

A photograph showing a rowing team of eight people in white shirts and dark shorts, carrying a long, narrow white boat on their shoulders. They are standing on a sandy beach with water and trees in the background under a bright sky.

## Compliance enforcement trends for the health care industry

### “Compliance Challenges for a Global Industry”

J. Famulare, former FDA staffer and ISPE chairman, used this title for the recent ISPE Cover Story. With the pending decline of FDA influence, via a decline in foreign inspections and the resulting loss of transparency through public information, like Warning Letters, it will certainly be a challenge to maintain global rules for a global industry. There is hope that the voluntary [PIC/S organization of regulatory authorities](#) will take up the baton. Launched in Europe, it is truly international now, with 19 of the 24 countries in the Asia Pacific region included as members.

However, Famulare acknowledges that one cannot expect the Western concept of GMP to be simply copied in the East. An Asian-light GMP has not yet been publicized, but different quality and price levels for the same product have been created in the emerging Asian markets. Famulare states that some firms in “emerging markets” are producing a drug as an export version with high quality, as well as a domestic version of the same drug for a fraction of the price, with presumably less GMP. Practically, we have a global industry confronted with sequestered markets.

In any case, the optimal quality levels to minimize compliance costs is shifting rapidly now in global concerns.

### PIC/S champions harmonized GMPs for ATM Products

Underscoring the role of PIC/S in maintaining global standards, it is [putting pressure on the EC](#) to pull back from establishing its own GMP standards for ATM (Advanced Therapy Medicinal) Products. Currently, the EU GMP and the PIC/S GMP Guides are basically identical in content. The proposed revision of Annex 2 covering GMPs biologicals and repealing Annex 13 covering GMPs for clinical products, would be a large step away from harmonization. However, the US, (also a member of PIC/S), has its [own regulatory framework for ATMPs](#), and PIC/S may have to accept the divergence on this issue.

### Top Data Integrity Concerns

A recent thread was started in the ISPE GAMP Forum to collect information about what the members see as the top data integrity concerns. With 38 replies to date, (perhaps a record), it is clear what is occupying the minds of compliance consultants. Although conceptually a simple issue, the general requirements of data integrity, issued by the regulators, cannot be simply codified into hard rules. This could never be achieved with GMP issues and is not a surprising situation. The top concern appears to be minimizing the compliance risk of an observed lack of integrity, but there was no consensus about how to do this.

Considerable attention was given to problems with implementing and maintaining complete audit trails. Again, comprehensive and definitive design solutions for an appropriate audit trail do not exist and could only be composed for the most simple processing scenarios. Following that thought, R. Castelnovo provided the following complications:

1. "A lot of manual steps are still performed. Consequence is the high level of human intervention and the risk of mistakes (no matter if intentional or not);
2. Complex processes and procedures that are not properly understood or implemented;
3. Lack of automation (not lack of computerised systems!!);
4. Too much paper: Mixed processes are difficult to follow, audit and implement."

## Warning Letters Review

Excluding numerous letters to internet providers of wonder cures for cancer and to domestic compounders, the FDA issued In April:

- 6 WLS to foreign drug facilities;
- 1 WL to a domestic drug facility;
- 3 WLS to domestic medical device manufacturers.

The [WL to Sal Pharma](#) provides another example of falsified Certificates of Analysis, prepared by replacing the original manufacturer with the company letterhead on the CoA. This is easily done but is simple to detect with an audit.

The [WL to Mylan Laboratories](#) is noteworthy since this Dutch firm, with HQ in the UK and principal offices in Pennsylvania, is a major player for generics, after recently acquiring businesses from such major players such as Merck KGaA and Abbott Labs. Firms created via rapid acquisition from other firms can be expected to have compliance problems. The FDA recently publicized a [recall of Epi-Pens](#), which Mylan acquired.

The inspected Indian site fails in investigating OOS results, by basically ignoring initial failures and retesting. It also has data integrity issues in the QC lab and must perform a FDA-style remediation. Of more impact is the potential blockage of all new Mylan licensing and supplier registrations.

Neeraj Jha is CEO of 2 domestic device firms, [Criticare Technologies](#) and [Unetixs Vascular](#), which are both located at the same site. The WLS document major holes in the Quality Management Systems, and are noteworthy in the documentation of complaints. Criticare had 1385 open complaints from the previous year; Unetixs had 1453. All reviewed complaints were missing critical information, especially a determination of patient harm. Only 13 CAPA records were opened collectively in these firms to address deficiencies in the previous year, and all CAPA records did not meet the minimal expectations of a CAPA record. One could conclude, non-compliance is well documented.

[Organ Recovery Systems](#) was started in 1998 and has rapidly grown, apparently making its own interpretations of the GMPs for medical devices. The WL gives examples of what are probably common misconceptions.