the same but not the same

a brief history of generic drugs

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# 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 amendment 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).

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- **CHEM Team:**
  - **Bio Team:**
  - **Activity:**
- **RPM:**
- [ ] FYI
- [ ] CHEM PQRPM:
  - **Clinical Review:** (No)
  - **Activity:**
- **CHEM Team Leader:**
  - **DMF Review Team Leader:**
  - **Labeling Reviewer:**
  - **Micro Reviewer:** (No)
  - **Activity:**

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### Regulatory Reviewer:
- **Recommendation:**
- **Date:**
  - [ ] FILE
  - [ ] REFUSE to RECEIVE

### COMMENTS:
- **Therapeutic Code:**
- **On Call:**
- **Archival copy:**
- **Sections:**

### MODULE 1: ADMINISTRATIVE

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<td><strong>PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 18: MANUFACTURING STEPS AND OR TYPE OF TESTING</strong></td>
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| 1.3.2 | Field Copy Certification (N/A for E-Submissions) (original signature) |

| 1.3.3 | Debarment Certification - CDEA (Generic Drug Enforcement Act)/Other; (no qualifying statement) |
|       | 1. Debarment Certification (original signature) |
|       | 2. List of Convictions statement (original signature) |

| 1.3.4 | Financial Certifications; Biocompatibility/Bioequivalence Financial Certification (Form FDA 3454) |
|       | Disclosure Statement (Form FDA 3455) |

| 1.3.5 | Patent Information |
|       | Patients listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluation |
|       | Patent Certification |
|       | 1. Patent number(s) |
|       | 2. Paragraph: (Check all certifications that apply) |
|       | MOG [ ] 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 letter 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 3562) |

| 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 |

| 1.12.11 | Basis for Submission |
|         | NDA#: |
|         | Ref Listed Drug: |
|         | 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 |
generic scandal!

Marvin Seife

John Dingell
generic scandal!
The Bungled Punishment of Prisoner Seife

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 col 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 grows 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...
thyroid storm

Betty Dong
thyroid storm

Betty Dong
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 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, 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.

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 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, Boots, in the first of their site visits, began asking for the preliminary results of a parallel in vitro study in which tablets were comp...
the same but not the same
Generic Medicines: Essential contributors to the long-term health of society

SECTOR SUSTAINABILITY CHALLENGES IN EUROPE
what’s in a name?

no such thing as a generic drug?

when is a medicine good enough?
what’s in a name?
what’s in a name?

Sen. Estes Kefauver, (D-TN)
what's in a name?

Sen. Estes Kefauver, (D-TN)
what's in a name?

Sen. Estes Kefauver, (D-TN)
a rational lexicon for rational therapeutics
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
Gentlemen:

We would appreciate your adding our name to your list of bidders to receive invitations to bid on pharmaceuticals.

We manufacture a complete line of pharmaceuticals, which include injectables, narcotics, vitamins and many generic products.

We list among our many customers, the following: Defense Supply Agency, U. S. Veterans Administration, City of New York, County of Los Angeles, and numerous other city, county and federal agencies.

Thanking you for any consideration given us, we are

Very truly yours,

PREMO PHARMACEUTICAL LABS., INC.

B. Tilkin
Sales Manager
Purepac offers the generic line for every state substitution law.

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
- competitive prices
- a quick-alert system that lets you know of any change in a product's status
- an extensive liability insurance policy

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.

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 the generics you're dispensing. You can trust and buy Purepac generics for these important reasons.

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

Pharmacists of America have dispensed over one billion Purepac drug products in the last 46 years... and those Pharmacists have made us and are keeping us Number One! No other generic manufacturer can match that record.

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

PUREPAC
Elizabeth, NJ 07207
THE LEADING NATIONAL BRAND OF GENERIC
Available from your wholesaler.
NUMBER OF STATES/PROVINCES WITH LAWS FAVORING GENERIC SUBSTITUTION

The chart shows the increase in the number of states/provinces with laws favoring generic substitution from 1972 to 1984. The number of states/provinces increased significantly over time, reaching 52 by 1984.
Here's what we've done

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

Here's what you can do

Specify "no substitution" on your prescriptions

(CHLOROTHIAZIDE | MSD)
when is a medicine good enough?
GENERIC DECEIT

“LOOK-ALIKE” DRUGS AND YOUR PATIENTS
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?

The one the patient takes is never tested.

Surprising, perhaps, but it makes sense when you think about it. Obviously, the actual dose of any prescription drug the patient takes cannot be tested because it would have to be broken down for analysis — after which it could never be used by a patient.

This means that you depend on the manufacturer for assurance that the dose the patient takes is identical to the ones which have been tested.

At each step in the manufacture of a Lilly drug, test after test confirms the ingredients, formulation, purity, and accuracy — all the critical factors which assure that every Lilly medicine is just what the doctor ordered.

That’s particularly important, as you know. The same drug made by different companies can be chemically identical yet may act differently in the human body because of the many variables in the way the drugs are manufactured.

And, of course, government standards alone do not assure the efficacy and consistency — the quality of each drug you dispense.

As we at Eli Lilly and Company see it, the ultimate responsibility for quality is ours.

For five generations we’ve been making medicines as if people’s lives depended on them.
conclusions: the generic future
the generic giant
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.
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 for commercial & sales activities in Japan, China, India, and other countries across Asia.
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.
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.
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 New York Times

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

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>U.S. PRESCRIPTIONS DISPENSED IN MILLIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva Pharmaceuticals</td>
<td>629.5</td>
</tr>
<tr>
<td>Mylan Labs</td>
<td>343.1</td>
</tr>
<tr>
<td>Pfizer</td>
<td>264.6</td>
</tr>
<tr>
<td>Novartis*</td>
<td>238.8</td>
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<tr>
<td>Watson</td>
<td>234.7</td>
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<tr>
<td>Merck</td>
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<tr>
<td>Qualitest Products</td>
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<tr>
<td>Apotex</td>
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<tr>
<td>AstraZeneca</td>
<td>93.2</td>
</tr>
<tr>
<td>Lupin Pharmaceuticals</td>
<td>92.8</td>
</tr>
</tbody>
</table>

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

Sources: Teva Pharmaceuticals; IMS Health