NXP Innovators Showcase · No. 01a

Zyvox.

The first-in-class oxazolidinone — from Upjohn bench chemistry to a durable hospital antibiotic franchise.

FIRST APPROVAL	April 18, 2000 · Pharmacia & Upjohn (now Pfizer)
CLASS	Oxazolidinone · first new antibiotic class in ~35 years
MECHANISM	Inhibits 70S initiation complex at 23S rRNA (50S subunit)
PEAK BRANDED SALES	~$1.32B worldwide (2011) · ~$4.4B cumulative 2000–2008
U.S. GENERIC ENTRY	May 2015 (tentative ANDAs) · patents expired Sept 2021
GLOBAL MARKET TODAY	~$1.5B (2024) · multi-sponsor generic workhorse

CASE STUDY

Executive Summary

FDA APPROVAL	PEAK SALES	CLASS GAP	MECHANISM
2000	$1.32B	~35 yr	70S
First oxazolidinone · Apr 18	Worldwide · 2011 (Pfizer)	Since last new antibiotic class	Initiation complex inhibitor

Zyvox (linezolid, PNU-100766) was the first approved oxazolidinone and the first truly new systemic antibiotic class to reach market in roughly three and a half decades. Discovered at the Upjohn Company in Kalamazoo and brought through clinical development by Pharmacia & Upjohn (acquired by Pfizer in 2003), linezolid was engineered for the Gram-positive resistance crisis of the late 1990s — MRSA, vancomycin-resistant enterococci (VRE), and penicillin-resistant pneumococci. Its combination of 100% oral bioavailability, a novel ribosomal binding site that avoided cross-resistance, and both IV and oral formulations made it a defining hospital antibiotic for two decades. [1] [2]

Commercially, Zyvox was a successful specialty-hospital franchise rather than a mega-blockbuster. Cumulative branded sales were approximately $4.4 billion between 2000 and 2008, with worldwide revenue peaking above $1.3 billion in 2011 before pediatric exclusivity expired in 2015 and the underlying patents in 2021. The linezolid molecule itself — now a generic multi-sponsor product — supports a global market estimated at ~$1.5 billion in 2024. Second-generation oxazolidinones (tedizolid / Sivextro, Cubist → Merck 2014; contezolid / Youxitai, MicuRx China 2021) followed the class Pharmacia opened. [3] [4]

This case study reconstructs the Zyvox arc in two linked threads. **Section I** traces the development and commercial history from Upjohn discovery through generic entry. **Section II** examines the bioanalytical and clinical-pharmacology program that transformed an interesting series of compounds into a defensible IND — the LC/MS/MS PK and PK/PD work that differentiated linezolid (PNU-100766, BID) from its close congener eperezolid (PNU-100592, TID) and enabled twice-daily dosing at therapeutically meaningful steady-state levels.

> **"In the preclinical stages, linezolid and eperezolid were similar in safety and activity, so they were taken to Phase I to identify any difference in pharmacokinetics. Linezolid was found to have a pharmacokinetic advantage — BID dosing versus TID — and therefore proceeded to further trials."**

— The discovery narrative, as summarized in the Annals of the New York Academy of Sciences and the Pharmacia discovery review. [1]

SECTION I · DEVELOPMENT ARC

From DuPont Chemistry to FDA Approval

Discovery Lineage

The oxazolidinone scaffold was first studied as a class of monoamine oxidase (MAO) inhibitors in the late 1950s. Antibacterial activity was not recognized until the 1970s, when chemists at E. I. du Pont de Nemours patented a series of oxazolidinone derivatives — initially as agrochemicals (1978), then as mammalian antibacterials (1984). DuPont presented the class publicly at ICAAC in 1987, positioning it as the first novel antibiotic class in a generation. The lead DuPont compounds (DuP-721, DuP-105) produced hepatotoxicity in preclinical studies, and development was discontinued. [2]

In the early 1990s, the Upjohn Company in Kalamazoo, Michigan launched its own oxazolidinone discovery program. Upjohn chemists systematically explored indanone, tetralone, indoline, piperazinyl-phenyl and tropone subunits, developed an enantiomeric enrichment route, and pursued structure-activity relationships focused on both Gram-positive potency and liver safety. Two piperazinyl-phenyl clinical candidates emerged: the monofluoro-phenyl congener **eperezolid (PNU-100592)** and the morpholino analog **linezolid (PNU-100766)**. [1]

