

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS, INC.,
Petitioner

v.

NIVAGEN PHARMACEUTICALS, INC.,
Patent Owner

IPR2025-00779
Patent No. 11,813,291

**DECLARATION OF BARRETT RABINOW, Ph.D. IN SUPPORT
OF PATENT OWNER'S REQUEST FOR DISCRETIONARY
DENIAL OF PETITIONS FOR *INTER PARTES* REVIEW**

I, Barrett Rabinow, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by Patent Owner Nivagen Pharmaceuticals, Inc. (“Nivagen”) as an independent expert consultant to render my opinions on a specific technical issue within my knowledge and expertise. This issue relates to both of Petitioner Amneal Pharmaceuticals, Inc.’s (“Amneal”) challenges of U.S. Patent Nos. 11,813,291 (“the ’291 patent”) in IPR2025-00779 and 11,925,661 (“the ’661 patent”) in IPR2025-00731.

2. I have been asked to explain what was the Phosphate Polyfusor® (“PPF”) product discussed in the “Terlevich” reference (Ex. 1009), how it was used when it was available in the United Kingdom (it was never approved in the United States), and whether and how that product differed in important ways from a sterile, ready-to-use (RTU) potassium phosphate solution or injection product claimed in the ’291 patent or the ’661 patent. In my opinion, PPF was not a sterile, RTU product, and its drawbacks and potential dangers to the patients were well-known and well-published in the relevant field of art.

II. QUALIFICATIONS

3. I am an expert in pharmaceutical research and development and sterile drug development. I have over 40 years of industrial chemistry experience. I am a

named inventor on at least 15 granted U.S. patents, as well as additional applications and foreign patents.

4. During a litigation in the District of Delaware involving the '291 patent and the '661 patent, case number 24-846, which I understand is still ongoing, I served as an expert declarant in a preliminary injunction proceeding and rendered opinions relating to the same field of technology as my opinions here.

5. I currently am a consultant for the pharmaceutical industry. My consulting practice includes R&D, manufacturing, regulatory, quality, and patent issues, with an emphasis on sterile injectable dosage forms, and issues concerning chemical reactions, formulations, stability, reaction rates, leaching, gas transmission through plastic, closure/container technology, impurities, and generally characterization and analysis of pharmaceutical products.

6. I received a Bachelor of Arts (A.B.) from Cornell University, *cum laude* with distinction in all subjects and honors in chemistry. I earned a Master of Science in organic chemistry (1969) and a Ph.D. (1974) in physical-organic chemistry from the University of Chicago. I also received a Postdoctoral Fellowship in Clinical Chemistry funded by the National Institutes of Health at Michael Reese Medical Center in Chicago.

7. Subsequently, I was Director of Chemistry at Norwegian-American Hospital in Chicago, after which I joined Baxter Healthcare in 1977. At Baxter, I

led corporate troubleshooting teams and task forces of industry-wide organizations for the most serious chemical problems of high commercial impact, developing novel methods and leading-edge techniques to solve critical research and manufacturing problems. I developed an IV container extractable program that became industry-standard. I further negotiated favorable outcomes for Baxter and the industry at the FDA.

8. I conceived of and developed a rapid testing approach for broad IV solution product lines, expediting change control, reducing stability testing, showing compliance with Good Distribution Practices, and minimizing testing for elemental impurities and leachables. I further presented this approach to the UK Medicines and Health Care Regulatory Agency, who endorsed the concept.

9. I was also responsible for global technical vision for new product and process design, a multi-disciplinary function. I led a research team in developing a nanoparticle drug delivery platform now used for long-term (i.e. 1 month) injections for HIV treatment.

10. I was Director of Chemistry at Baxter and supervised over one hundred scientists. I was also appointed a Baxter Distinguished Scientist, a position held by only around fifteen scientists and engineers throughout Baxter's 50,000-person workforce. At Baxter, I resolved many problems related to the formulation and manufacturing of drug products. I have formulation experience in over 40 of

Baxter's premixed ready-to-use injectables drug line. I worked for Baxter for nearly 40 years.

