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NEWSLETTER

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Exben Pharma & Chemical Benchmarking

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Will we see GOOD PUBLICATION PRACTICE?

Some things need to change in Scientific Publishing

By The Editor

I must confess I hadn't noticed **"Retraction Watch"** until a recent important article in The Economist*.

The **Retraction Watchs'** website lists almost **19,000 biomedical science papers** that have been retracted. It's online database arose from concerns about dubious and false scientific papers which had been published in both respected and obscure journals. RW analyses of these shows how retractions have grown over time; the reason for the retractions (suspected and confirmed fraud dominates); and the share of scientific papers retracted, by country of authorship (China is the worst culprit).

A reputable scientific journal will employ **peer reviewers** to scrutinise articles submitted for publication, however some more obscure journals do not follow this practice. In recent years a number of reviewers & other scientists, had come across clues leading them to doubt the findings of certain papers they had studied.

The clues included data fabrication, eg tables on patient characteristics that contained only even numbers, results with values that were clinically unlikely, the implausible 40:60 sex ratio of babies when the mothers-to-be had purportedly been selected at random. Other indicators include unusually large effects of the reported treatments, unexpected drop out rates among trial participants, or the same data appearing in different trial reports!

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"Show me the data"

A key issue is the inclusion or not of individual patients underlying numbers in the papers reviewed. In 526 clinical trial supply studies, when these were provided, the % of false data detected jumped from 2% to 44%. However, herein lies a key problem - this detailed backup data is not always made available even after specific requests, and if provided may not be analysed by "hasty" reviewers.

When alerted, respected journals will retract dubious articles ie Corrective Action. The "white hats" are also alerted by such retractions and investigate other articles by the same author(s). The more they investigated the more doubtful published & unretracted articles they found.

Bad publications have very significant and serious effects:

1. Firstly, the fabricated studies can divert other scientific teams on red herring themes, wasting huge budgets & research time, & delaying progress.
2. Secondly, some fraud can cause medical guidelines & clinical practice to change in a harmful way. Examples include critically patients undergoing surgery receiving starch infusions to boost their blood pressure. Later review of evidence on a wider scale concluded that this practise caused kidney damage and sometimes killed people. In Europe beta blockers were used before surgery with the intention of reducing heart attacks and strokes which rested on a study based in part on fabricated data. The harmful practise is believed to have called numerous deaths. Similarly, a "Systemic Review" of papers (all by the same researcher!, "showing" that use of high dose sugar solutions reduced mortality after head injury), was retracted after an investigation failed to find evidence that clinical trials had actually occurred.
3. Thirdly there is an adverse effect on associated scientists. Research is often carried out in teams of leader(s) and subordinates or associates, of different disciplines. If any one of the researchers uses fraudulent or doctored data the rest of the innocent team can suffer serious reputational and financial damage, when the paper(s) is exposed & retracted.

Who is carrying out the fraud and why? Some frauds, particularly those claiming to report clinical trials, are the products of prolific individual fraudsters or groups of fraudsters. Retraction Watch data shows that the 200 authors with the most retractions account for over 25% of the 19,000 retractions.

Other frauds, often concerning basic science such as molecular biology, are written for a fee by outfits known as "paper mills" copying legitimate published papers but substituting another gene or disease to the one the legitimate paper featured.

No surprise that a key motive is financial. "In China publication quotas are often needed to get the best jobs in hospitals and those who publish in top journals also get big cash bonuses. Almost all retractions linked to paper mills list Chinese authors amongst submissions to journals. Some 20% have at least one contributor from a Chinese institution, however this fifth accounts for nearly half of papers subsequently retracted".

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Secondly, in academia “publish or perish” carries weight; and given that journals like clear simple positive studies (who likes “inconclusive” in a must-read headline?) - there is an unhealthy incentive to produce papers to meet this market demand and advance one’s career.

Perhaps the 3rd reason for bias (eg omitting awkward data), is to fit in with an authors’ pet hypothesis.

CAPAs

If retraction of a dubious article is analogous to detection of a batch nonconformity; how do we get to a system where all “batches are tested”? We could consider retraction of dubious articles as Corrective Action. However, experts report that there is a vast difference in the reaction of publishers to reports of fabricated data, and that self-correction is patchy, with an “expression of concern” or retraction usually taking 2-3 years for publication, even if investigation has occurred.