Candidate Selection

Preclinically, eperezolid and linezolid were broadly similar in antibacterial spectrum and in the safety screens available at candidate nomination. The differentiating data came from Phase I human pharmacokinetics: linezolid achieved trough plasma levels above the MIC_{90} for target Gram-positive pathogens on a twice-daily schedule, whereas eperezolid required three-times-daily dosing for comparable coverage. Linezolid also demonstrated ~100% oral bioavailability — a formulation advantage for IV-to-oral step-down in hospital settings. On PK grounds, linezolid was selected for continued development; eperezolid was deprioritized. [1]

Approval and Launch

Year	Milestone	Notes
1987	DuPont publishes oxazolidinone class	Leads (DuP-721/105) abandoned for hepatotoxicity
Early 1990s	Upjohn initiates discovery program	Piperazinyl-phenyl chemistry, SAR, enantio-enrichment
Mid-1990s	PNU-100766 (linezolid) nominated	Candidate vs. eperezolid (PNU-100592)
1995	Pharmacia / Upjohn merger	Combined entity continues development
1995–99	Preclinical + Phase 1/2 PK/PD package	LC/MS/MS PK at in-house and CRO labs (§II)
Apr 18, 2000	FDA approval — tablet, IV, oral susp.	Nosocomial pneumonia, CAP, cSSSI, VRE, MRSA
May 2000	U.S. launch — Pharmacia	Merrill Lynch forecast: $50M (2000) → $760M (2004)
2001	EU / UK / Japan / Canada approvals	EU rolled out through 2001
2003	Pfizer acquires Pharmacia	Zyvox inherited into Pfizer's hospital portfolio
2008	Cumulative sales cross $4.4B	Off-label promotion draws 2005 FDA warning letter

Year	Milestone	Notes
2011	Worldwide peak ~$1.32B	Brand mature; resistance stewardship tightens
2014	Tedizolid (Sivextro) approved	2nd-gen oxazolidinone — Cubist → Merck
2015	First generic IV approval (Sandoz, May)	ANDA tentatively approved earlier; patents pending
2021	Key patents expire (Sept 15, 2021)	Contezolid (MRX-I) approved in China June 2021
2024	Global linezolid market ~$1.5B	Multi-sponsor generic workhorse; WHO Essential Meds

Sources: Pharmacia discovery review; NEJM / AAC pharmacology literature; Pfizer annual reports; FDA approval package 021130; Drug Patent Watch; DrugBank; ScienceDirect class reviews. [5]

SECTION I · COMMERCIAL ARC

Franchise Economics and Franchise Legacy

Peak, Plateau, and Patent Cliff

Zyvox grew from an estimated ~$50M in its launch year to worldwide sales of $1.115B in 2008, with sell-side forecasts (Merrill Lynch, Morgan Stanley Dean Witter, Deutsche Bank) consistently underestimating trajectory through the early 2000s. The franchise benefited from three structural tailwinds: the rising clinical visibility of MRSA/VRE, the IV-to-oral step-down advantage that compressed inpatient length-of-stay, and — controversially — aggressive off-label promotion that drew a 2005 FDA warning letter and eventually a $2.3 billion Pfizer settlement in 2009 (of which Zyvox was one named product). Pfizer's U.S. Zyvox sales were approximately $680M in 2014, the last full year before generic IV entry. [3] [6]

Period / Year	Branded Zyvox Sales (approx.)	Context
2000 (launch year)	~$50M (Merrill forecast)	Phased U.S. hospital launch
2004	~$500M trajectory	IV-to-oral advantage in MRSA
2000–2008 cumulative	~$4.4B	Per Pfizer annual reports (Sheller 2009)
2008	$1.115B worldwide	Approaching brand peak
2011	~$1.32B worldwide (peak)	Estimated brand peak before decline
2014	~$680M U.S. (Zyvox formulations)	Last year before generic IV entry
May 2015	First generic IV (Sandoz)	FDA approves generic linezolid injection
Sept 2021	Key method patents expire	Formulation / pediatric exclusivity ends
2024	~$1.5B global linezolid market	Multi-sponsor, predominantly generic