11. My professional activities have included the Committee on Aluminum Methodology with the Parenteral Drug Association, consultant on aluminum methodology and appropriate levels in dialysis solutions for the Association for the Advancement of Medical Instrumentation, consultant on systematizing evaluation of leachables from medical devices for the International Standards Organization (ISO), and a consultant to and presenter to the FDA on behalf of the Health Industry Manufacturers' Association on issues of aluminum methodology, toxicology, and formulations for large volume parenteral solutions, osmolarity and stability storage labeling issue. I further have served as a reviewer for the Journal of Pharmaceutical Sciences.

12. Other details concerning my background, academic work, and professional history are set forth in my curriculum vitae, which will be filed concurrently with this Declaration as Exhibit 2007.

13. I am being compensated at my normal consulting rate for the time I spend on this matter. My compensation is in no way contingent on the nature of my findings, the presentation of my findings in testimony, or the outcome of this or any other proceeding. I have no other interest in this proceeding.

III. DOCUMENTS AND MATERIALS CONSIDERED

14. I have reviewed the two petitions for *inter partes* review Amneal filed with the Board, including the exhibits relevant to my opinions here, and in particular the Terlevich reference, the '001 Application (the published version attached to Amneal's petitions, Ex. 1006), and the two Declarations of Dr. Mansoor M. Amiji dated April 11, 2025 that were filed with the two petitions in IPR2025-00779 and IPR2025-00731. I have also found and reviewed the additional publications and other publicly available information regarding the Fresenius Kabi Phosphates Polyfusor® ("PPF") product discussed in this Declaration. In forming my opinions, I also relied on my experience and my education.

IV. QUALIFICATION OF A PERSON OF ORDINARY SKILL IN THE ART

16. A POSA for the '291 patent and the '661 patent would have had at least a Ph.D. degree in chemistry or biochemistry and at least 2 years of experience (or less education but more years of experience, i.e., an M.S. with at least 3-5 years of experience, or a B.S. with a minimum of 6 years of experience) with pharmaceutical drug product formulation, analysis, and development, optimization, and manufacture, including experience with processes and techniques for minimizing impurities in and improving the stability of, pharmaceutical drug products during manufacture and storage.

17. I have reviewed the POSA definition given by Dr. Amiji in his Declaration in support of Amneal's petitions. (Ex. 1003 at ¶¶24-26). Dr. Amiji opined that "a POSITA would have had an advanced degree in chemistry, biology and/or pharmaceuticals, plus a few years (e.g., 2-3) of experience in *preparing parenteral formulations*. Additional education may serve as a substitute for a lack of experience and vice versa." (*Id.* at ¶26 (emphasis added by me)). I am not quite sure what Dr. Amiji meant by "preparing parenteral formulations." If he meant activities relating to "pharmaceutical drug product formulation, analysis, and development, optimization, and manufacture, including experience with processes and techniques for minimizing impurities in and improving the stability of, pharmaceutical drug products during manufacture and storage," as I set forth above but further limited to "parenteral formulations" which includes injectables like the claimed subject matter in the '291 patent and the '661 patent, I can accept Dr. Amiji's definition. I do not believe Dr. Amiji's definition of a POSA would change my opinions below.

**V. THE PHOSPHATES POLYFUSOR® PRODUCT IS THE
OPPOSITE OF A STERILE, READY-TO-USE PRODUCT
CLAIMED IN THE '291 PATENT OR THE '661 PATENT**

**A. POLYFUSOR® USES A "SEMI-RIGID CYLINDRICAL
POLYETHYLENE CONTAINER" AND AN OPEN SYSTEM,
WHICH IS *NOT* A FLEXIBLE POLYMER CONTAINER
AND A CLOSED SYSTEM**

18. The Terlevich reference (Ex. 1009) describes Fresenius Kabi's Phosphates Polyfusor® or "PPF" product as follows: "A Polyfusor is a sealed *semi-rigid cylindrical polyethylene container*, with a twist-off seal at one end and a ring tab at the other. A 500-mL PPF contains 50 mmol phosphate, 81 mmol sodium and 9.5 mmol potassium." (Ex. 1009 at 1326 (emphasis added by me)). That is the extent of the description of PPF's structure in Terlevich. (*Id.*; see also Ex. 1003, Amiji Decl. at ¶ 94).

