



EXPERT INTERVIEW

Perspectives on the Multidisciplinary role of Bioanalysis: an Interview with Prof. Marcello Locatelli



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The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of University "G. d' Annunzio", Department of Pharmacy.

Prof. Locatelli is Associate Professor in Analytical Chemistry and his research activity is aimed at the development and validation of chromatographic methods for the qualitative and quantitative determination of biologically active molecules in human and animal, cosmetics, food, and environmental complex matrices. These procedures have been applied to different analytes and drug associations also finding application in clinical and pre-clinical studies, to characterize new delivery systems of the active principle to improve their pharmacological properties. In the development of the method are predictive models and chemometrics applied both for the optimization of extraction protocols and for final data processing. Particular attention is given to innovative (micro)-extraction techniques and new instrumental configurations for the quantitative analysis of complex matrices.

This interview was conducted by Dr. Roland J.W. Meesters, Editor-in-Chief Journal of Applied Bioanalysis.

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Foreword

Before considering the different questions related to this interview, we need to know about the definition of "Bioanalysis": "*Bioanalysis is a sub-discipline of analytical chemistry covering the quantitative determination of xenobiotics (e.g. drugs, metabolites, and biological molecules in atypical locations or concentrations) and biotics (e.g. macromolecules, proteins, DNA, large molecule drugs, metabolites, biopharmaceuticals) in biological systems. Its main focus in the pharmaceutical field is to provide quantitative information about the active drug and/or its metabolite(s) for pharmacokinetics, toxicokinetics, bioequivalence, exposure-response, and adsorption/distribution/metabolism/excretion (ADME). Bioanalysis also applies to drugs used for non-specific purposes, forensic investigations, anti-doping testing, and environmental concerns.*"

This definition embraces an extremely wide and varied range of applications that involves the presence/communication between different figures and expertises. In it, the Analytical Chemist is called to provide the fundamental methodological and instrumental bases for robust, reliable, and reproducible data.

As can be seen from the definition, not only nowadays the Analytical Chemist must know how to apply his knowledge on a large series of analytes, but he also know how to manipulate, manage, and process information on different biological matrices, on the physiological interactions that occur in the ADME process on both drugs and organic and inorganic pollutants, illicit drugs, and used in doping. He must also be able to interface and communicate with professional colleagues ranging from the Doctor, the Magistrate, to the Lawyer, who often do not “speak the same language”.

In this context, the Analytical Chemist is extremely important and his task is not easy as he must know how to combine and manage different figures, needs, “languages”, without ever losing sight of the main target: to provide reliable, reproducible results that comply with current regulations.

For this, when Dr. Roland J.W. Meesters asked me to answer to a series of questions concerning “the multidisciplinary role of Bioanalysis” I accepted the hard task not only for the esteem for Dr. Meesters, but also because I think that in this field today there is a big “confusion” in the tasks and roles that belong to every professional.

What began your interest in the field of Bioanalysis?

My interest in Bioanalysis began during my Master thesis period in 2002 (about 18 years ago) in a laboratory of Bioanalytical Chemistry of the University of Bologna at the end of a course focused entirely on Analytical Chemistry at the Department of Chemistry “G. Ciamician”. In this laboratory, I started to deepen all the aspects of this application field and the big challenges that Bioanalysis tries to win. From the beginning, I understood the importance of the Analytical Chemist role in this field, the multidisciplinary skills required, and the need to know how to dialogue with professional colleagues who often “speak a different language”.

What are your thoughts about the recently published 2019 FDA Guidelines for Industry on Bioanalytical Method Development and Validation? Do they guide all aspects of a professional method development and validation?

This update of the Guidelines is certainly more complete than the previous versions as it considers all the fundamental variables necessary to obtain robust, reproducible, and accurate data (precise and true).

It also considers new technologies based on “dried Matrix sampling” like Dry Blood Spot (DBS) or similar, even if it does not accurately report all the parameters that are required during the validation process. Generally, hematocrit, homogeneity, and size of the sample and pre-analysis reconstitution are indicated, without specifying in detail which parameters should be considered, and how these should be evaluated according to the application. This could leave ample possibilities for misunderstanding and/or indecision as to which elements are indispensable to guarantee the final data and if the proposed/validated technique can actually be used.

An important element that is considered and clarified is the application of the validated method to the batches analysis and to the acceptance parameters of an analytical session. This is very important for all those protocols that are applied/developed to meet the needs of the Pharmaceutical Industry and for pharmacokinetic, pharmacodynamic, bioavailability, bioequivalence, and ADME applications.

Another element that I think is very important is that the parameters relating to diagnostic and commercial kits that have seen extensive development in recent years are also included and specified. These in fact are very important above all from the pharmaceutical point of view, as we are increasingly moving towards a “Pharmacy of the Services” where we can find analysis systems that constitute the “point-of-care” for the diagnosis of the

patient. This will lead to a reduction in the workload of Hospital laboratories and greater capacities in the Health Service, provided that the protocols and the instrumentation have been effectively validated considering that often the procedures are performed by not specifically trained personnel.

I have positively seen that exclusively exogenous analytes are disjointed from those that are also endogenous and for which it may be difficult to have a blank matrix available and that the samples for the validation of trueness are distinguished from the samples used to evaluate the recovery of the method.

