the same but not the same

a brief history of generic drugs

Jeremy A. Greene, MD, PhD

Departments of Medicine and the History of Medicine, JHUSOM

ANDA FILING CHECKLIST

(CTD or eCTD FORMAT)

FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA:
APPLICANT:
RELATED APPLICATION(S):

DRUG NAME:
DOSAGE FORM:

LETTER DATE:
RECEIVED DATE:

☐ P-IV
☐ FIRST GENERIC
☐ EXPEDITED REVIEW REQUEST: MaPP 5240.1 or MaPP 5240.3 (Approved/Denied)
☐ PEPFAR
☐ PET

Electronic or Paper Submission: Type II DMF#

BASIS OF SUBMISSION:
NDA/ANDA:
FIRM:
RLD:

**Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to these reviewer(s) instead of the default random team(s).

Review Team:

CHEM Team ☐ Activity	Bio Team: ☐ Activity
RPM: ☐ FYI	Bio PM: ☐ FYI
CHEM PQRPM: ☐ FYI	Clinical Review: (No) ☐ Activity
CHEM Team Leader: ☐ No Assignment Needed in DARRTS	DMF Review Team Leader: ☒ FYI
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SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):	

Regulatory Reviewer: Date:	Recommendation: ☐ FILE ☐ REFUSE to RECEIVE

Comments:
Therapeutic Code:
On Cards:
Archival copy:
Sections:

MODULE 1: ADMINISTRATIVE

		COMMENT(S)
1.1	**1.1.2 Signed and Completed Application Form (356h)** (Rx/OTC Status) (original signature) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **** PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 20: MANUFACTURING STEPS AND/OR TYPE OF TESTING****	
1.2	**Cover Letter**	
1.2.1	**Form FDA 3674** (PDF)	
*	**Table of Contents** (paper submission only)	
1.3.2	**Field Copy Certification** (N/A for E-Submissions) (original signature)	
1.3.3	**Debarment Certification-GDEA** (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) 2. List of Convictions statement (original signature)	
1.3.4	**Financial Certification:** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Disclosure Statement (Form FDA 3455)	
1.3.5	**Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **Patent Certification** 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: State marketing intentions?	
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient b. Type II DMF# c. Type III DMF authorization letter(s) for container closure 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	
1.12.4	**Request for Comments and Advice - Proprietary name requested** If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing: 1. Yes 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	**Basis for Submission** NDA#: Ref Listed Drug: Firm: **ANDA suitability petition required?** If Yes, provide petition number and copy of approved petition **ANDA Citizen's Petition Required?** If Yes, provide petition number and copy of petition	

Marvin Seife

Marvin Seife

John Dingell

generic scandal!

Marvin Seife

John Dingell

generic scandal!

generic scandal!

The Bungled Punishment of Prisoner Seife

MARVIN SEIFE
..."look at what they've done to me"

By Phil McCombs
Washington Post Staff Writer

THREE RIVERS, Tex.—The story of Marvin Seife's fall from the heights of bureaucratic power in Washington to the steel cot of a Texas prison cell, and thence to the critical care unit of a hospital where he hovers near death, is at once a great personal tragedy, an apt Washington morality tale and proof on a near-Sophoclean scale—should anyone need reminding—that there is absolutely, positively no such thing as a free lunch.

Seife's decline brought him to the federal prison here, an arrangement of beige cinder block and concertina wire sprawled across green rolling hills under the vast South Texas sky. It was here on Feb. 10 that the physician and former Food and Drug Administration official, who is considered one of the fathers of the generic drug boom, turned himself in to serve five months for perjury after a jury found he'd lied about lunches he'd had with industry representatives. At the age of 67, he became inmate No. 27472-037.

It was here that they threw him into solitary for 12 days because the Federal Bureau of Prisons misplaced his paperwork—including a letter from his doctor warning that Seife was prone to serious infections. It was here that they confiscated his shoes and left him to walk around in socks, then issued boots that he says were too small and blistered his feet. Here that the blisters became infected, that the infection spread, and that Seife nearly died before authorities drove him 40 miles to the Bee County Regional Medical Center on March 1, where, two days later, a surgeon amputated his gangrenous left leg below the knee.

"What has happened to me is the most horrible thing on Earth," Seife now growls in his bed at the Nix Medical Center in San Antonio, where he was subsequently moved. "It almost killed me. I won all those awards, I was one of the most honored employees of the federal government, they wrote that I was 'a breath of fresh air.' And look at what they've done to me!...

"Out of nothing, I was totally destroyed. Thirty years, I gave my whole life to public service! . . . It's cost me $250,000 to defend myself. I have to pay it myself, and these crooks in the generic drug industry get their legal bills paid."

He pulls up the sheet to reveal his stump, spotted with lesions, and his right leg, which is wrapped in

See SEIFE, A18, Col. 1

thyroid storm

Betty Dong

thyroid storm

Betty Dong

Boots PHARMACEUTICALS TM

thyroid storm

Thyroid Storm

To study, to finish, to publish.

—Benjamin Franklin

I stopped a flawed study that would have put millions of patients at risk.

—Carter Eckert

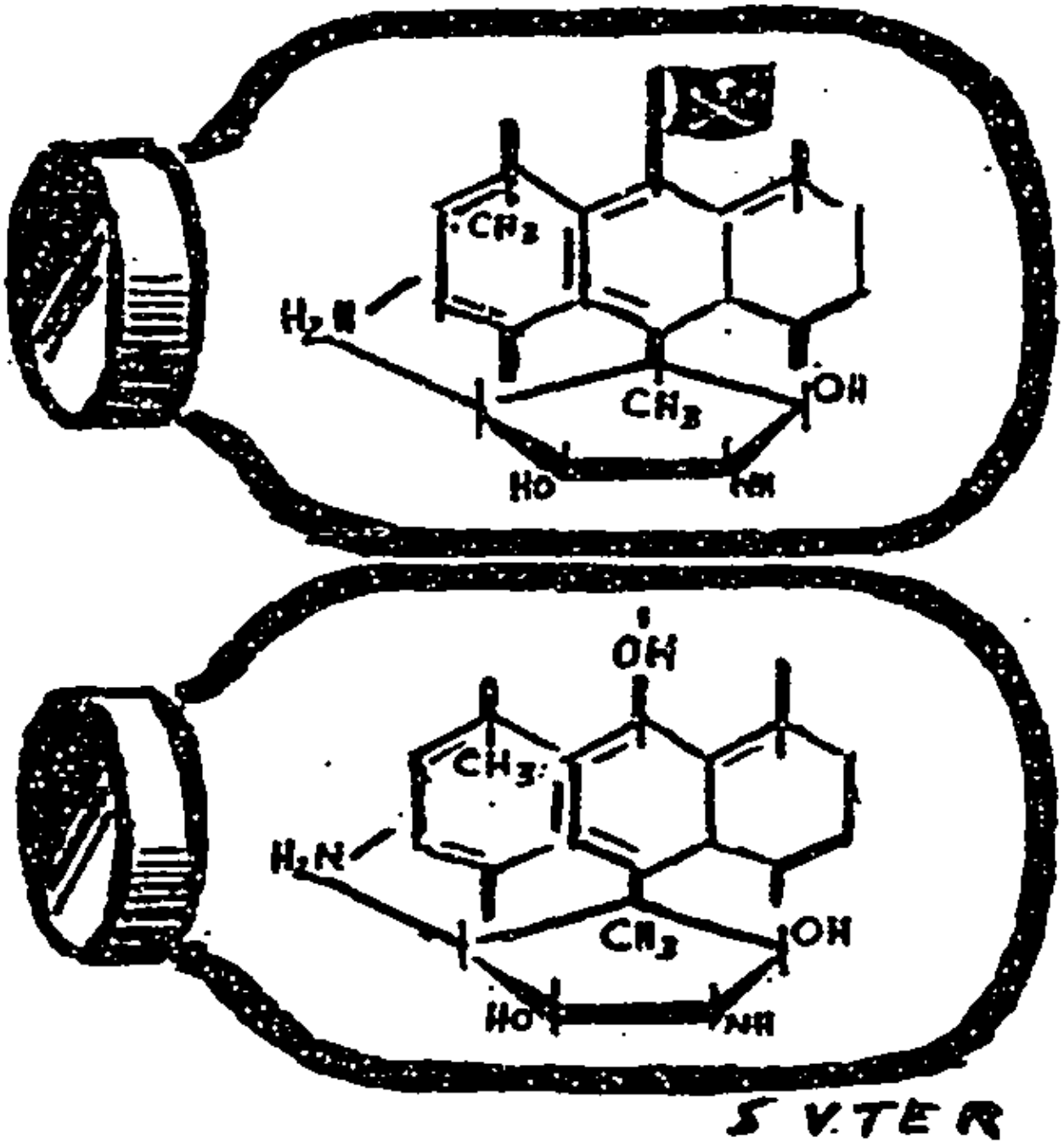
In this issue of THE JOURNAL, we are publishing a report[1] of work that started 9 years ago, was concluded in December 1990, and the data from which were published in another journal in July 1995. Given that we at *JAMA* like to keep up-to-date and that we try never to republish what others have already put in print, the reader might well ask what is going on. The story necessary to answer this question provides a cautionary tale that illustrates the sharply differing views of research taken by the university researcher and the company sponsoring that research, if the company's product is at stake. At a time when an increasing proportion of research funding is provided by private companies,[2] the story holds lessons for both, as well as for university faculties, administrators, regulatory agencies, and for physicians who prescribe on the basis of evidence.

See also pp 1199, 1205 and 1224.

In 1987, to establish that Synthroid was truly more effective than competing preparations, Flint Laboratories, then the manufacturers of Synthroid, approached Betty J. Dong, PharmD, at UCSF. This seemed a good choice because in 1986, Dong et al[3] had published a letter showing that the levothyroxine content of different thyroid products, 2 brand-name products and 7 generic, differed widely. They noted that the 2 brand-name preparations, 1 of them Synthroid, were the preparations of choice. Flint and Dong signed a lengthy protocol/contract to finance comparative studies of the bioequivalence of Synthroid and 3 other preparations, and both sides expected the study to show that Synthroid was superior (letter from B. J. Dong to N. M. Kurtz, March 31, 1994). The contract detailed the experimental design and analysis of the data. Representatives of Flint, and after their takeover, Boots Pharmaceuticals Inc, made regular site visits, about 3 a year, to satisfy themselves that the work was being done properly. During these visits small problems were ironed out, but there was no hint of any bigger cloud.