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"Joined up" and enforced regulation?

It is obvious that **Preventative Action** must involve both the research institution or company, and the publishing journals. Now, publishing journals rarely have the specialist staff to investigate problematic studies.

Should this remain the case, and should journals employing such expertise receive accreditation & recognition?
Should Peer Reviewers be registered as are QPs?
Should **provision of individual patients underlying data be obligatory** in submitted papers to such accredited journals? The "scientific method" includes the vital feature that claimed results, if true, can be replicated in subsequent confirmatory work. (However, this can't prevent likely short-term damage by bad papers).

We note that social media and the news business, in some developed countries, are subject to regulation, which some scientists call for in order to ensure journals take on the **responsibilities & costs** of "article validation".

In America institutions accepting federal grant money are required to follow **government rules** requiring investigation of allegations of research misconduct within 60 days. But such rules remain largely unenforced partly because of the complexity of follow up investigation. In most countries however there is no equivalent regulation.
There needs to be incentives for university research whistle-blowers to act, in order to balance out the penalties often specified for spurious allegations.

One can however report some preventative actions are being taken:

- "Cochrane" a UK charity for the promotion of evidence-based medicine, reviews retraction databases for new additions and is repeating the analysis that included them; **it is also starting to check new papers for integrity.** They have already "excluded" 11 of 44 drug research studies in one field of medicine.
- The UK National Institute of Health and Care Research is paying for the development of tools to integrity check systematic reviews, like those conducted by Cochrane; and STM a publishing industry association is working on a similar system for submitted papers, to support editors.
- "Sense about Science" another UK charity, & the journal Nature recently awarded Dr Bik, a pioneering whistle-blower, the John Maddox prize "for courage and integrity in standing up for sound science and evidence".

At the moment self-regulation is weak or non-existent. Given the evidence whistle blowers have unearthed, one may conclude that the "front end" (research publication) of the pharmaceutical & medical life cycle needs to be as regulated as the "back end" (manufacturing, distribution, and clinical practice).

Although there will be push back to the proposal, the reported findings make a strong case for Good Publication Practice.

*The Economist February 25th 2023
TheEditor

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THE FDA GET THERE TOO

By Steve Biddulph
Fellow of Royal Institute of Microbiology. Board level pharma experience. QSM and Aseptic Manufacturing & Control Expertise

It is sometimes surprising to see how far the reach of the FDA can extend, (and to find what's behind a company name). A company dealing in Wallpaper and Decor (!) has recently received a warning letter from the FDA for several products that its places on the market. The warning letter was addressed to **"Old Tiles Wallpaper, LLC DBA Old Tiles Deco"** and concerned the following products all for sale in the United States:

Wind River Skin Comfort Blend," "Wind River Cayenne Tincture," and "Wind River Elderberry Tincture"

The FDA concluded that the products are unapproved new drugs sold in violation of section 505(a) of the Federal Food, Drug, and Cosmetic Act. The company viewed the products as purely cosmetic, however the products claimed improvement in human well-being which, in the eyes of the FDA, places them firmly in the category of drug products, albeit OTCs.

Another such case involved **"Urban Electric Power"** who received a warning letter for hand sanitiser products.

The company was correctly registered with the United States Food and Drug Administration as a manufacturer of over-the-counter (OTC) drug products, including consumer antiseptic hand rub drug products. When tested by the FDA these drug products were found to be adulterated with the impurities acetaldehyde and acetal, at unacceptable levels.

A warning letter was sent to the company advising them to cease marketing the products in question.

It is a good lesson for all manufacturers to check their products for contaminants and not just for compliance with specification, and to check that their product claims are not "overenthusiastic".

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"Contamination Control Strategy Development in Pharmaceutical Manufacturing"

By Jose Zapata
Galenisys Pharma Senior Expert. Pharmacist with frontline experience in Quality, Operations & Project Management.
PDD Certified

In an earlier Galenisys Newsletter, we commented as follows about a Contamination Control Strategy (CCS):

"When the draft of the new Annex 1 of EU GMP´s was published first time, there were many phone calls and questions to Galenisys, from different clients / companies asking for clarification about the CCS (Contamination Control Strategy) that appeared in the text like a key point around which different parameters are linked.

