

Baxa Corporation

The Exacta-Mix™ 2400 Compounder

Technical Paper

Understanding the design and
performance standards for the
Baxa automated compounder.



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Introduction

Baxa Corporation is the only medical device manufacturer that designs, builds, markets and supports automated compounders and software as a principle business. As a result, Baxa systems must offer product value and performance that stand on their own.

The Exacta-Mix 2400 Compounder (EM2400), introduced in December 2001, represents the most advanced technology for automated compounding and medication safety in the industry. This paper focuses on the performance of the EM2400 and how these attributes are measured and verified.

Performance Requirements for Automated Compounders

Using automated compounding technology offers a number of advantages over manual mixing.¹ Automated mixing provides greater accuracy for delivery volumes. Pharmacies can reduce the opportunity for contamination, particularly with compounders which combine macro and micro mixing capability, by reducing the number of container manipulations. Facilities with high nutritional patient census can use far less labor, and software can facilitate calculations, order entry, quality assurance, worksheets and label generation.

The American Society for Health-System Pharmacists (ASHP) published guidelines that state automated compounding devices should be used for “improving patient care and enhancing efficiency while remaining cost-effective.”² Safe automated compounding devices, the guidelines state, should meet specific objectives related to cost justification:

1. Enhanced efficiency and worker safety...and patient safety with parenteral use.
2. Reduction in labor associated with manually compounded parenteral nutrition admixtures.
3. Reduction in waste through more efficient use of base solutions and additives.²

Automated compounding systems, therefore, should be designed to minimize or eliminate the opportunity for medication errors thereby enhancing patient safety. Further, they should simplify the compounding operation, saving time and reducing overall costs for labor and materials.

The guidelines define three areas to assist in the selection and use of automated compounders – *system performance* requirements, *manufacturer’s* responsibilities and *pharmacy* responsibilities.

The EM2400 System automates up to 24 ingredients, reducing contamination points and reducing the potential for errors in manual additions. Automated delivery of 24 ingredients produces higher throughput than any other micro add system, allowing mixing to be performed later in the day and reducing the need for change orders.

Core Performance Requirements for Automated Compounders

The following are the system performance requirements outlined by the ASHP guidelines for safe automated compounding², and a description of how the EM2400 meets or exceeds the requirements.

Accuracy to within 5% of the amount programmed, with verification.

Repeatable accuracy for single ingredient delivery on the EM2400 is $\pm 3\%$ for volumes above 1 mL; ± 0.02 mL or 3% whichever is greater for volumes of 0.4 to 1.0 mL; and ± 0.02 mL for volumes of 0.2 to 0.4 mL. The table below states the EM2400 delivery accuracy specification.

Delivery Volume	Accuracy Range
0.2 mL	+/- 0.02 mL or 10%
0.4 mL	+/- 0.02 mL or 5%
1.0 mL and greater	+/- 3%

Compliance to this specification was proven by measuring the weight of fluid removed from the source containers of different ingredients under careful laboratory conditions. Data was collected at multiple delivery volumes and the mean and standard deviation of deliveries at each volume were calculated.

The table below summarizes the raw data results.

Volume Tested	Resulting Mean	Standard Deviation	# of data points
0.2 mL	0.202 mL	0.00648 mL	441
0.4 mL	0.402 mL	0.00755 mL	441
1.0 mL	0.997 mL	0.0107 mL	441
10 mL	10.01 mL	0.106 mL	441
20 mL	19.99 mL	0.165 mL	441
100 mL	100.3 mL	0.911 mL	441

The table below states the results in terms of a percentage.

Volume Tested	Average Accuracy	% Error
0.2 mL	101%	3.21%
0.4 mL	100.5%	1.88%
1.0 mL	99.7%	1.07%
10 mL	100.14%	1.65%
20 mL	99.96%	0.825%
100 mL	100.3%	0.908%

From the data above it is easy to conclude that the compounder delivers a final bag weight within $\pm 3\%$, with typical performance within ± 1 to 2% .

Inherent safeguards, including the ability to detect inadvertent source solution mixups; ability to detect situations that could result in inaccurate deliveries; and the ability to keep incompatible source solutions separate.

System set up and verification, using bar code technology, is the key to ensuring proper medication delivery. The EM2400 requires a prime and verify step to ensure that source solutions match the configuration. Error detection features in the EM2400 also alert the user for tube set occlusions and empty source containers which could result in inaccurate deliveries.