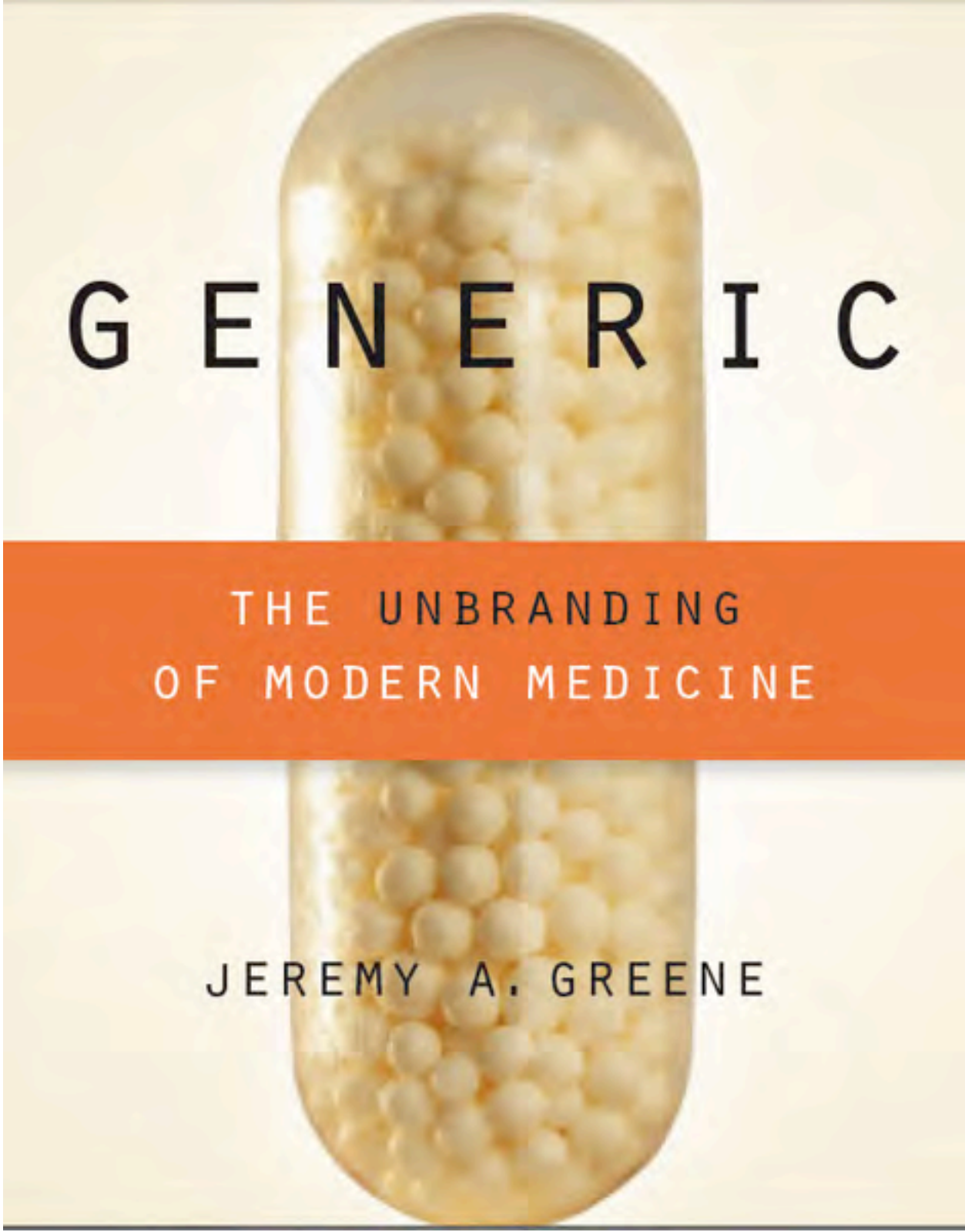
In January 1989, at a time when there was a move to add a competitor's preparation to the Massachusetts formulary,[4] Boots, in the first of their site visits, began asking for the preliminary results of a parallel in vitro study in which tablets were com-

the same but not the same



Generic Medicines: Essential contributors to the long-term health of society

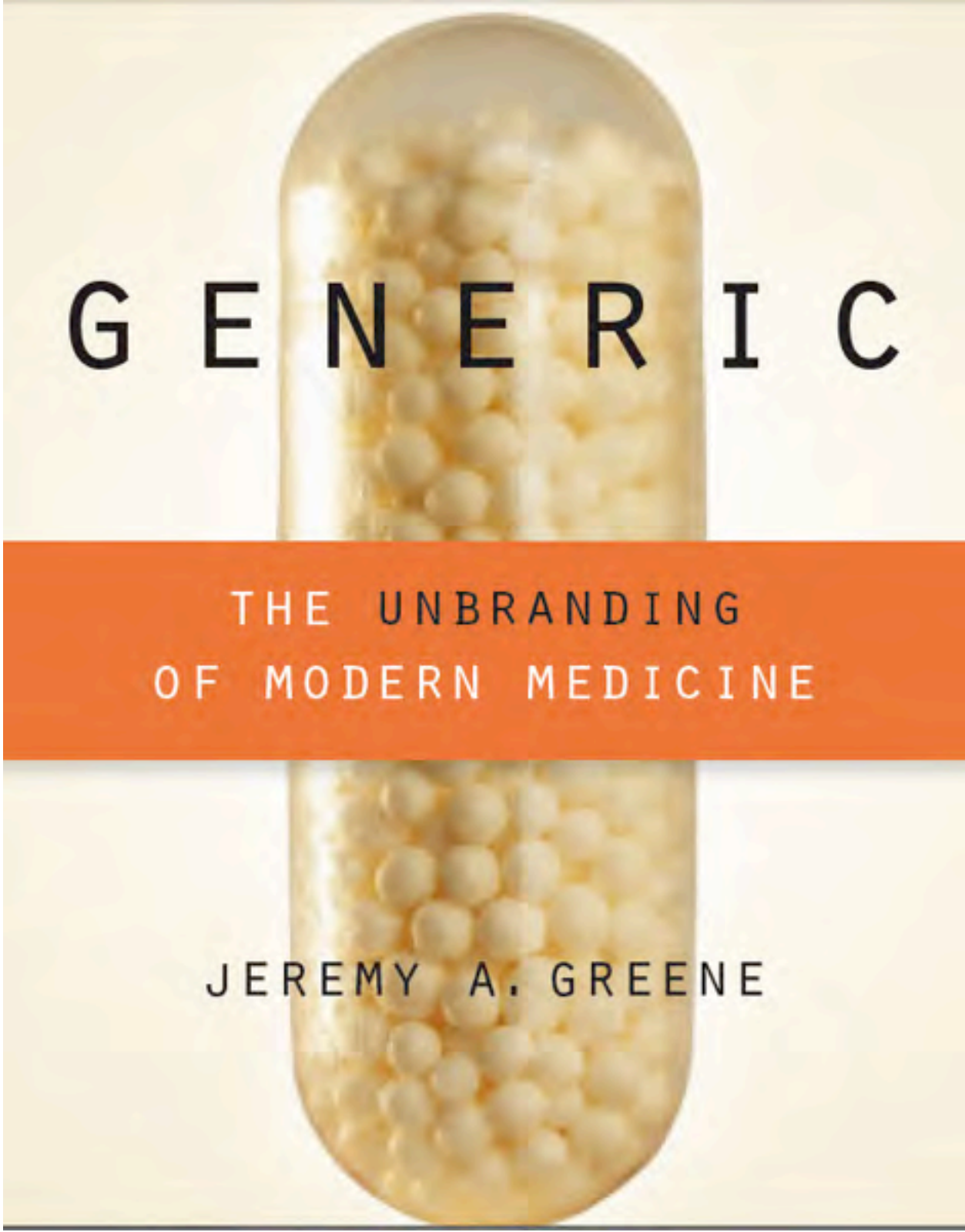
SECTOR SUSTAINABILITY CHALLENGES IN EUROPE


GENERIC
THE UNBRANDING
OF MODERN MEDICINE
JEREMY A. GREENE

what's in a name?

no such thing as a generic drug?

when is a medicine good enough?



what's in a name?

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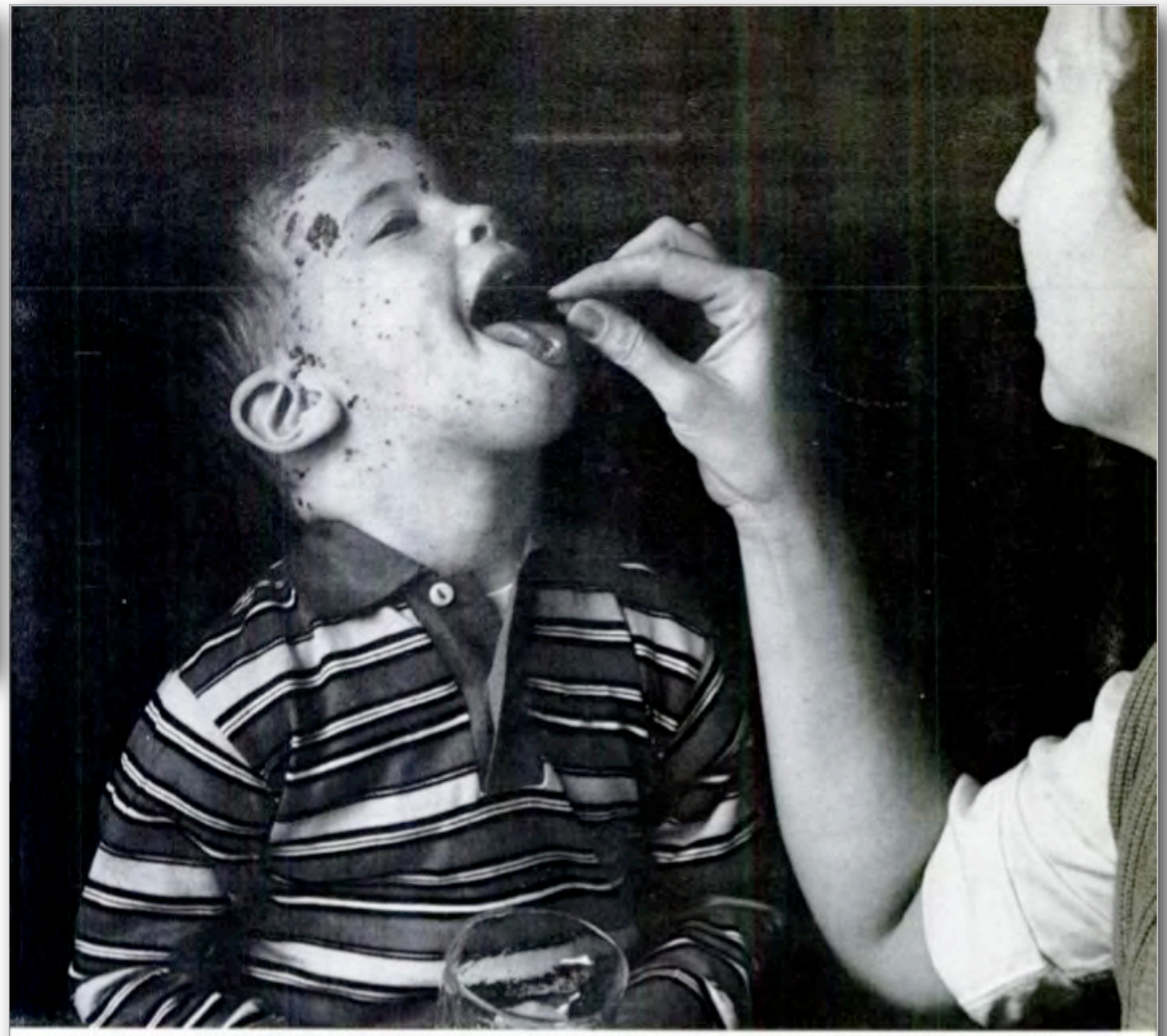
Sen. Estes Kefauver, (D-TN)