19. Regarding how to use the PPF product, Terlevich gives this description: "we now use 50 mmol of intravenous phosphate, infused over 24 h via a dedicated peripheral intravenous cannula, in all refeeding syndrome patients except those in renal failure." (Ex. 1009 at 1326). There is no disclosure on whether or how a PPF container must be prepared before the infusion can be properly carried out. (*Id.*; see also Ex. 1003 at ¶¶ 92-94 (no discussion from Dr. Amiji on how PPF was actually used, which would have revealed that PPF was *not* a sterile, ready-to-use product.)).

20. The sterile, ready-to-use product or composition claimed by the Nivagen patents, in contrast, uses a flexible container.

21. The "semi-rigid" container for the PPF product requires an *opening* that *connects* the contents of that container to the outside air, for pressure equalization as the fluid volume drained out. Such a semi-rigid plastic container is

a “noncollapsible container,” which “must be vented externally to allow air to enter and the fluid to egress.” (Joint Commission 2013 (Ex. 2014); *see also* Rangel-Frausto 2010 (Ex. 2008), at 1 (semi-rigid plastic containers are “open infusion containers” which must be vented or “admit air (air filter or needle) to empty the contents”); Rosenthal 2004 (Ex. 2009), at 136 (“if the system needs to be vented, as is mandatory with glass bottles or semirigid plastic containers in developing countries”)).

22. Such an opening that is necessarily present on a semi-rigid container for infusion allows an ingress of air via an air filter or needle. (Rangel-Frausto 2010, Ex. 2008, at 1). Air ingress could then lead to microbial contamination of the remaining fluid within the container, particularly in hospital environments. (Joint Commission 2013 (Ex. 2014); Rangle-Frausto 2010 (Ex. 2008); Rosenthal 2004 (Ex. 2009) at 136 (“open, semirigid, noncollapsible” systems bring “additional risks of extrinsic contamination”)). By contrast, a flexible plastic container does not require external venting because it can *fully* contract (collapse) to remove any empty space (which would contain a partial vacuum) as the fluid was extracted, does not require external venting, is a “closed system,” and thus offers a safe, “closed” system while still allowing a proper flow of the contents and, therefore, a proper infusion process. (Rangel-Frausto 2010 (Ex. 2008) at 1).

23. To be clear, a “semi-rigid” container is an inflexible container. Dr. Amiji opines that semi-rigid containers “have some flexibility,” and “a POSITA would recognize semi-rigid polyethylene containers are ‘flexible polymeric containers.’” (Ex. 1003 at ¶ 205). This is not correct. A semi-rigid container does not contract or collapse fully as the liquid contents drain out, which would create a vacuum behind the liquid and prevent proper flow. On that important point, a semi-rigid container is not the same as a flexible polymeric container, and Dr. Amiji does not appear to understand this important point.

24. Dr. Amiji does not seem to appreciate that “there are two types of i.v. infusion containers (open and closed infusion systems) in use worldwide.” (Franzetti 2009 (Ex. 2009) at 1041-43; *see also* Joint Commission 2013 (Ex. 2014)). “Open i.v. infusion containers are rigid (glass, burette) or *semi-rigid plastic containers* that must admit air to empty (air filter or needle).” (Franzetti 2009 (Ex. 2009) at 1041-42 (emphasis added by me)). In contrast, “closed i.v. infusion containers are fully collapsible plastic containers that do not require or use any external vent (air filter or needle) to empty the solution, and injection ports are self-sealing.” (*Id.*). Similarly, the Joint Commission stated unequivocally that “[w]orldwide, there are two types of IV fluid containers in use: a collapsible plastic container that requires no external venting for the bag to empty (a closed infusion container) and a noncollapsible container (glass bottle or semirigid plastic bottle or

burette) that must be vented externally to allow air to enter and the fluid to egress (an open infusion container).” (Ex. 2014 (citing Maki 2011)).