Air Detection. An empty vial will result in air being pumped. Therefore, an ultrasonic air bubble detector was incorporated to detect this condition. The EM2400 air detector will reliably detect an empty source container. As with all air detectors, a specific air volume was chosen to maximize sensitivity without generating nuisance alarms. The pumping parameters were set to correspond to a 0.2 mL volume sensitivity.

Occlusion detection. The occlusion detector senses the negative pressure (vacuum) in the pump tubing upstream of the pump. Negative pressures of varying magnitudes are present in the tubing during normal operation. The pump is designed to pump accurately under these normal pressures. However, conditions such as an occluded line would result in no fluid pumping and the occlusion detector is designed to detect this. Sophisticated algorithms were used to ensure that all occluded line conditions would be detected without generating nuisance alarms under normal operating conditions.

Source solution identification. Bar codes on containers and fluid lines are different, and the software requires that the correct ingredient be matched to the correct port. Mixcheck™ Reports provide complete information for each bag pumped as an added assurance of quality.

The EM2400 valves are opened and closed via a software-controlled mechanism. The software in this process ensures repeatability. Since it is paramount that the correct valve be opened each time, a separate monitoring check was put in place. Monitoring systems independently verify that the motor is positioned at the correct valve, the correct motor is energized (one of two) and that the motor rotated the valve to the correct position. The same monitoring process is used when closing the valve.

Separation of Incompatible solutions. The linear valve design on the EM2400 System makes ingredient placement arbitrary. As long as the mix sequence is correct, incompatible ingredients will not mix. The compounding software allows ingredient groups to be set and marked as requiring a specific flush to avoid incompatibility. The compounder will not pump a formula in which incompatible groups are not adequately separated.

Software alerts user when formulation issues arise.

Software assists pharmacist in providing physicochemically compatible parenteral nutrition formulations.

The (optional) TPN-PC Plus™ Order Entry Software has user-defined parameters to warn when ordered amounts of electrolytes and bases substrates are higher or lower than acceptable limits. Other warnings include volume in excess of that ordered; calcium and phosphorus in solutions with final amino acid concentrations < 5%; and calcium phosphate solubility curves.

Meets the standards of the American Society for Parenteral and Enteral Nutrition (ASPEN) for nutrition label formats.

TPN-PC Plus was the first commercial software product to support the guidelines. It is available as an optional accessory to the EM2400 System. Label formats include adult and pediatric.

Software provides useful clinical information.

The (optional) TPN-PC Plus Order Entry Software provides final amounts of all relevant nutrients in a variety of formats, including rates (mEq/kg/min for electrolytes and mg/kg/min for nutritional substrates).

In addition all communication with the compounder, including operator commands and entries, are stored and retrievable for up to 30 days. This information can also be archived indefinitely.

Software integrates with existing pharmacy programs.

There are direct interfaces with the compounder and with TPN-PC Plus. Specifications for both are available on request.

Equipment Manufacture

Baxa Corporation's electromechanical equipment is 100% tested as a release criteria. Baxa Corporation has also validated all manufacturing processes to ensure that they produce a product that meets specifications every time. Built into the manufacturing process is a multi-level testing regime, which products must pass prior to release. Additional testing is performed prior to installation. This testing starts with a 100% test of all sub-assemblies, prior to a 100% final assembly test. Before shipping the product to a customer, Baxa Technical Support installs the software for peripherals, assembles all products as a system and fully tests them. Final product testing is done during the installation process.

Baxa Corporation's Quality System includes a Corrective and Preventive Action (CAPA) program. This program regularly trends quality data derived from vendor issues, incoming inspection, manufacturing processes and customer contacts. These trends are reviewed monthly and specific plans are established to resolve any undesirable results.

Sterility

The current method of sterilization for EM2400 disposables is Radiation Sterilization. The radiation validation was performed in accordance AAMI/ANSI/ISO 11137. The procedure used to establish the sterilization dose is Method 1, found in Annex B of the ISO 11137 sterilization standard. Method 1 is a procedure for establishing a sterilization dose based on determination of the product bioburden and comparison of that bioburden information to a model population having a defined resistance to radiation.