FOUR-YEAR-OLD JIMMY PORTER RECEIVES A PILL FROM MOTHER. DRUGS AND DOCTORS COST PORTERS (FIVE CHILDREN) A TENTH OF THEIR INCOME LAST YEAR

BIG PILL BILL TO SWALLOW

The wonder-drug makers get handsome profits from their captive consumers

DRUG INSPECTION HELD INADEQUATE

Head of Standards Group Warns of Prescriptions Using Generic Names

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what's in a name?

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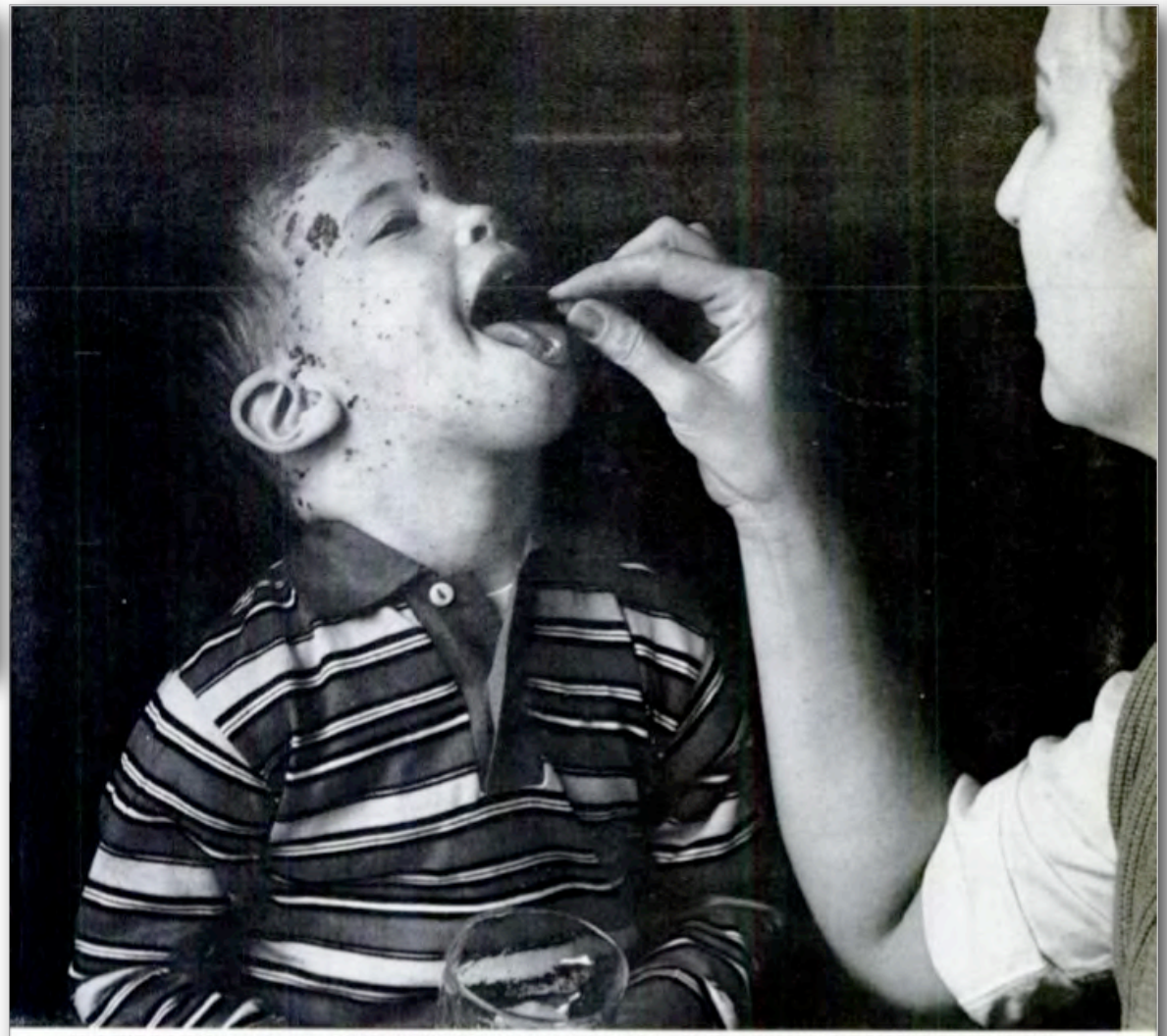

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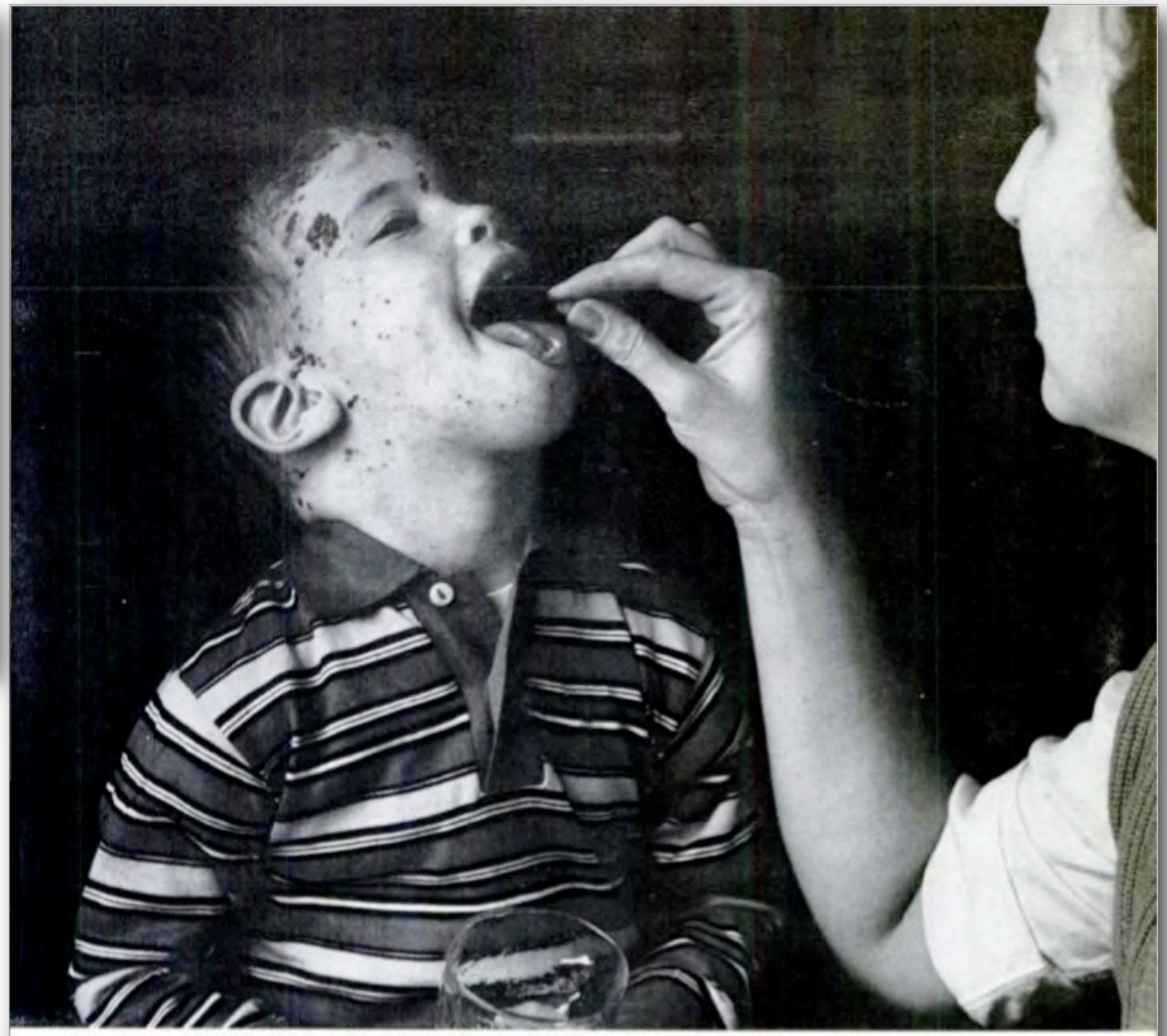