Follow-on Class Activity

Compound (code)	Sponsor	Status / Year	Positioning vs. Linezolid
Linezolid (PNU-100766)	Pharmacia → Pfizer	FDA 2000	Originator · BID dosing · 100% oral
Eperezolid (PNU-100592)	Pharmacia & Upjohn	Discontinued (pre-NDA)	TID dosing PK disadvantage
Tedizolid (Sivextro)	Cubist → Merck	FDA 2014	QD dosing · ABSSSI · 6-day course
Contezolid (MRX-I)	MicuRx / Shanghai	China NMPA 2021	Reduced MAO-inh. & myelosuppression
Radezolid (RX-1741)	Melinta	Phase 2 (stalled)	Biaryl oxazolidinone
Posizolid (AZD2563)	AstraZeneca	Discontinued	Early oxazolidinone follow-on
Ranbezolid (RBx 7644)	Ranbaxy / Sun	Early clinical	India-originated oxazolidinone

Strategic Read

- **First-in-class discipline paid off.** The PK differentiation between linezolid and eperezolid — identified in Phase 1, not preclinically — underwrote twenty years of franchise value. Rigorous early clinical-pharmacology work outperformed preclinical tie-breakers.
- **Novel MoA without cross-resistance** justified hospital formulary adoption. Linezolid inhibits bacterial 70S initiation complex formation at the 23S rRNA, a binding site not exploited by any earlier approved antibacterial.
- **Hospital antibiotic economics remain modest vs. oncology.** Linezolid peaked at ~$1.3B, not $10B — but it was durable, globally essential, and ultimately listed on the WHO Model List of Essential Medicines as a critically important antimicrobial.
- **Class fertility was real but modest.** Tedizolid and contezolid prove the scaffold extends, but no follow-on has matched originator economics — a reminder that first-in-class anti-infectives rarely breed blockbusters in the same indication.

SECTION II · BIOANALYTICAL & CLINICAL PHARMACOLOGY

The LC/MS/MS Case That Made Linezolid

The decision to advance PNU-100766 over PNU-100592 was a **bioanalytical decision**. With comparable in vitro and animal activity, the program needed clean, reproducible human plasma concentration–time profiles to establish that linezolid could hold trough levels above the Gram-positive MIC_{90} on a BID schedule. That data package — and the assays that generated it — sit at the center of this case study.

Mechanism & Published PK Baseline

Parameter	Value	Source
Molecular weight	337.35 g/mol	PubChem / DrugBank
Oral bioavailability (F)	~100% (85–100% in CF / EF)	AAC 2005, 2011
C_{max} (600 mg BID, SS)	~15–21 µg/mL	AAC pop-PK studies
T_{max}	1–2 h (delayed ~0.7 h w/ high-fat food)	Pfizer label / wikidoc
Plasma protein binding	~31% (concentration-independent)	Pfizer label
Volume of distribution	~40–50 L (≈ total body water)	AAC 2003
Half-life ($t_{1/2}$)	5–7 h	PubMed 14531724
Clearance	~9.5 L/h · 2 parallel pathways	Saturable non-renal + linear renal
Primary metabolites	PNU-142300, PNU-142586 (non-enzymatic)	No CYP induction / inhibition
Renal elimination (unchanged)	~30% of dose	Pfizer label
MAO interaction	Weak, reversible, non-selective	Tyramine / SSRI caution

Representative published LC-MS/MS methods for linezolid quantification in human plasma/serum cover the 25 ng/mL to 15 µg/mL range with ±15% accuracy/precision and negligible matrix effects; more recent multiplexed methods quantify linezolid, tedizolid, and contezolid simultaneously to support TDM in modern clinical practice. [7] [8]

What an IND-Grade Linezolid Bioanalytical Package Looked Like (1995–2000)

- **Platform:** triple-quadrupole LC/MS/MS — PE Sciex API III (and later API 365 / API 3000) class instruments — with reversed-phase C18 chromatography and a short isocratic or shallow-gradient run suitable for 100+ samples per day.
- **Matrix:** primarily human plasma (K_2EDTA or heparin), with secondary methods for urine, CSF, and epithelial lining fluid to support penetration studies; microdialysate and interstitial fluid methods came later for tissue PK work.
- **Sample prep:** protein precipitation or solid-phase extraction; small plasma volumes (~50–100 µL) to support pediatric and sparse-sampling Phase 1 protocols.
- **Range and linearity:** typical validated range covered trough to peak at 600 mg BID with >3 orders of dynamic range (tens of ng/mL to ~20 µg/mL); $R^2 > 0.99$ across calibrators.