25. Plainly stated, there is no middle ground for a “some flexibility” closed system using a semi-rigid plastic container, such as what Dr. Amiji erroneously envisioned and opined. (Ex. 1003 at ¶ 205).

26. Because the PPF product uses a semi-rigid container, it must contain a port with air filter that is opened to allow air ingress before the infusion process can be carried out, or alternatively a needle must be inserted into the container to create a mandatory vent. (*See* Rangel-Frausto 2010 (Ex. 2008) at 1; Franzetti 2009 (Ex. 2010) at 1041-42).

27. This “external vent” structural feature was not mentioned in the Terlevich reference, which contained a very terse description of the structure of PPF. However, it was not necessary for Terlevich to describe this structure. A POSA would readily understand that the PPF product with its semi-rigid plastic container is in fact an “open” system that includes an external vent (air filter or needle) and requires a preparatory step of opening or generating the vent before use, which is the opposite of the sterile, ready-to-use, and closed system (no opening to the outside air) described and claimed in the ’291 patent and the ’661 patent.

28. The semi-rigid container used in infusion products brought very important consequences which turned out to be detrimental to patients using this

product and the healthcare system in general, and became a well-known concern in the field. I will discuss these well studied health consequences in the next section.

29. The PPF product was never approved for use in the United States. I make this conclusion both on my own memory working in this field, and my search of publicly available information regarding this product. The Joint Commission, which is a healthcare industry group, noted in 2013 that “open infusion systems ... are still in use in many parts of the world, including Eastern Europe, Germany, Asia, Africa, and Latin America,” but not in the U.S. (Ex. 2014).

30. The PPF product was used by the National Health Services in the United Kingdom for a few years, but I understand that it was discontinued in early 2020.

**B. THE SEMI-RIGID CONTAINER FOR POLYFUSOR®
MEANS THIS PRODUCT WAS NEITHER STERILE NOR
READY-TO-USE**

31. It had become appreciated around 2004-2010 by practitioners in this field, that IV administration in the critical care setting could be associated with a higher incidence of blood stream infection, BSI. (Rosenthal 2004 (Ex. 2009); Franzetti 2009 (Ex. 2010); Rangel-Frausto 2010 (Ex. 2008); Graves 2001 (Ex. 2011); Joint Commission 2013 (Ex. 2014)).

32. This unfortunate increase in BSI was traced to several factors, one of the major factors being the type of container for the IV solution. (*Id.*) An inflexible

glass or plastic container, such as the “semi-rigid cylindrical polyethylene container” of the PPF product, was associated with a higher incidence of BSI compared with a flexible plastic bag. (*Id.*).

33. As I mentioned above, a container that allows air ingress could lead to microbial contamination of the remaining fluid within the container, particularly in hospital environments. By contrast, a flexible plastic container fully collapses as the liquid contents drain out, preventing any vacuum from forming behind the liquid, thus offering a “closed” system while still allowing a proper flow of the contents and, therefore, a proper infusion process.

34. Higher BSI rates of open systems led to increased morbidity and mortality, significantly higher costs to treat the bloodstream infection, and an overburdened healthcare system, which could potentially deprive other patients of a critical care bed, depending upon resource availability.

35. To determine if these detrimental consequences were occurring and the magnitude of the problem, a series of comparative prospective, clinical trials were conducted in those parts of the world still using the cheaper, semi-rigid containers. At the same hospitals, one cohort of several hundred critical care patients was treated with an open system, and then another cohort was treated with a closed system. The hospitals otherwise utilized the highest form of infection control procedures

available to maintain a relatively low baseline level of infection, so as to clarify more accurately the role of the container.