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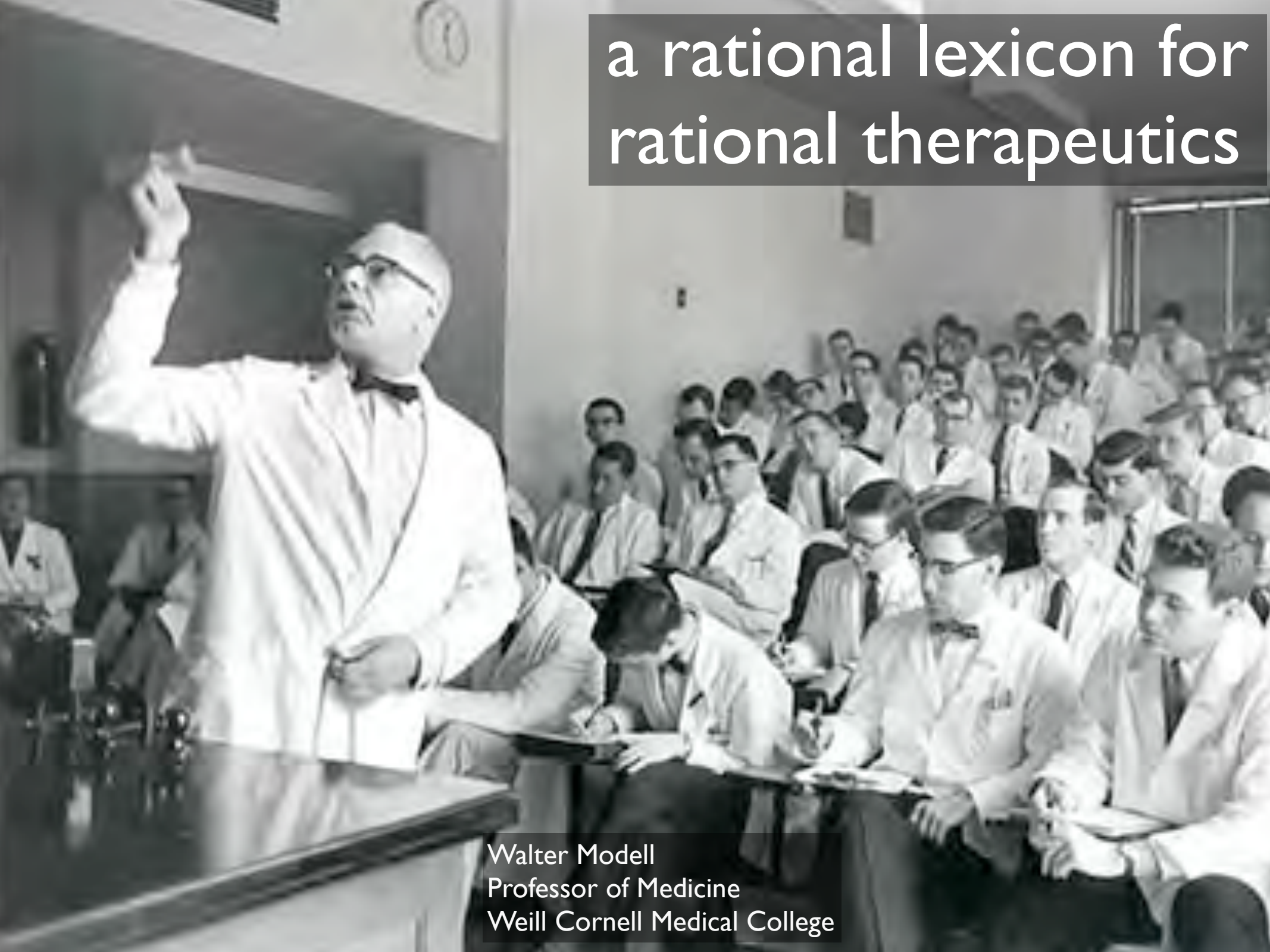
a rational lexicon for rational therapeutics



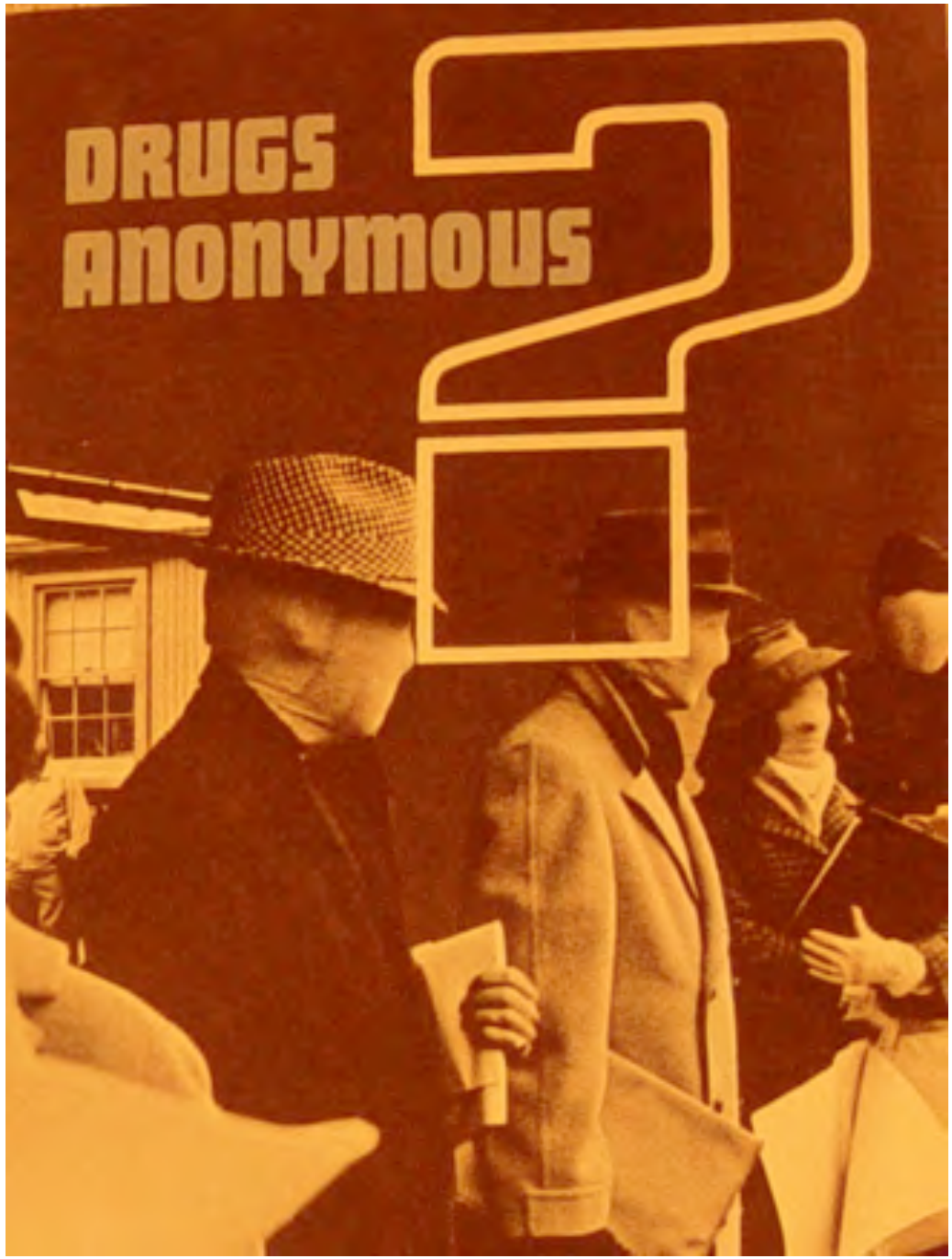
Walter Modell
Professor of Medicine
Weill Cornell Medical College

Singoserp®

(syrosingopine CIBA)

Minimizes the side effects problem in most hypertensive patients

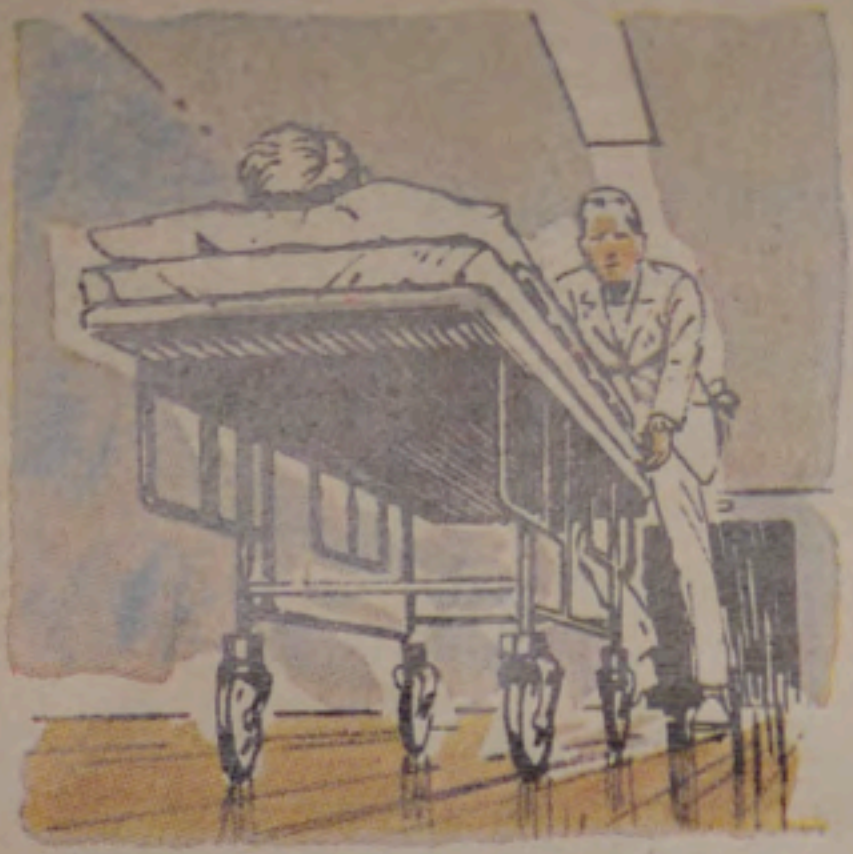
the perils of namelessness



no such thing as a generic drug?

the politics of equivalence

Gaylord Nelson (D-WI)



An ailing man
was switched
to a "generic" drug
and landed in the hospital...

The Anonymous Drug That Hospitalized a Patient

Readers' Digest November 1967

premo

Pharmaceutical Laboratories, Inc.