- **Internal standard:** structurally similar analog; later work used stable-isotope-labeled linezolid-d_3 or ^{13}C analogs for absolute quantitation.
- **QC & GLP:** runs followed contemporary FDA guidance (the 2001 Bioanalytical Method Validation Guidance crystallized the practice the industry was already following): intra-/inter-day precision ≤15% CV, accuracy ±15%, LLOQ ±20%; documented freeze/thaw, bench-top, long-term, and autosampler stability.
- **Output for clinical pharmacology:** non-compartmental and 2-compartment modeling (often in WinNonlin) — the analyses that yielded 100% bioavailability, ~31% protein binding, ~5–7 h half-life, and the saturable non-renal clearance signal that later underpinned population-PK refinements in special populations (cystic fibrosis, renal impairment, pulmonary tuberculosis).

SECTION II · PERSONAL ROLE

Bioanalytical Support Behind the Curtain

AvTech Laboratories · 1995–1999 · Bioanalytical Support to Pharmacia & Upjohn

Role: Bench chemist, LC/MS/MS bioanalytical **method development** & sample analysis, under the mentorship of **Alex Cazers**. Helped build the department around a PE Sciex API III triple-quadrupole — one of the earliest commercial LC-MS/MS platforms adopted across contract bioanalysis — and developed / executed small-molecule PK assays in support of preclinical and clinical PK/PD studies for tier-one pharma sponsors. Method development — extraction chemistry, chromatographic conditions, MS transitions, internal-standard selection, validation design — was a core part of the job, not a handoff.

Linezolid contribution: bioanalytical method development and sample analysis in support of Pharmacia & Upjohn's oxazolidinone program — including the preclinical-through-Phase 1/2 window that generated the PK differentiation between PNU-100766 (linezolid, BID) and PNU-100592 (eperezolid, TID). That differentiation — reproducible twice-daily trough coverage at clinically relevant Gram-positive MICs — was the technical basis on which linezolid was selected for full development and ultimately approved by the FDA on April 18, 2000 as the first oxazolidinone.

Published output: co-author on the AvTech / Pharmacia & Upjohn bioanalytical method paper — Hopkins, Stalker, Johnson, Gammill, Cazers (1999). Determination of linezolid (PNU-100766) in human plasma by isocratic HPLC-MS-MS with liquid-liquid extraction (Proc. 10th Int'l Symp. Pharm. & Biomedical Analysis). The method was developed under Alex Cazers and refined at the bench — extraction chemistry, chromatography, MS transitions, and deuterated internal standard were all worked out in-house before being transferred to routine sample analysis. The assay became the reference method cited in subsequent peer-reviewed PK work, including Conte et al. (AAC 2002) intrapulmonary PK and Kearns et al. (Clin Pharmacol Ther 2003) neonatal disposition — both using [D_3]PNU-100766 as internal standard.

Other clients during this period: Parke-Davis, Eli Lilly and other tier-one sponsors. AvTech Labs was subsequently acquired by Eurofins as its entry into the U.S. pharmaceutical services sector.

Relevance to the fund thesis: direct hands-on exposure to how first-in-class small molecules move from discovery through IND to pivotal trials — specifically the clinical-pharmacology evidence base that discriminates between comparably-active candidates. That perspective informs diligence on today's early-stage anti-infective, oncology, and radioligand assets, where bioanalytical rigor and PK/PD discrimination remain the predictable choke points between a promising molecule and an approvable one.

Published Method · Cited in the Peer-Reviewed Linezolid PK Literature

Primary reference: Hopkins N.K., Stalker D.J., Johnson R.A., **Gammill J.C.**, Cazers A.R. Determination of linezolid (PNU-100766) in human plasma by isocratic HPLC-MS-MS with liquid-liquid extraction. AvTech Laboratories, Inc. / Pharmacia & Upjohn, Kalamazoo, Michigan. Proceedings of the Tenth International Symposium on Pharmaceutical and Biomedical Analysis, 1999.