36. In Argentina for example, it was found that “The incidence of (central venous catheter) CVC-associated bacteremia during use of the closed system was significantly lower than during use of the open system (2.36 vs 6.52/1000 catheter-days, relative risk=0.36, 95% confidence interval=0.14-0.94, P=.02); ... In all, 17 patients with catheter-associated bacteremia died during the period when the open system was in use (2.8%), versus only 1 (0.2%) during use of the closed system (relative risk 0.09, P=.003). The calculated cost savings in the 20 hospital-month intervention period was \$53,768 and 130.9 ICU days.” (Rosenthal 2004 (Ex. 2009) at 138).

37. In Italy, it was found that “[o]verall, the chance of a patient acquiring a CVC-BSI was significantly decreased by 61% in the closed period (Cox proportional hazard ratio 0.39, P=0.0043).” (Franzetti 2009 (Ex. 2010)). The comparison in cumulative probability for developing a bloodstream infection is shown in the Figure. Cumulative probability remains constant over time on central venous catheter for closed system, but rises precipitously for open systems. The sickest patients, who spend longer time in the ICU, would thus have very high rates of contracting infection.

38. Of the parameters listed in Table 2 of Franzetti 2009 (Ex. 2010), copied below, only those related to CVC indicate statistically significant findings. The relative risk of a BSI per 1000 CVC days is statistically significantly greater for open than for closed containers.

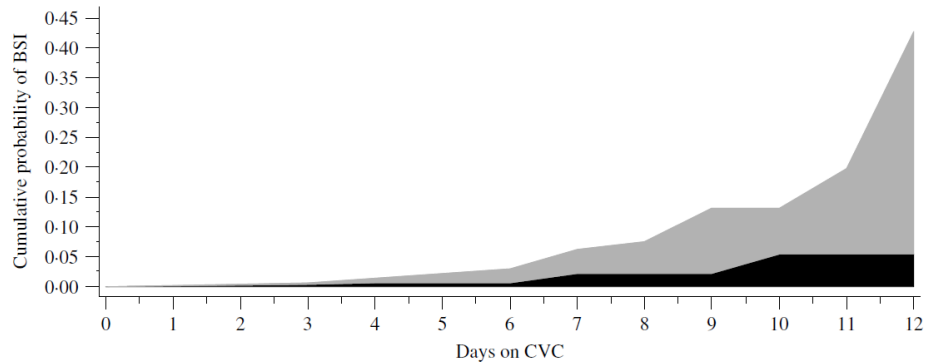


Fig. 2. Cumulative probability of first bloodstream infection (BSI) displayed by days on central vascular catheter (CVC). Numbers at risk for closed (■) vs. open (▒) containers: closed (day 0=507, day 4=505, day 7=123, day 10=30, day 12=10); open (day 0=558, day 4=553, day 7=116, day 10=28, day 12=7).

Table 2. Incidence of CVC-associated BSI (LCBI and CSEP), CAUTI, VAP, and mortality during the two study periods

	Open infusion container period (N = 608)	Closed infusion container period (N = 565)	RR	95% CI	P value
CVC days (n)	3545	3426			
CVC-associated BSI (n)	29	12			
CVC-associated BSI/1000 CVC days	8.2	3.5	0.43	0.22–0.84	0.011
Patients with CVC-associated BSI (%)	4.8 %	2.1 %	0.45	0.23–0.86	0.014
Urinary catheter days (n)	2133	2135			
CAUTI (n)	7	4			
CAUTI/1000 catheter days	3.3	1.9	0.57	0.17–1.95	0.36
Mechanical ventilator days (n)	1039	999			
VAP (n)	4	7			
VAP/1000 mechanical ventilator days	3.8	7.0	1.82	0.53–6.20	0.33
Deaths (n)	25	30			
Patients (n)	608	565			
Patients who died (%)	4.1 %	5.3 %	1.29	0.77–2.17	0.33

CVC, Central vascular catheter; BSI, bloodstream infection; LCBI, laboratory-confirmed bloodstream infections; CSEP, clinical primary nosocomial sepsis; CAUTI, catheter-associate urinary tract infection; VAP, ventilator-associated pneumonia; RR, relative risk; CI, confidence interval.