111 LEUNING STREET, SOUTH HACKENSACK, N. J. 07606
NEAR TETERBORO AIRPORT
DIAMOND 3-5000

September 20, 1966

A F. 13-610 FILE

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BT:GF

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No other manufacturer of generics can make compliance with the state model substitution law easier. Because Purepac, America's leading manufacturer of a national brand of generics, offers virtually all the FDA's listed multi-source generic drugs. And Purepac gives you a lot more:

- the ease of stocking just one major generic line
- the assurance of consistent supply
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So next time you shop generics, shop the generic company Purepac. The model line for the model state substitution law.

PUREPAC. Competitive prices and peace of mind.

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THE LEADING NATIONAL BRAND OF GENERICS

"Purepac generics are low priced... but not risky cheap."

Listen, if you're buying generics that are cheaper than Purepac, chances are you're buying from a mail order house and mail order houses are not manufacturers. Most likely you have never even heard of the manufacturers they buy from. And what you don't know, could hurt you. Look, mail order houses buy for price and price alone, from one manufacturer to the next. So, if there's a product liability suit and you can't pinpoint the manufacturer, you, Mr. Pharmacist, may be the only one liable for damages because you made the product selection and bought risky cheap generics.

Don't take chances. Know who's making t
generics you're dispensing. You can tru
and buy Purepac generics for these imp
tant reasons.

Purepac's bioequivalence is every bit
good as SKF's, Lederle's, Pfizer's or a
other brand name manufacturer who h
just recently started selling generics.

Pharmacists of America have dispens
over one billion Purepac drug products
the last 46 years . . . and those Pharmaci
have made us and are keeping us Numb
One! No other generic manufacturer c
match that record.

*"Purepac generics are low priced . . . but n
risky cheap."*

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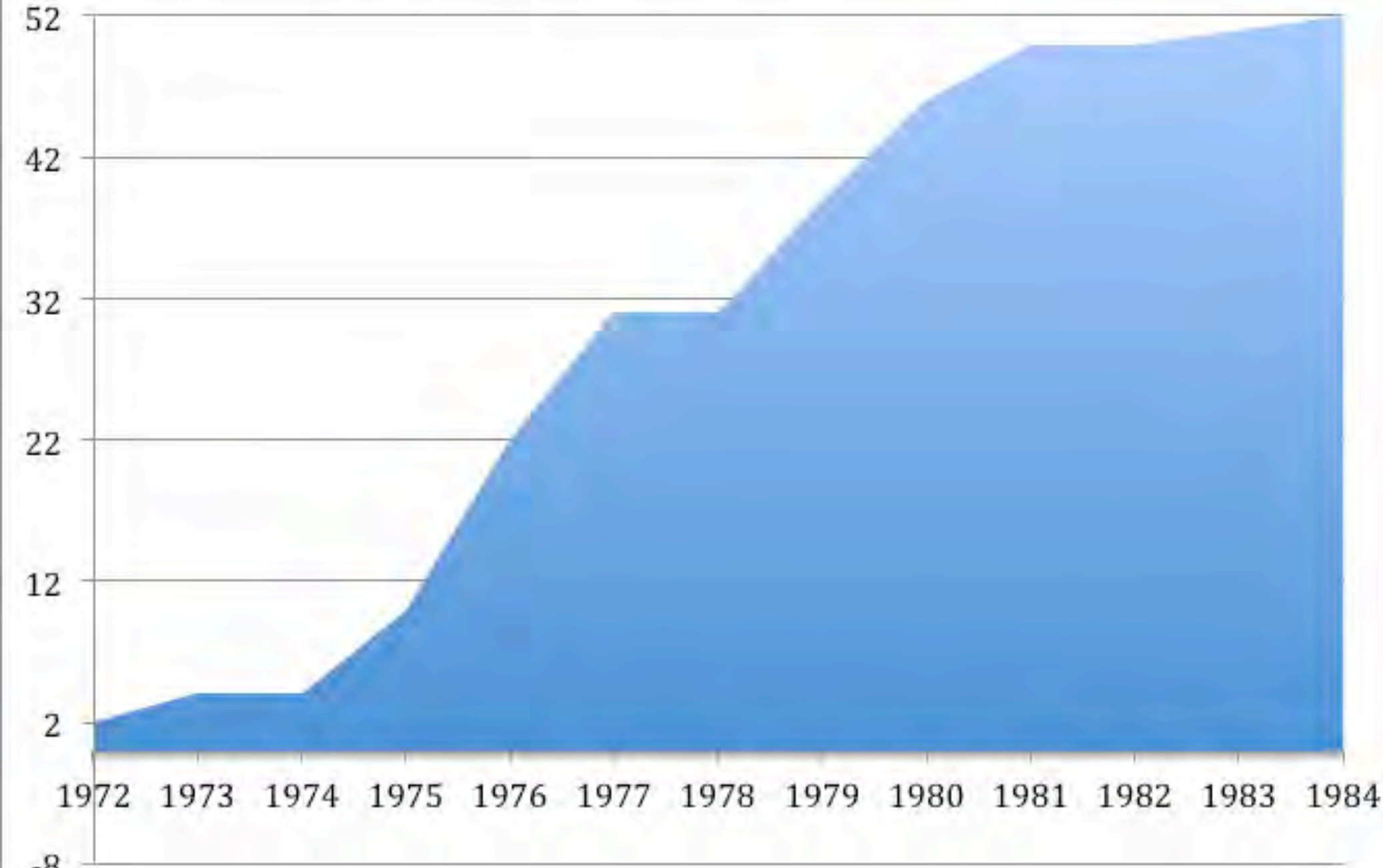
Elizabeth, NJ 07207
THE LEADING NATIONAL BRAND OF GENERI
Available from your wholesaler.

NUMBER OF STATES/PROVINCES WITH LAWS FAVORING GENERIC SUBSTITUTION




WHEN YOU BUY GENERICS—
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☐ liberal return goods policy
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☐ The expanded line-up of Standard Products is an integral part of the total Lederle line.
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penicillin G potassium
SK-Penicillin VK
penicillin V potassium
SK-Tetracycline
tetracycline HCl
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Smith Kline &French Laboratories
Div. of SmithKline Corp. Phila. Pa.

for added certainty that your patient gets the high quality of DIURIL®... (CHLOROTHIAZIDE | MSD)

TABLETS: 250 mg and 500 mg

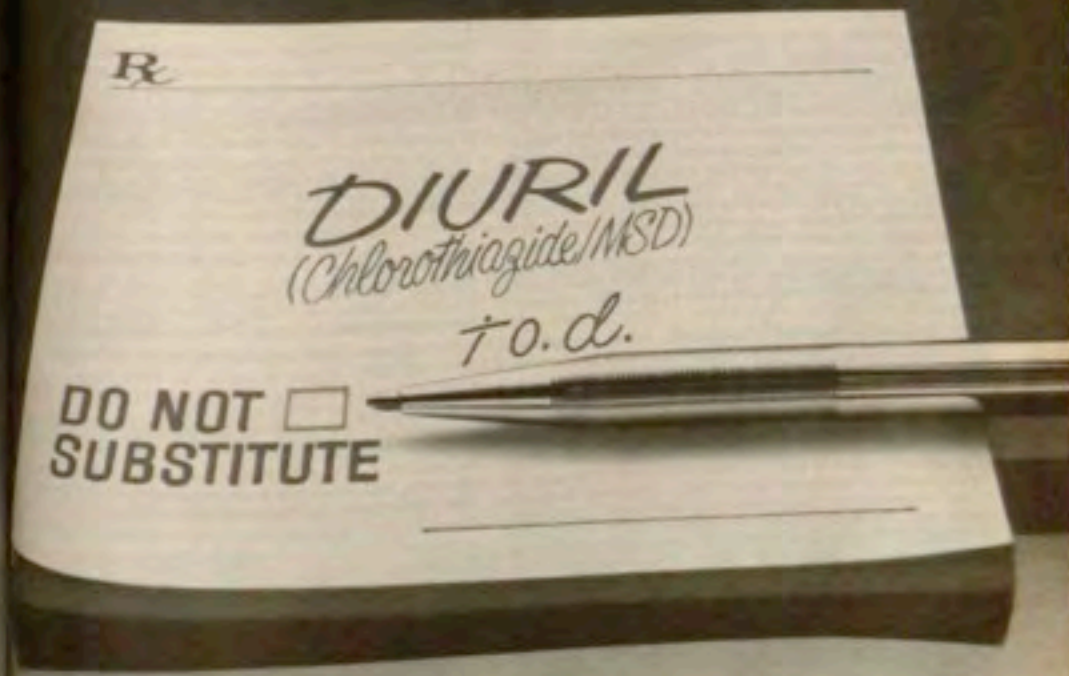
Here's what we've done

We've put the name on the tablet for quick identification

(CHLOROTHIAZIDE | MSD)