The method developed at AvTech Labs became the **reference bioanalytical assay** for linezolid in human plasma during its clinical development at Pharmacia & Upjohn — and was subsequently cited in downstream PK literature as the standard from which later LC-MS/MS methods were derived. Co-authored with chemistry colleagues and the P&U clinical-pharmacology team, it is the bridge between the bench work and the published pharmacokinetic record.

More broadly, the isocratic HPLC-MS/MS / liquid-liquid extraction workflow established here — deuterated internal standard (D_3-PNU-100766), single-quad-to-triple-quad transfer, validated across the full clinical concentration range — became a working **standard operating procedure template** for first-in-class oxazolidinone bioanalysis. Downstream LC-MS/MS methods for tedizolid, contezolid, and the BPaL-regimen linezolid TB work still trace their architecture back to it.

Selected studies citing the Hopkins/Stalker/Johnson/Gammill/Cazers 1999 method:

• **Conte J.E. et al., 2002.** "Intrapulmonary Pharmacokinetics of Linezolid." Antimicrob. Agents Chemother. 46(5):1475–1480. Cited as reference 18; [D_3]PNU-100766 used as internal standard. journals.asm.org/10.1128/aac.46.5.1475

• **Kearns G.L. et al., 2003.** "Impact of ontogeny on linezolid disposition in neonates and infants." Clin. Pharmacol. Ther. 74(5):413–422. Cites the 1999 method; [D_3]PNU-100766 internal standard. doi.org/10.1016/S0009-9236(03)00226-1

A Personal Footnote · Three Gammills on One Molecule

My contribution to linezolid's development turns out to be one of three Gammill threads running through the same Pharmacia & Upjohn program — a fact I only fully appreciated in hindsight.

Chemistry. My brilliant and inspirational father, **Ronald B. Gammill**, is a co-inventor on the diazine-substituted oxazolidinone series — the direct structural precursor class to linezolid — alongside Hutchinson, Barbachyn, Brickner, and Patel. See **US 5,547,950** (1996) and **US 5,700,799** (1997). That diazine scaffold is what became linezolid's morpholine ring.

Law. My amazing stepmother, **Martha A. Gammill**, is one of the two attorneys of record on the foundational composition-of-matter patent, **US 5,688,792** (Barbachyn, Brickner, Hutchinson — 1997), alongside Donald L. Corneglio.

Clinical. On the bench at AvTech Laboratories, under the mentorship of my incredible boss **Alex Cazers**, I helped **develop and run** the LC/MS-MS plasma assay later published as Hopkins, Stalker, Johnson, **Gammill**, and Cazers (1999, Proceedings of the Tenth International Symposium on Pharmaceutical and Biomedical Analysis) — the reference method used across Pharmacia & Upjohn's linezolid clinical development program. Method development was part of the job: extraction, chromatography, MS transitions, and internal-standard design were all worked out at the bench.

Chemistry, legal protection, and clinical verification — three small steps, three Gammills, quietly converging on the same first-in-class antibiotic.

Impact on Humanity

Linezolid is, by most measures, one of the most consequential antibiotics approved in the last forty years — the first genuinely new antibacterial class since the late 1970s, and the drug that kept a wave of multi-drug-resistant Gram-positive infections treatable.

- **A new antibiotic class, at the worst moment.** FDA approval in April 2000 made linezolid the first fully synthetic oxazolidinone and the first new antibiotic class in roughly two decades[15]. It bound the 50S ribosomal subunit at a site no earlier antibiotic used — no pre-existing cross-resistance, active against strains that had defeated every other class on the shelf.
- **The MRSA crisis.** In 2005, at the peak of the epidemic, invasive MRSA caused an estimated **94,360 infections and 18,650 deaths in the U.S. alone** — more than HIV at the time[16]. Linezolid, alongside vancomycin, became the backbone of MRSA therapy, with ~100% oral bioavailability that enabled earlier hospital discharge, outpatient step-down, and first-line use in MRSA pneumonia per IDSA guidelines[17]. In the pivotal ZEPHyR trial and subsequent meta-analyses, linezolid delivered a **~15-percentage-point absolute survival benefit over vancomycin in MRSA nosocomial pneumonia** (80.0% vs. 63.5%; P=0.03)[21].
- **Reach.** Pfizer disclosed **~450,000 patients treated with Zyvox by mid-2003**[22]; branded worldwide sales peaked at $1.115B in 2008[3]. With generic linezolid available globally since 2015, cumulative exposure is in the **tens of millions of patient courses**.
- **The MDR-TB rescue.** Repurposed into the **BPaL regimen** (bedaquiline + pretomanid + linezolid), linezolid turned multi-drug-resistant and extensively drug-resistant tuberculosis from a near-untreatable disease into a largely curable one. The Nix-TB trial reported a **90% favorable outcome at six months** vs. historical XDR-TB cure rates in the 14–20% range — and collapsed treatment from 18–24 months of injectables to six months of oral therapy[18]. The WHO now recommends BPaL / BPaLM as standard of care for drug-resistant TB[19]. Global projections put linezolid use at **~188,500 MDR-TB patients per year by 2026**, with cumulative BPaL/BPaLM reaching **~500,000 patients**[23].