The validation study that was performed uses the following method to determine a bioburden estimate. A 10^{-2} verification dose was calculated based on the bioburden estimate, and a test of sterility was conducted on 100 product samples exposed to the 10^{-2} verification dose. A statistical verification was confirmed in the verification experiment, and the radiation dose selected from the Method 1 resistance table to achieve the desired sterility assurance level of 10^{-6} for established bioburden estimates.

The Method 1 validation procedure allows for dosimetric release of sterilized product, but requires confirmation of the continued validity of the established sterilization dose through performance of periodic dose audits, which are typically performed every three months.

Biocompatibility

Biocompatibility testing for sterilized Exacta-Mix™ 2400 Disposables was performed in accordance ISO 10993-1. All materials passed.

Specifications

Performance targets for the EM2400 Compounder were developed through work with pharmacists and from feedback from users of our older-model Micro Macro™ 12 and 23 Compounders.

The EM2400 specification indicates water delivery to a maximum flow rate of 16.6 mL/second, which equates to a rate of 996 mL/min. This flow rate capability was significantly exceeded during product testing. The compounder will nominally deliver water at a rate greater than 1300 mL/min.

Average Maximum Water Flow Rate	Standard Deviation	# of Data Points Collected
1319 mL/min	43 mL/min	30

The EM2400 delivers accurately to volumes as low as 0.2 mL. The test data described earlier in this paper, combined with that in the table above, clearly indicates compliance with this specification.

Volumetric Delivery

The term “volumetric” describes the condition where the volume of liquid pumped is directly related to the rotation of the pump rotor, independent of inlet and outlet pressure conditions or ingredient type. Therefore, to deliver a

specific volume, the pump must rotate a specified number of revolutions. Sophisticated characterization of a peristaltic pump is required to make it volumetric. Rotor position, ingredient specifications and speed have all been characterized so that the EM2400 can reliably deliver volumes as low as 0.2 mL +/- 0.02 mL under all expected conditions. Unexpected conditions have been mitigated by the use of occlusion and bubble detection.

Since the pumping process is volumetric, a weigh scale can be used to independently check the volume pumped. This volumetric pumping with an independent gravimetric check provides double-fault protection against incorrect delivery. Simple calibration of the pump when the tube set is first installed ensures that variations associated with tubing are eliminated, while trimming of the calibration during the pumping process ensures that pump delivers the correct volume over the life of the tube set.

Failure Modes

Baxa used two independent methods to ensure that all potentially hazardous failure modes would be mitigated in the final EM2400 design. To ensure that the design was safe to start with, a Fault Tree Analysis was used. This process consisted of identifying all the hazards associated with TPN compounding, such as incorrect ingredient, precipitation, contamination, etc. A logic tree was then created for each top level hazard consisting of “AND” and “OR” gates down to basic fault events. The machine was then designed to ensure that no hazard could result from a single base-fault event. For example, a top level event of “wrong ingredient” would require a user to connect the wrong ingredient and then fail to detect the wrong connection as part of the Prime and Verify process.

Once the machine design was completed, a separate process called Failure Modes and Effects Analysis was performed. This process analyzes the effects of a single fault condition. For example, a single fault condition might be a failure of the pump motor to turn the pump rotor at the correct rate. Such a condition would result in less fluid being pumped for each ingredient, since the same pump pumps all ingredients, resulting in a bag of insufficient volume. The weigh scale would detect this condition and thus prevent the bag from being used. Human factors were applied as a final check in both methods.

Baxa Certifications

Baxa Corporation is a registered medical device manufacturer with the FDA. Its operations are certified to ISO 9001, and meet the requirements for EN46001 (CE). Baxa automated compounders are UL certified (UL E205932).

The MicroMacro Compounders hold a 510(k) clearance for marketing. However, as of March 21, 2001, the FDA determined that automated compounders no longer require 510(k) clearance.



Trademarks

Exacta-Mix and MicroMacro are trademarks of Baxa Corporation.

References

1. Barber, Jacqueline. *Selection of Parenteral Nutrition Compounding Methods: Safety and Efficiency Considerations: An Online Continuing Education Course for pharmacy, nursing, and allied health-care professionals.* www.baxter.com. 2002.
2. American Society of Health-System Pharmacists. *ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures.* Am J Health-Syst Pharm 2000. www.ashp.org.

Additional Resources

More information is available at the following resources:

www.baxa.com

Exacta-Mix™ 2400 Compounder Operator Manual

Baxa Product Catalog

Baxa Technical Support at 800.567.BAXA (2292)