Here's what you can do

Specify "no substitution" on your prescriptions



MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

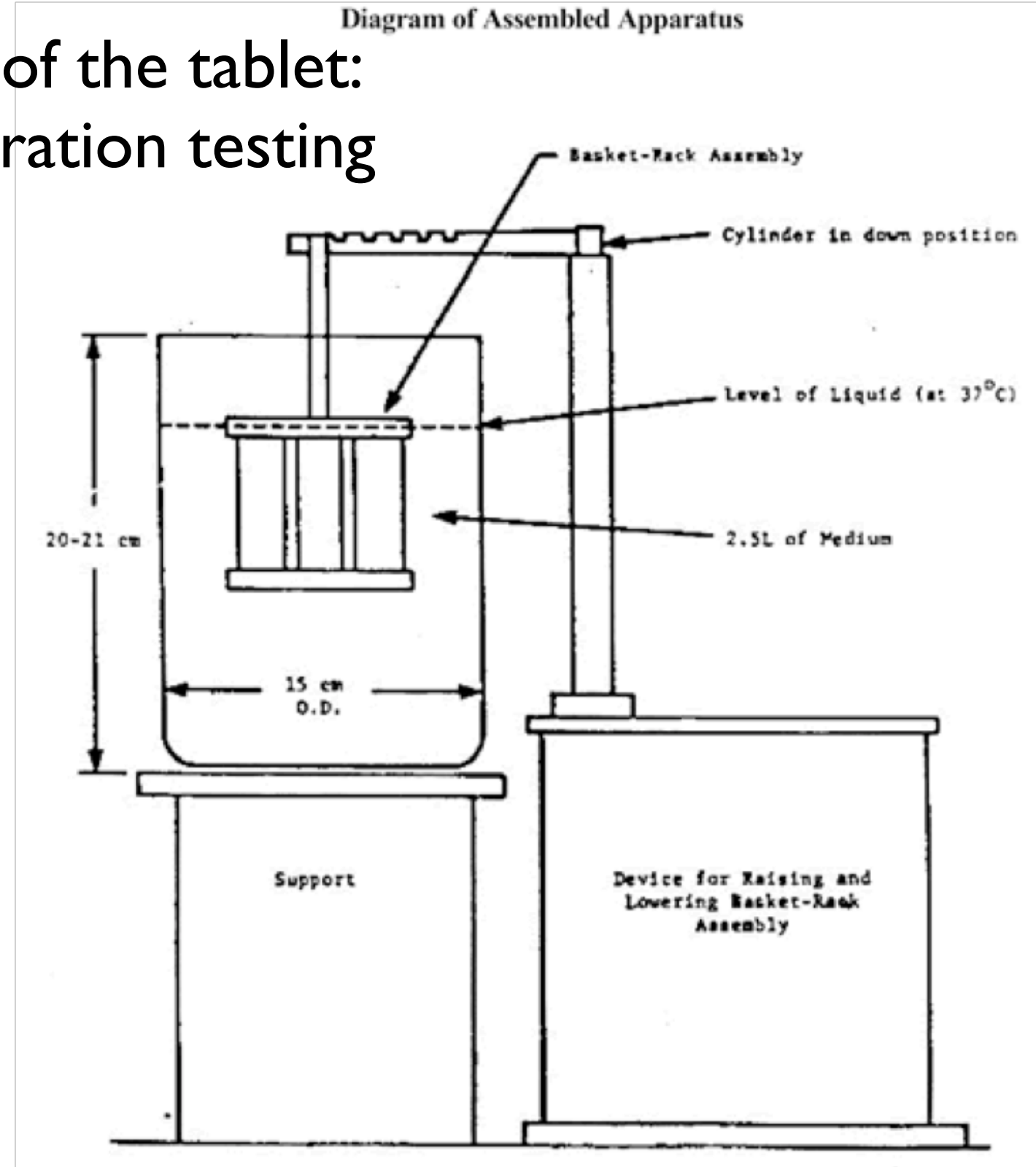
when is a medicine good enough?

GENERIC DECEIT

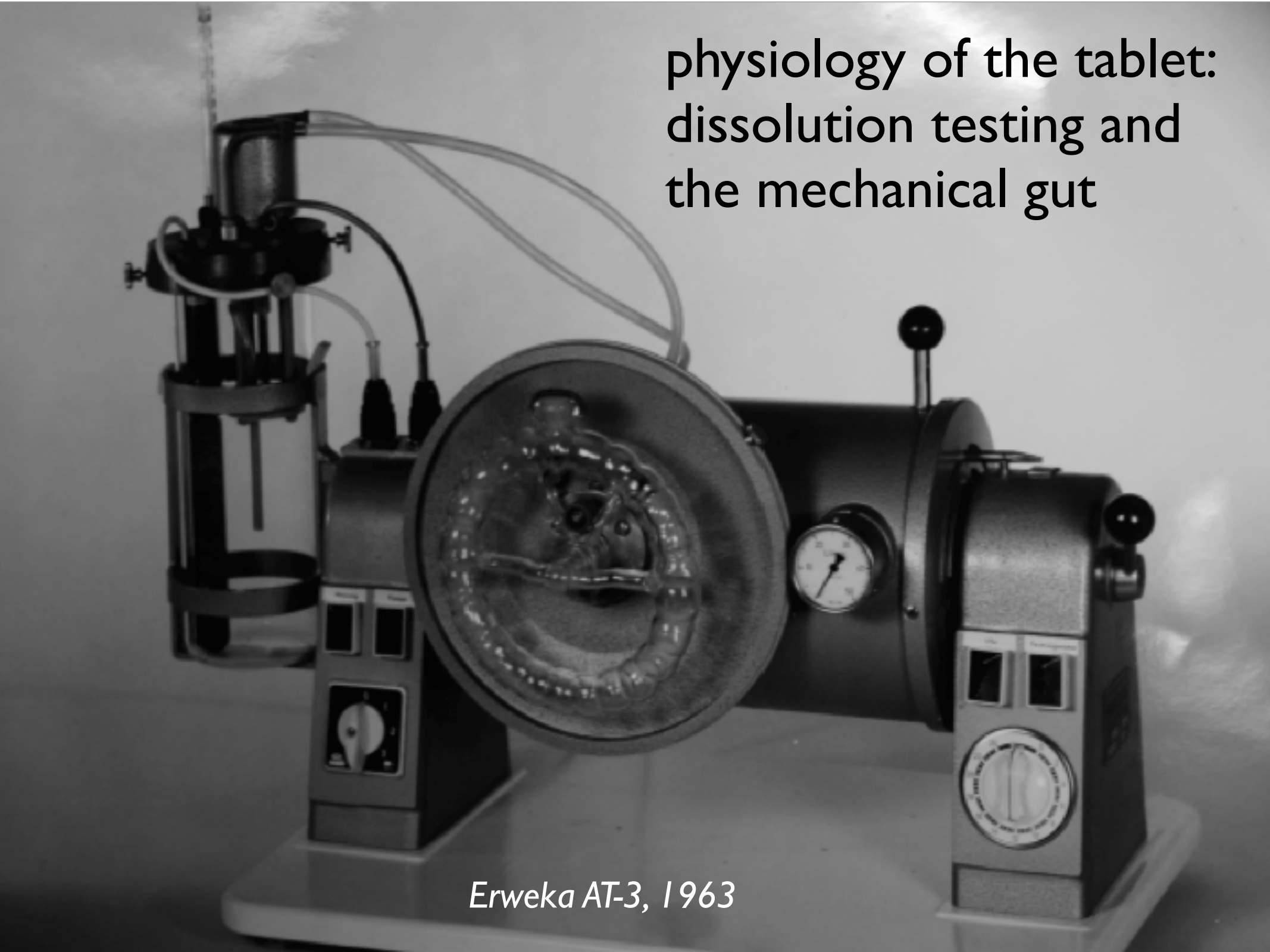
"LOOK-ALIKE" DRUGS AND YOUR PATIENTS

NATIONAL BRAND		GENERIC "LOOK ALIKE"
TIVERT 12.5 mg (Roerig)		Meclizine HCl 12.5 mg (Pharmecon,Inc.)
DARVON COMPOUND-65 (Lilly)		Propoxyphene Compound-65 (Pierrel America, Inc.)
CADRON 0.75 mg (Merck)		Dexamethasone 0.75 mg (Three P Products Corp.)
AROTID 250 mg (Roche)		Amoxicillin 250 mg (Biocraft Laboratories)
LIBRIUM 5 mg (Roche)		Chlordiazepoxide 5 mg (Cord Laboratories)
POLYCILLIN 250 mg (Bristol)		Ampicillin 250 mg (Biocraft Laboratories)
EMARIN 2.5 mg (Ayerst)		Conjugated Estrogens 2.5 mg (Heather Drug Co.)