- **WHO Essential Medicines.** Linezolid is on the WHO Model List of Essential Medicines — both as a reserve antibiotic for resistant Gram-positives and as a core drug for drug-resistant TB[20].
- **A template for an entire drug class.** Because linezolid proved oxazolidinones were clinically viable, tedizolid (Sivextro, 2014) and contezolid (China, 2021) followed against the same template, with several TB-specific oxazolidinones now in late-stage trials[10][11].

Why This Matters · Beyond the Box Score

This is why people go into pharma — and it is certainly why I did.

The returns, the exits, the sales figures are the box score. The drug itself is the game: a new class at the moment older classes were failing, ~100% oral bioavailability that got patients out of the hospital, a regimen that turned XDR-TB from a ~15% cure rate into a ~90% cure rate on six months of pills, and a place on the WHO Essential Medicines list for indications it was never originally designed for.

That is what the money is actually underwriting, and what the box score measures imperfectly — the patient who went home, the TB clinic in Johannesburg or Chennai where "we can treat this" replaced "there's nothing more we can do."

First-in-class medicines are how a small group of people quietly move the mortality curve for everyone else.

Why the Linezolid PK Story Still Teaches

- **PK is a gating criterion, not a downstream exercise.** Linezolid's selection over eperezolid was made on Phase 1 human PK data, not preclinical screens. Programs that under-invest in early clinical pharmacology (or in the bioanalytical infrastructure behind it) routinely fail at this stage.
- **Bioanalytical method quality compounds.** Methods that performed well in 1996–1999 plasma PK work continued to serve therapeutic drug monitoring, myelosuppression exposure-response analysis, and tuberculosis / CF special-population studies well into the 2010s.
- **First-in-class opens subsequent generations.** The rigor that got linezolid approved (ribosomal MoA, 100% F, well-characterized saturable CL) became the reference template that tedizolid and contezolid were measured against.
- **Anti-infective franchise economics are durable, not explosive.** Useful analog when underwriting novel antibacterials, phage-enhancers, or resistance-breakers: expect sub-$2B peaks, long tails, generic displacement — but global essential-medicine status and 20+ years of clinical relevance.

Sources

[1] Brickner SJ et al., "The discovery of linezolid, the first oxazolidinone antibacterial agent," Curr Drug Targets Infect Disord 2001; Leach et al., Ann NY Acad Sci 2011. pubmed.ncbi.nlm.nih.gov/12455414

[2] Linezolid — Wikipedia (history, chemistry, class). en.wikipedia.org/wiki/Linezolid

[3] Sheller P.C., "$2.3 Billion Settlement — Pfizer/Zyvox" (cites Pfizer annual reports: ~$4.4B cumulative Zyvox sales 2000–2008; $1.115B WW 2008). sheller.com/2-3-billion-settlement-pfizer-zyvox

[4] DrugPatentWatch & Pharsight — Zyvox patent / ANDA landscape. pharsight.greyb.com/drug/zyvox-patent-expiration

[5] FDA Approval Package NDA 021130 — Zyvox Tablets, IV, Oral Suspension, April 18, 2000. accessdata.fda.gov (21130)

[6] P&T / PMC — Sandoz generic linezolid injection approval (2015); Pfizer FY2014 Zyvox ~$680M U.S. pmc.ncbi.nlm.nih.gov/articles/PMC4571841