The CCS concept is not really a new idea. From our point of view is just verbalizing what we have been working for years, and provide a little bit more structure to the Sterility Assurance conception"

The concept is important, but not so obvious is its implementation; and that is why the PDA decided to write the complete Technical Report N90 to clarify and unify the approach in the industry. I was pleased to see it.

After first describing the elements of a CCS, **new document focuses on**:

- Knowledge of the process and technical aspects of manufacturing.
- Quality Risk Management (QRM) as a key tool to keep contamination under control.
- Personnel awareness of contamination risks.

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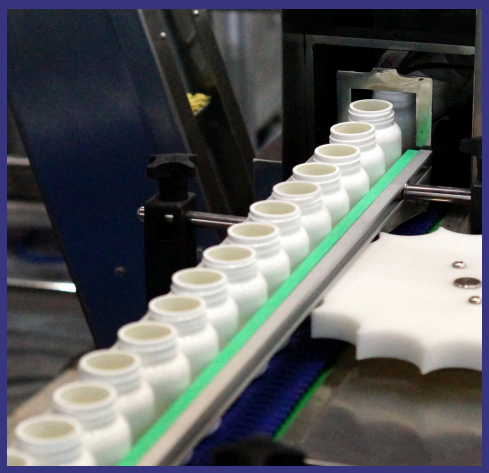
Galenisys Highlights the following summary points for serious consideration:

- It's vital to consider sources of contamination, proliferation, & during process design & CCS development. Process validation needs to be done properly. And for sure it has to be adequately monitored.
- For "old processes", changes to may need to be implemented, with attendant implications.
- Facilities and utilities. Design, flow of personnel and materials, cleaning and disinfection are aspects for the facility to be controlled. All utilities: HVAC, PW, WFI, clean steam, compressed air, nitrogen, including their source and generation need to be well designed, validated and monitored.
- Raw materials being potential sources of contamination, makes vendor qualification and laboratory testing key components of a CCS.
- Environmental controls (EM), will be the vital tool to provide contamination alerts on site. That is why well designed EM, for appropriate locations, materials and personnel is absolutely necessary in the CCS.
- Training is obviously essential, especially personnel behaviour in classified areas needs to be continuously verified.
- Machinery and equipment design, cleaning, monitoring (contact EM) are elements for the CCS.
- Containers and closures are part also of the CCS. An incorrect design could lead to contamination problems.
- The Quality System. This will provide the framework for the CCS implementation: Investigations / CAPA, Change control, QRM, Metrics.



The document underlines the need to have a governance structure to verify the effectiveness of the CCS. Finally some practical aspects including several **case studies** are included in the technical report.

In summary, Report N90 is a "must read" for implementing a CCS inside a facility. As a Pharma industry worker & consultant I want to thank the PDA and the new TR N90 authors & contributors for this effort.

At Galenisys, our experts are available to provide support in the design and implementation of the Contamination Control Strategy described in the new Annex 1.

WOULD YOU DO IT AGAIN ?

We've been interested by the attitudes & choices of young professionals starting out on their careers, and thought it useful to discover from those who are well into their career in pharmaceuticals & the life sciences, (or who have retired); how they see things now.

By The Editor

First up is a retired UK male graduate in Pharmacy

1. If you had your time over again, would you choose the same training / college course -
YES

2.Afterwards, would you choose pharmaceuticals / life sciences, or some completely different occupation -
YES

3.Afterwards, would you choose pharmaceuticals / life sciences, or some completely different occupation -
I'D CHOOSE THE SAME INDUSTRY

4.What branch of this pharmaceuticals / life sciences industry are / were you in; for example research, marketing, sales, retail, production, development, other (please specify).

AT VARIOUS TIMES I WAS IN PHARMACEUTICAL PRODUCTION, THEN QUALITY ASSURANCE.

5.What is / was the highlight of your career –

BEING TECHNICAL DIRECTOR OF A SOUTH AFRICAN SUBSIDIARY AT A DIFFICULT TIME POLITICALLY

6.How would you describe your career compared with others -
Extremely interesting with lots of things to learn and continuous challenges

7.Overall is / was it a satisfying time -

OVERALL, YES IT WAS A SATISFYING TIME