Can analytical testing of excipients be 'volkswagenized'?

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Editorial

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"Tell me, would you feel any pity if any of those 'dots' stopped moving forever"
Orson Welles in *The Third Man*

Pecuniary gain, when stretched past the altruistic; carried through the protestant means to salvation and, past Adam Smith's 'hidden hand' hypothesis; usually ends up at the other extreme of Hobbesian callousness, as portrayed by Orson Welles' penicillin diluting character in *The Third man*. In light of the Volkswagen scandal, where software was surreptitiously installed to generate false, in-specification, results when the automobile was tested for emissions, it is prudent to examine whether a similar stratagem can be applied to the testing of pharmaceutical excipients (and APIs').

This is a timely exercise because different opportunities for adulteration are projected to be utilized due to the ramping up of attention and legislation pertaining to securing an earlier preferred avenue pharmaceutical excipient supply chains.

A minority of high school students respond that the answer to the mathematical question, 1 divided by 2 is 5, while a majority of them reach for their calculators. These days, I stoically point out that they have failed to spot the exponent (10^{-1}) tucked away to the extreme side of their calculator screens. I then point out that a lesser number divided by a larger number would not be expected to be >1. Over-reliance on technological 'black boxes', teaching procedural, rather than conceptual mathematics, and a general belief in the immutability and accuracy of generated/displayed computational or "system" results, with potentially dangerous consequences, has produced a generation that can be easily duped by the 'volkswagenized' (a term apt for inclusion in the Dictionary) system.

A 'how it's made' Coca-Cola video I showed my students had a shot of an analyst at a bottling facility pointing to a display unit of

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what was obviously a black box instrument to her, explaining that if the line fell between two red lines, the product had the required sweetness and she could make the call to have the line begin filling.

With most of the attention being paid to excipient supply chains, it may be also be prudent to examine the testing aspect of excipients from an as yet neglected 'volkswagenized' perspective. Specifically, we can ask the question: are the usual attributes of analytical instrument and procedure validation, QbD, documentation traceability and system suitability sufficiently robust and secure enough to prevent interference, tampering or falsification of the (analytical) results? Is the implicit assumption that whatever is measured, indeed is what is displayed, transcribed and saved as binary digits, that the measurement is not doctored, or its results not fraudulently altered based on a testing protocol or analyte ID, necessarily true (in the case of Volkswagen, it wasn't)?

Consider the generation of UV/VIS absorbance data by conventional HPLC systems. Is it possible to code software for intranet connected analytical systems that generates actual (true) absorption data when validation, system suitability or standards are being run and generate falsified data when samples are analysed? Can the coding software 'hold off' on transcribing data (in a RAM temporary buffer file, for example) so as to detect if a 'standard' or a 'sample' is being run and then not-falsify, or falsify (respectively) that particular data (this can be as simple as a fraudulently built in time lag between the solvent front actually traversing the detector and the solvent front appearing on the display screen)? Can a UV/VIS spectrophotometer display a certain set wavelength while the software directs the diffraction grating to turn to a different angle and project a different wavelength based on analyte ID and/or file/injection set point parameters? Can peak area calculation algorithms be rigged or hacked to over/under-calculate sample (but not standard) data so that the analyte meets specifications? Can software code be programmed to overwrite data with 'noise'(blank) for a fixed time interval into the chromatography sample run so as not to detect an adulteration peak while normally collecting data for a standard to make it appear that the sample was not adulterated?

Such rogue code or trapdoor algorithms could be generic enough to be applicable to any analytical instrument and technique such as infrared spectroscopy, calorimetry, titrimetry, atomic absorption or emission spectroscopy, nuclear magnetic resonance etc. because little or no physical modification of instrumentation is required. Instead, coding modifications to the lab reporting software and/or instrument software is enough to pull off the deception.

Obviously, collusion at a large magnitude (which, in this case, does not necessarily imply a large number of perpetrators) must occur for such elaborate and intricate machination to occur. However, the egregious aspect of such legerdemain is that, once set into motion for a given fixed set of protocols, it may become systemically endemic and virtually go on being undetected for ever, as happened when Volkswagen succeeded in falsifying emission test results for a significant period of time by installing software that sensed when automobiles were being tested. 'Volkswagenization' is the perfect con for scenarios where repetitive assays or ID tests are run, where the sequence, method and chronology of testing of standards and samples remain unchanged, where standard operating procedures dictate that an analyte be identified by its file name, where the same instrument and analyst are assigned to a particular product/material, where preventative maintenance is either performed in-house or contracted to a third party (that is not the

instrument manufacturer), where a third party analytical testing lab has a business relationship with the supplier, packer or re-distributor and where 'analysts' need have no other qualifications than an ability to follow SOPs'.

Testing excipients is different from testing for emissions. Excipients are usually subjected to a battery of analytical tests using different instruments and for different attributes, preferably at multiple locations. Unscrupulous and ingenious operators will nonetheless search and identify situations, where only one or two tests, are able to identify adulteration thus recognizing that only those need be 'volkswagenized'.

Evolutionary theory dictates that the pace of deception must keep pace with the methods of detection. Intelligent adulteration will have the same (limited) amount of adulterant in every batch so that it can escape detection (paradoxically) due to the adjustment of QbD 'design spaces' and 'volkswagenized' analytical protocols, yet yielding considerable pecuniary benefit to its practitioners. Although intuitively and logistically improbable, pharmaceutical manufacturers must not assume that such deception will never occur, as the Volkswagen scandal has demonstrated.

Hardware, software, data security and laboratory information systems validation must be vigorously pursued and implemented. Where possible, standards and sample ID, system suitability and/or analytical validation protocol file names could be encrypted prior to running, a random chronological order of standard and sample runs may be instituted, machines may not be dedicated to running only one product or machine modules interchanged at random intervals, all designed to downgrade the capability of rogue code to change sample results and which together will allow for the detection of any intrusions. On the specifications side, a long term *modus operandi* may be to require a minimum of two different instrumental methods to detect known adulterants. Constant vigilance must be maintained against 'volkswagonization' so that this avenue of deception becomes unworthy of exploitation.