IVAC Corporation, like many other companies in the electronic medical device industry, incorporates computer technology into its products to perform various functions. The regulatory path to market which must be followed depends on the functions performed by the device and its associated computer technology, the Food and Drug Administration (FDA) classification of the device, and the claims made about the device.

Currently, the FDA regulatory class a device is placed in determines what type of submission is required before it can be distributed in interstate commerce. Typically, FDA Class I and II devices require a premarket notification. Class III devices require a premarket approval (PMA). There is a tremendous difference in the format, information required, and volume of paper needed to support this approval over a simple notification.

December 17, 1987 - a milestone in both IVAC's and the medical device industry's history. This is the day the Titrator® Sodium Nitroprusside Closed Loop Module - Model 10K received FDA premarket approval. In the past, the focus of the use of computers in medicine has been on monitoring and documenting patient data, figuring administrative records, or controlling routine functions of a device. The Titrator device is the first of its kind to be approved by the FDA, and has brought advanced computer technology to the patient's bedside. The Titrator module advancement represents the beginning of IVAC Corporation's application of advanced control theory to closed loop drug delivery.

Getting approval took years of planning, testing, documenting, and contact with the FDA. The evolution of the Titrator dates back to 1981. The stages to confirm the usefulness of such a device included development from an idea to a breadboard, from there to a prototype and then to production. Bench testing was conducted to show performance to design specifications, followed by catastrophic animal trials to demonstrate control using closed loop physiological response. What follows is a brief chronology of major regulatory hurdles that were passed before the FDA allowed IVAC to market the Titrator.

July 1983 - The FDA regulatory review process for the Titrator began when IVAC submitted a premarket notification claiming the Titrator was substantially equivalent to a pre-amendment device described as a Servo Controlled Liquid Pumping System. New devices which are found to be substantially equivalent to devices which were on the market prior to May 28, 1976 (the date of enactment of the medical device amendment) can be marketed without undergoing the lengthy approval process.

August 1984 - Over one year later and after numerous discussions and supplying additional information, the FDA determined the Titrator was not substantially equivalent to the device claimed. Their decision was based primarily on the fact that the devices use different drugs to control different conditions; IVAC's Titrator lowers blood pressure and the Servo System raises blood pressure. Therefore, the Titrator was classified by statute in Class III, premarket approval. In the absence of a premarket approval, the Titrator could only be distributed for investigational use.

November 1984 - IVAC sent to the FDA an Investigational Device Exemption (IDE) application. An approved IDE allows an investigational Class III device, like the Titrator, to legally move in interstate commerce for the purpose of conducting clinical trials involving human subjects. The results of these trials are used to prove the device is safe and effective. Approval was given in less than 30 days allowing IVAC to proceed with clinicals at three hospitals.

August 1986 - At the conclusion of the clinicals, a premarket approval application was mailed to the FDA with valid scientific evidence on all laboratory, animal and human tests to substantiate that the Titrator was safe and effective for its intended use.

Between August, 1986 and the December, 1987, the FDA was wrestling with ways to address the medical device industry issues on regulating computer products and preventing or slowing the number of computer-related problems with medical devices. The FDA announced in September, 1987, the availability of a document entitled, "Draft FDA Policy For The Regulation Of Computer Products". About the same time, the FDA began asking IVAC and other submitters of premarket notifications, investigational device exemptions, and premarket approval applications to provide information on software validation.

December 30, 1986 - The Titrator PMA was accepted for filing by the FDA approximately six weeks after
their PMA regulations became officially effective. IVAC's PMA was thus one of the first required to follow these procedures and be reviewed under them by the FDA.

April 7, 1987 - FDA's General Hospital Advisory Panel met to review IVAC's PMA. We were asked to prepare and discuss the method used to validate the Titrator software; we believe this to be the first such request made of a PMA submittor. As part of IVAC's overall presentation, a section was developed for software that reviewed:

- Requirements Definition
- Software Design and Test Planning
- Software Implementation and Design Verification
- System Validation Testing
- Software Configuration Management

This presentation dealing with software was allowed to be given in a closed session, not opened to the public, because proprietary information was being shown. The panel later voted unanimously to approve the Titrator PMA.

July 27, 1987 - FDA completed its review of IVAC's PMA and sent an "approvable letter" indicating the agency would approve the application if additional information was provided and specific conditions agreed to. Included in the letter, with regards to software, was a request to describe:

- The methods used to identify system hazards, critical system functions, and critical software functions.
- The methods used to analyze the system software for its effect on system hazards.

September 8, 1987 - IVAC mailed in its response to the approvable letter as an amendment to the original PMA. Arrangements were made to meet with the FDA to discuss the amendment material, particularly the parts concerning software. At this meeting, the FDA software representative acknowledged, from discussion and reviewing supportive documentation, that IVAC had satisfactorily addressed software issues.

December 17, 1987 - Received FDA approval of Titrator PMA.

If the time it took from IVAC's first attempt to get permission to market the Titrator to final approval seemed extremely long, it was. Both IVAC and the FDA share, in different proportions, the responsibility for the delays: IVAC in not anticipating early in the process that a PMA would be required and preparing for it in advance, the FDA in not filing IVAC's PMA until after the regulations for approval became final and then attempting to work out a policy on what information to ask for to determine and verify software validation in submissions. Additionally, nine amendments to the PMA, each addressing additional information requested, added considerable time.

There are a number of ways and areas where a PMA submittor can run into difficulties and slowdowns. There is also no way to avoid them all. If it's a first attempt at the IDE/PMA process, I suggest:

- Have someone on staff thoroughly understand the regulations.
- If necessary, hire a consultant with a proven track record to advise on unique issues particular to your device.
- Make the appropriate contacts at the FDA and use them for information. They can be one of the best resources.
- Don't try shortcuts with anything required to be submitted.
- Know up front what the FDA will require pertaining to software data.

This paper only presents a brief look at a complex process. Many thousands of hours went into designing, testing, documenting, and countless other technical and administrative tasks to reach final product approval.