39. Regarding mortality, the authors note “[w]hile no differences were found in mortality rates between the two periods, it should be noted that the power to detect such differences in the study was low due to the small study sample size (relative to a mortality endpoint), the few BSI-related deaths, and the short length of follow-up (relative to a mortality endpoint).” Franzetti 2009 (Ex. 2010 at 1046).

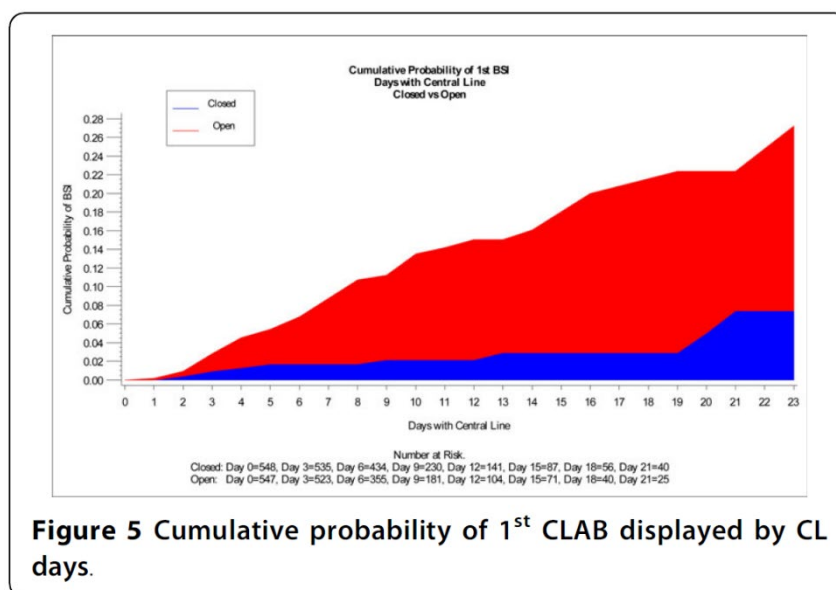
40. The authors additionally note “[a] recent meta-analysis of the cost studies published in the last 5 years found that the average cost of one BSI was US\$36,441 (range US\$1,822-107,156). Most importantly, CVC-BSIs are apparently related to increased attributable mortality as reported by Pittet and colleagues who cited an attributable mortality of 25%.” (*Id.* at 1045-46).

41. In Mexico, it was found that “[o]verall, the chance of a patient acquiring a (central line-associated bloodstream infection) CLAB decreased significantly-by 81%- in the closed container period (Cox proportional hazard ratio 0.19, $P < 0.0001$). Mortality during the closed container period (16.1%) was statistically significantly lower than during the open container period (23.4%) (RR = 0.69; 95% CI = 0.54 -0.88; $P = 0.002$) (Table 2).” (Rangel-Frausto 2010 (Ex. 2008) at 4). Again, the only parameters that changed significantly were associated with central line infections. Similar to a previous study, the cumulative probability of a BSI with increasing time spent with a central line was nearly constant for a closed container, but rose ominously for the open container.

Table 2 Incidence of CLAB, CAUTI, VAP, and mortality during the two study periods

	Open infusion container N = 548	Closed infusion container N = 548	RR	95% CI	P-value
CL days no.	3661	4055	-	-	-
CLAB no.	59	13	-	-	-
CLAB per 1000 CL days	16.1	3.2	0.20	0.11 - 0.36	<0.01
Percentage of patients with CLAB	10.8	2.4	0.22	0.12 - 0.40	<0.01
Urinary catheter days no.	3302	3590	-	-	-
CAUTI no.	30	36	-	-	-
CAUTI per 1000 catheter days	9.1	10.0	1.10	0.68 - 1.79	0.69
Mechanical ventilator days no.	2344	2592	-	-	-
VAP no.	66	71	-	-	-
VAP per 1000 mechanical ventilator days	28.2	27.4	0.97	0.70 - 1.35	0.87
Deaths no.	128	88	-	-	-
Percentage of patients who died	23.4	16.1	0.69	0.54 - 0.88	<0.01

no., number; CL, central line; CLAB, central line-associated bloodstream infection; CAUTI, catheter-associated urinary tract infection; VAP, ventilator-associated pneumonia



