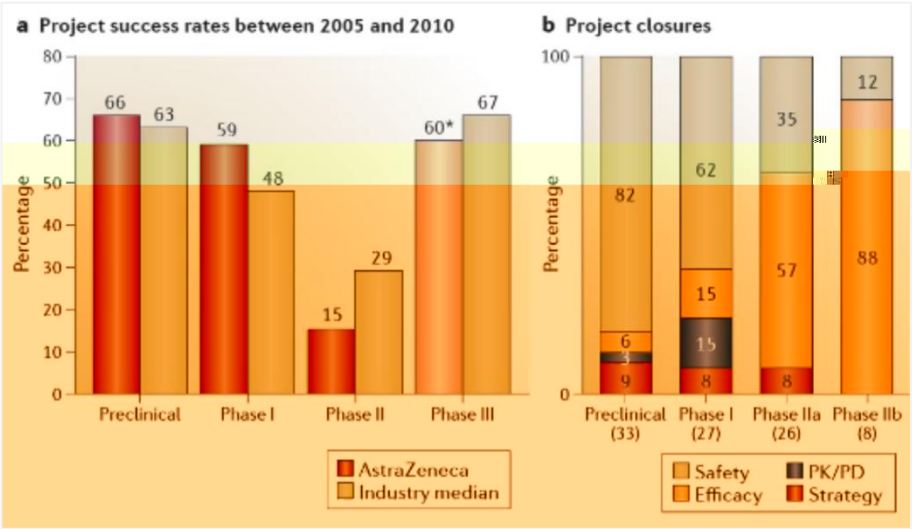
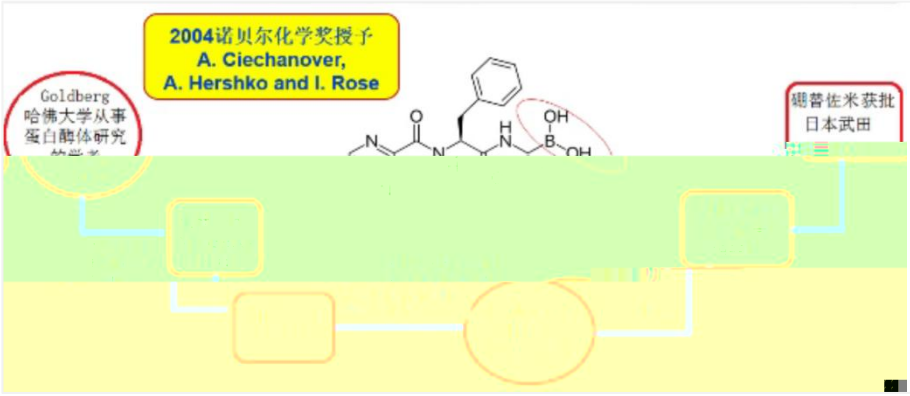
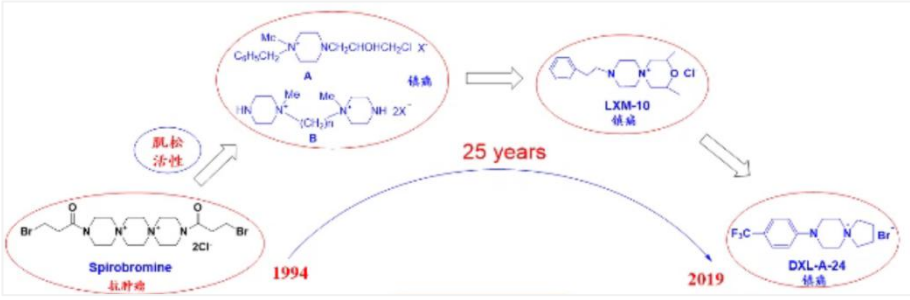
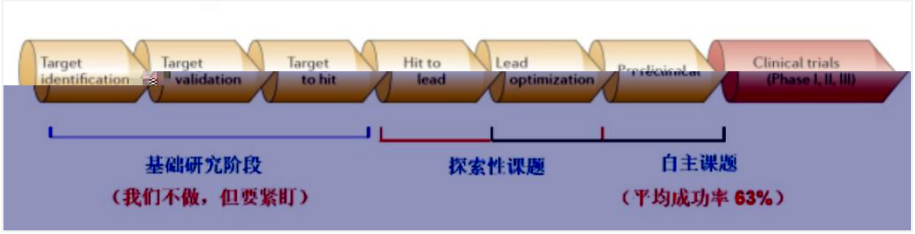

a Project success rates between 2005 and 2010
Percentage
80
70
60
50
40
30
20
10
0
66
63
59
48
15
29
60*
67
Preclinical
Phase I
Phase II
Phase III
AstraZeneca
Industry median
b Project closures
Percentage
100
0
82
6
3
9
62
15
15
8
35
57
8
12
88
Preclinical (33)
Phase I (27)
Phase IIa (26)
Phase IIb (8)
Safety
Efficacy
PK/PD
Strategy


2004诺贝尔化学奖授予
A. Ciechanover,
A. Hershko and I. Rose
Goldberg
哈佛大学从事
蛋白酶体研究
硼替佐米获批
日本武田


A
镇痛
B
LXM-10
镇痛
肌松
活性
25 years
Spirobromine
抗肿瘤
1994
2019
DXL-A-24
镇痛


Target identification
Target validation
Target to hit
Hit to lead
Lead optimization
Preclinical
Clinical trials (Phase I, II, III)
基础研究阶段
（我们不做，但要紧盯）
探索性课题
自主课题
（平均成功率 63%）