physics of the tablet: disintegration testing

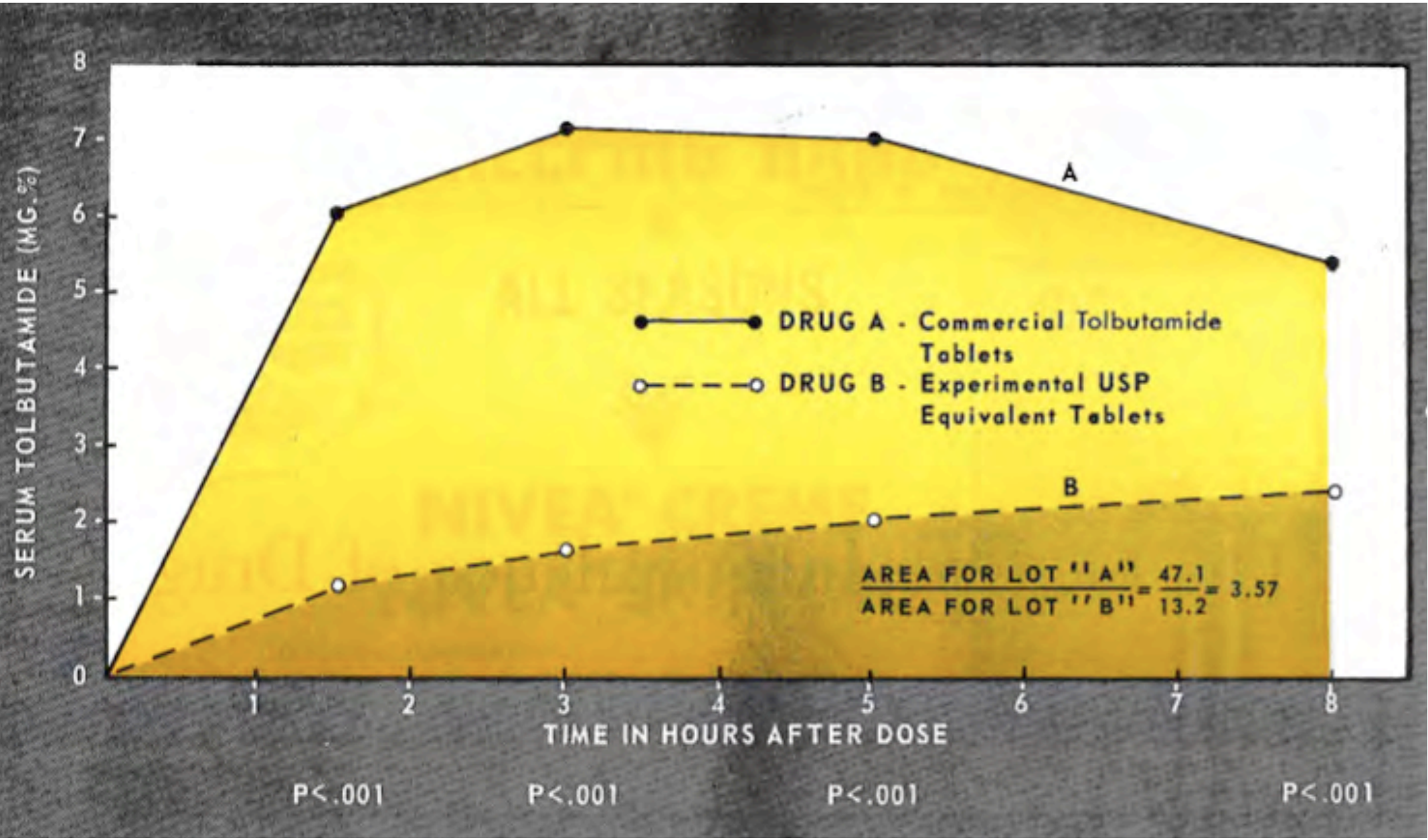


physiology of the tablet: dissolution testing and the mechanical gut



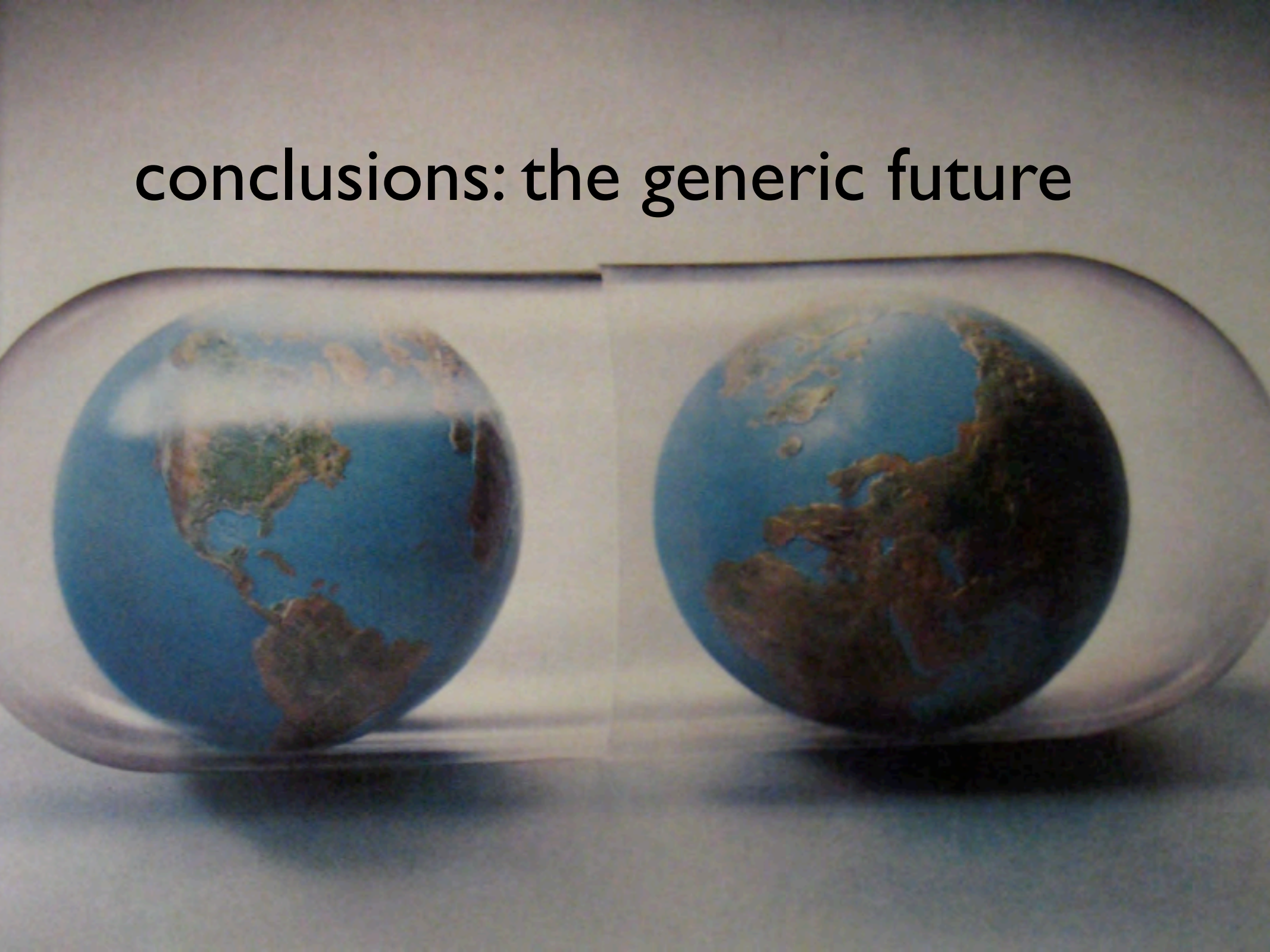
Erweka AT-3, 1963

physiology of the tablet: *in vivo* availability

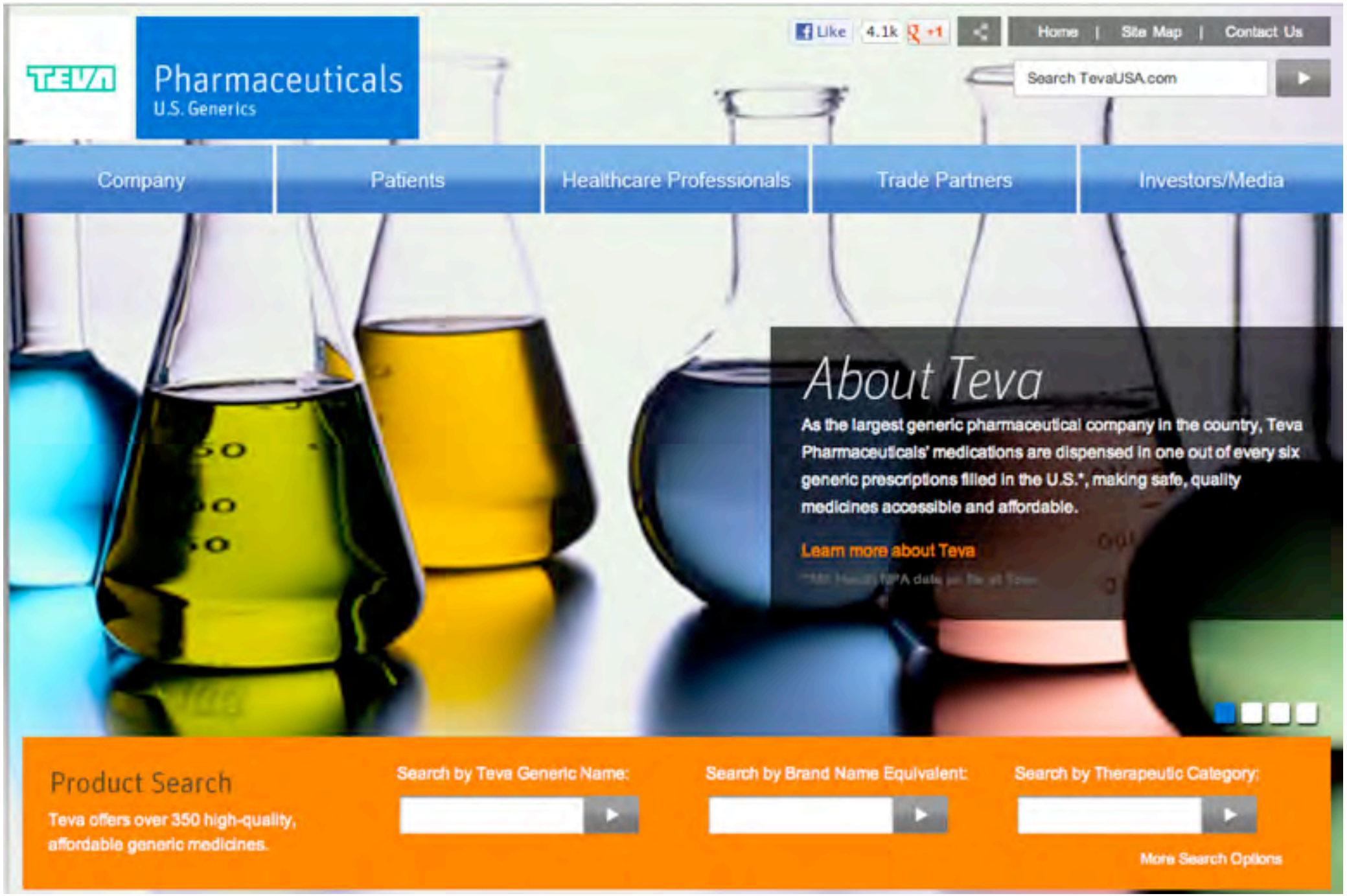


is bioequivalence enough?