42. The authors further note: “[m]oreover, CLABs are apparently related to increased attributable mortality: In an Australian study, CLABs resulted in excess mortality of 12% [37], and in a study from the United States, Pittet et al reported an attributable mortality of 25% [38,39]. Rosenthal et al likewise published an attributable mortality of 25% in a study of CLABs in medical/surgical ICUs in

Argentina [12], and Higuera et al recently reported an attributable mortality of 20% in a study of ICUs in Mexico [2].” (*Id.* at 5-6).

43. In a comparison study performed in Mexico and Brazil, it was found “[a] closed system reduced the risk of CLABSI. The hazard ratios for the closed versus open container were between 0.15 and 0.31 (p values <0.001), indicating a clinically significant reduction in the risk of admissions having a CLABSI. A simulation study showed that a closed system reduced the number of infections, costs and deaths.” (Graves 2011 (Ex. 2011 at 1)). The table below copied from the Graves 2011 reference depicts the total numbers of patients infected and dead for open vs. closed containers.

Table 3 Difference in the number of infected and dead admissions, and the difference in total bed days for the open and closed systems based on 1000 simulated admissions with a central line

	Mexico Mean (95% CI)	São Paulo Mean (95% CI)
Numbers infected		
Open system	146 (76 to 266)	92 (37 to 182)
Closed system	26 (9 to 61)	28 (8 to 73)
Difference*	120 (62 to 213)	64 (24 to 129)
Numbers dead		
Open system	251 (102 to 395)	267 (125 to 407)
Closed system	161 (47 to 294)	187 (74 to 322)
Difference*	90 (27 to 158)	81 (25 to 143)
Bed days		
Difference*	34 (–1211 to 1246)	2693 (1152 to 4569)

Simulated for admissions of an average age and ASIS score.

*Open minus closed.

CI, credible interval.

44. Based upon all of the above as well as other work, the International Society for Infectious Diseases issued a position statement on the topic:

Open vs closed intravenous infusion systems

The impact of the infusion system on CLABSI rates has been studied by comparing open and closed intravenous systems. It has been widely accepted that open systems may increase the risk of contamination and administration-related CLABSI, because of microbial entry into the system through air entry (Maki et al., 2011). As reported in a recent systematic review (Perin et al., 2016), by way of illustration, the rate of CLABSI was 35.3% greater among patients who received compounded parenteral nutrition (PN) through an open system in comparison to those who received PN through a closed system.

In a randomized clinical trial comparing rates of CLABSI between patients using an open system (three-way stopcocks) and standard flushing, and patients using a closed system (pre-pierced septa) and single-use prefilled flushing devices, it was shown that closed systems had significantly lower rates of CLABSI (2.21 per 1000 CL-days vs. 6.40 per 1000 CL-days, 95% CI 0.16-0.76, $p = 0.006$) and was cost-effective (Rosenthal et al., 2015). However, open infusion containers and systems, such as three-way stopcocks, continue to be widely used in limited-resource settings.

(Lutwick 2019, Ex. 2012).

45. In conclusion, reference to a semi-rigid container for the PPF, perhaps “widely used in limited-source settings” (Lutwick 2019), is quite far apart from and not a valid comparison to the sterile, ready-to-use, closed-system Nivagen phosphates in flexible container. In my opinion, the open system of PPF is the *opposite* of the claimed closed system. The PPF represents an older and cheaper product for locations and situations with limited resources, and is something to be replaced by a closed system when practical.

46. I reserve the right to amend or supplement my opinions in this Declaration based on the rules of the Patent Trial and Appeal Board, and in view of any claim construction positions that may be adopted by the Board, or any discovery, declarations, testimony, or arguments proffered by Amneal later in these proceedings.

Date: 16 July 2025

Signature: Bernett E. Palmar