[7] Wu et al., "LC-MS/MS for simultaneous quantification of linezolid, tedizolid, contezolid in human plasma," 2025. pubmed.ncbi.nlm.nih.gov/41054619

[8] Meagher AK et al., "Population pharmacokinetics of linezolid in patients treated in a compassionate-use program," AAC 2003. pmc.ncbi.nlm.nih.gov/articles/PMC151778

[9] Stalker DJ & Jungbluth GL, "Clinical pharmacokinetics of linezolid, a novel oxazolidinone," Clin Pharmacokinet 2003. pubmed.ncbi.nlm.nih.gov/14531724

[10] Contezolid (MRX-I) — First Approval, Drugs 2021. pmc.ncbi.nlm.nih.gov/articles/PMC8536612

[11] Sivextro (tedizolid) — Cubist FDA approval, 2014. fda.gov — Sivextro

[12] Hopkins N.K., Stalker D.J., Johnson R.A., Gammill J.C., Cazers A.R. "Determination of linezolid (PNU-100766) in human plasma by isocratic HPLC-MS-MS with liquid-liquid extraction." AvTech Laboratories, Inc. / Pharmacia & Upjohn, Kalamazoo, MI. Proceedings, 10th Int'l Symposium on Pharmaceutical and Biomedical Analysis, 1999. (Conference proceedings; cited as reference in Conte 2002 and Kearns 2003.)

[13] Conte J.E. et al., "Intrapulmonary Pharmacokinetics of Linezolid," AAC 2002; 46(5):1475–1480 — cites Hopkins/Stalker/Johnson/Gammill/Cazers (ref. 18). journals.asm.org/10.1128/aac.46.5.1475-1480.2002

[14] Kearns G.L. et al., "Impact of ontogeny on linezolid disposition in neonates and infants," Clin Pharmacol Ther 2003; 74(5):413–422 — cites the 1999 method. pubmed.ncbi.nlm.nih.gov/14586382

[15] Barbachyn M.R. & Ford C.W., "Oxazolidinone structure–activity relationships leading to linezolid," Angewandte Chemie Int. Ed. 2003; 42:2010–2023. onlinelibrary.wiley.com/doi/10.1002/anie.200200528

[16] Klevens R.M. et al., "Invasive Methicillin-Resistant Staphylococcus aureus Infections in the United States," JAMA 2007; 298(15):1763–1771 — 94,360 invasive infections, 18,650 deaths (2005). jamanetwork.com/journals/jama/fullarticle/209197

[17] Liu C. et al., "Clinical Practice Guidelines by the IDSA for the Treatment of MRSA Infections in Adults and Children," Clin. Infect. Dis. 2011; 52(3):e18–e55. idsociety.org/practice-guideline/mrsa

[18] Conradie F. et al., "Treatment of Highly Drug-Resistant Pulmonary Tuberculosis" (Nix-TB), N Engl J Med 2020; 382:893–902 — 90% favorable outcome at 6 months post-treatment. nejm.org/doi/full/10.1056/NEJMoa1901814

[19] World Health Organization, "WHO consolidated guidelines on tuberculosis. Module 4: Treatment — drug-resistant tuberculosis treatment, 2022 update." who.int/publications/i/item/9789240063129

[20] WHO Model List of Essential Medicines — Linezolid. list.essentialmeds.org/medicines/185

[21] Wunderink R.G. et al., "Linezolid in Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Randomized, Controlled Study" (ZEPHyR), Clin. Infect. Dis. 2012; 54(5):621–629 — survival 80.0% vs. 63.5% (P=0.03) in MRSA pneumonia subgroup. academic.oup.com/cid/article/54/5/621/325602

[22] Pfizer Inc. / Infection Control Today, July 2003 — Zyvox diabetic foot infection approval release disclosing ~450,000 patients treated worldwide with Zyvox by mid-2003. infectioncontroltoday.com — Zyvox 2003

[23] Suresh K. et al., "Global adoption of 6-month drug-resistant TB regimens," PLOS ONE 2024 — projected linezolid use in ~188,500 MDR-TB patients/year by 2026; cumulative BPaL/BPaLM ~501,000 patients. pmc.ncbi.nlm.nih.gov/articles/PMC10769048