conclusions: the generic future



the generic giant



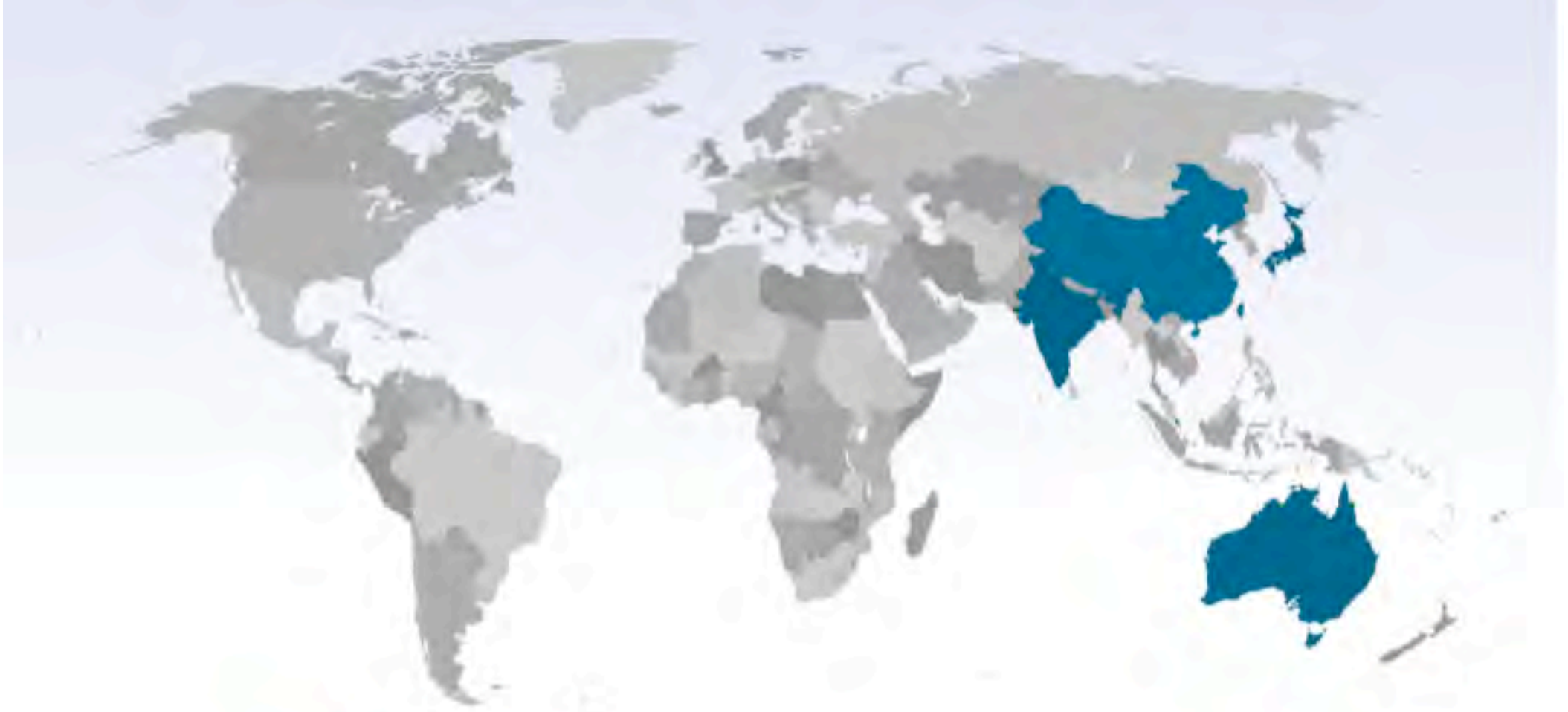
Americas | Asia | EMIA | Europe

Teva is the leading generics company in America, with $8.8 billion sales in 2011. Headquarters are in North Wales, Pennsylvania, Teva Americas has more than 12,000 employees in 13 US states, the District of Columbia, Canada and Puerto Rico. Over 1.5 million Teva prescriptions are written each day in the US alone, 1,052 prescriptions per minute, while 1 out of every 7 generic prescriptions in the US and Canada is filled with Teva product.

 Argentina

 Brazil

 Canada



Americas | **Asia** | EMIA | Europe

Teva Asia is based at Teva headquarters in Israel, with representatives across the region, overseeing all aspects of the regional activity including marketing, registration logistics and distribution. Teva Asia supports Teva's strategic objectives and continuous global expansion. Teva Asia is responsible of commercial & sales activities in Japan, China, India and other countries across Asia.

Australia

China

India

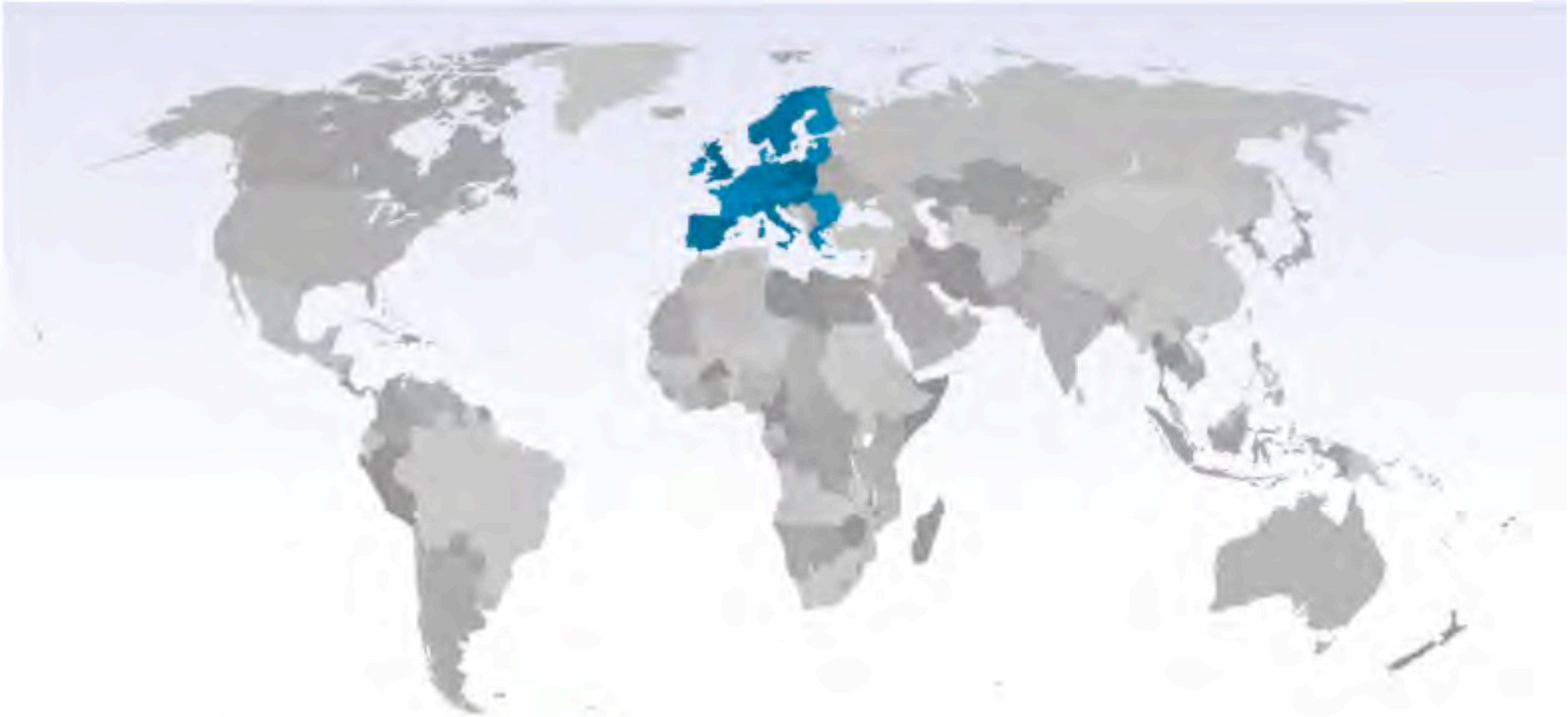
Americas | Asia | **EMIA** | Europe

EMIA is a division within Teva, coordinating all commercial activities in Eastern Europe, Israel, the Middle East and Africa. Headquartered in Israel, EMIA's representatives are positioned across the region, overseeing all activities, including marketing, registration, logistics and distribution. EMIA's people are committed to maintain fruitful, ongoing relationships with local communities and to achieve sustained profitable growth in each market.

Belarus

Bosnia and Herzegovina

Croatia



Americas | Asia | EMIA | **Europe**

Teva is the leading generics company in Europe, with $5.7 billion sales in 2011. Headquartered in the Netherlands, Teva Europe specializes in the development, production and marketing of a wide range of generic, innovative and branded pharmaceuticals, biosimilars and Active Pharmaceutical Ingredients (APIs). Teva Europe has 14,000 employees in 29 European Union member states, plus Norway and Switzerland. About 1,186 doses of Teva medicine are taken by patients in Europe every second.

 Austria

 Belgium

 Bulgaria

the generic giant

PERHAPS YOU ARE NOTICING SOMETHING DIFFERENT ABOUT YOUR TEVA PRODUCT?

We are excited to announce that we are adding the "TEVA" name to some of our capsules and tablets. In some cases, the new "TEVA" imprint will replace another number that had been on those products previously.

Review the product pages to see which products have been updated and compare the current and former imprints. Each time you receive a product made by Teva, you can have confidence that it's made to Teva's highest standards and that it's been approved by the Food and Drug Administration (FDA).

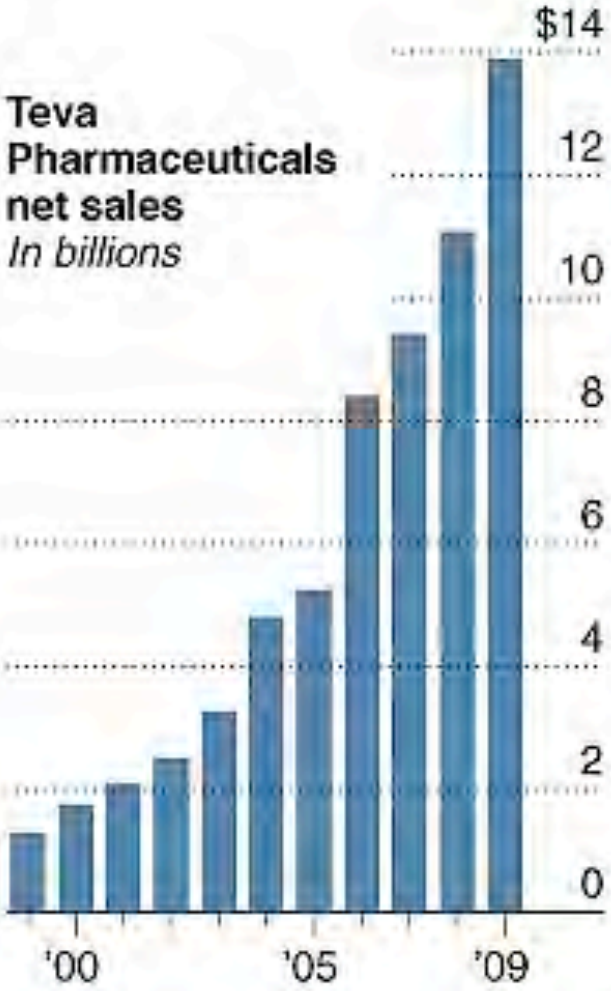
the generic giant

The New York Times

May 9, 2010

Generic Giant

Teva Pharmaceuticals, which specializes in generics, has grown to be the largest drug manufacturer in terms of U.S. prescriptions dispensed.



Top pharmaceutical companies, by U.S. prescriptions, 2009

Shaded companies specialize in generics

COMPANY	U.S. PRESCRIPTIONS DISPENSED IN MILLIONS
Teva Pharmaceuticals	**629.5**
Mylan Labs	343.1
Pfizer	264.6
Novartis*	238.8
Watson	234.7
Merck	123.1
Qualitest Products	99.5
Apotex	97.9
AstraZeneca	93.2
Lupin Pharmaceuticals	92.8

*Includes sales at Sandoz, Novartis's generic division.

Sources: Teva Pharmaceuticals; IMS Health