It should be noted, however, that the term “accuracy” is still used to indicate the BIAS of the analysis, while based on the indications of the IUPAC (Pure Appl. Chem., Vol. 74, No. 5, pp. 835-855, (2002); doi.org/10.1351/pac200274050835) it would be more correct to make the following distinction:

“Trueness is the closeness of agreement between a test and the accepted reference value of the property being measured. Trueness is stated quantitatively in terms of bias, with smaller bias indicating greater trueness”

“Precision is the closeness of agreement between independent test results obtained under stipulated conditions. It is specified in terms of standard deviation or relative standard deviation”

In this case, therefore, we can say that a method is accurate if we have the simultaneous presence of precision and trueness.

Another critical point is related to the absence of the role of the Chemometric approach in the validation process. In the last years, it was highlighted how this statistical approach could be very useful in the data processing and elaboration, and how with a chemometric approach we could enforce the entire method.

What are the main technological challenges used in the field of Bioanalysis you are working in?

Currently, thanks to the collaboration with Prof. A. Kabir (Florida International University, Miami, USA), a friend before then a colleague, we are applying innovative technologies for the sample clean-up process before the instrumental analysis, especially on non-conventional matrices that could be interesting for clinical/pharmaceutical/forensic applications.

What have been the most exciting developments in your field of Bioanalysis?

In the last period, surely the most important developments are associated with the methods development on whole blood for the determination of low molecular weight xenobiotics. In this sense, studies of this kind had never been published. Furthermore, we have demonstrated, through conventional HPLC-PDA methods, to compete in terms of analytical performances with LC-MS/MS or UPLC-MS/MS instruments, with massive savings of money both with respect to the instrumentation used and in terms of trained personnel.

What (is)are the challenge(s) of the technique(s) you are using in Bioanalysis?

The main challenges are multiple, in fact, we want to get/to demonstrate:

- Usability of non-conventional matrices (whole blood, saliva, vitreous humor, post-mortem matrices) for quantitative purposes
- Correlation between concentrations in the various types of matrix applicable to clinical/pharmaceutical/forensic studies
- Development of innovative (micro)extraction techniques, based on solid phase and liquid phase.
- To obtain analytical performances with known, robust and non-complex instrumentation comparable to more expensive and complicated configurations
- Open new opportunities for analytical applications in the field of Bioanalysis

Do you think that Bioanalysis in academia gets the same recognition as in the pharmaceutical industry? Can you please motivate in a few words your opinion.

In both academic and industrial contexts, bioanalysis plays a very important role as it is used by different sectors all related to Human Health, health status assessment, characterization, and monitoring of new drugs (including biotechnological molecules) that are placed each year on the market. It should be emphasized that often, unfortunately, personnel who have not studied Analytical Chemistry and all its direct implications in the course of studies, develop the methods applied in bioanalysis. This leads to having methodologies that too often are not reproducible or that do not allow the correct interpretation of the phenomenon as suffering from several (and often serious) scientific shortcomings. As with all things, everyone has to do their job without wanting to cross over into other fields. This element is the basis of the need for multidisciplinary approaches in which each "actor" makes his deep and specific expertise available in order to fully understand the phenomenon based on "unassailable" information.

How important is Bioanalysis to your point of view in your field of work?

Bioanalysis plays a very important role in my research activity since, scientifically, I was born in this field. The most interesting aspect is that what is studied and carried out in the Bioanalysis finds possible users/fields of application also in other sectors, making the field of Bioanalytical one of the fundamental pillars of Applied Analytical Chemistry.

With the increase in research how can the field of Bioanalysis be regulated and standardized? Do you have high expectations of the ICH M10 guidelines that are at this moment in development? Can you please motivate in a few words your opinion.

Concerning to Bioanalysis for the future, I have great expectations and above all, I hope that the final version of the ICH M10 guidelines will cover all aspects of this application field. I also hope that the terminology (and any changes thereto) may finally find use in the Scientific Community in order to avoid misunderstandings. I hope that, together with the final version, a sort of "handbook" will also be published where we can find the specific and detailed procedure for determining the several parameters. This would certainly help to reduce confusion and could help "non-analytical chemists" (see the answer above) in the development and validation process.

In this perspective, the field of Bioanalysis will certainly be better regulated and standardized as soon as the ICH M10 guidelines come into effect in their final version.

What are your thoughts about Education in Bioanalysis (Bioanalytical Chemistry)? Do universities offer sufficient knowledge or courses to students from this exciting field of analytical chemistry? Can you please motivate in a few words your opinion.

Often, for purely academic reasons and not dictated by a far-sighted vision in the establishment of Degree Courses, Analytical Chemistry is taught not by Analytical Chemists but by colleagues in related subjects or worse. Analytical Chemistry sees the commitment of students only for a few hours a week and often without laboratory training, "binding the hands" to this discipline and to all the applications that it can offer for a great variety of problems. Consequently, Bioanalysis also often sees limited its teaching.

From my point of view, it would be to strengthen this teaching and couple it with Clinical Analytical Chemistry, natural completion of the topics necessary to achieve the objectives of Bioanalysis.

The field of Bioanalysis is a rapidly changing and developing research field. How does the field to your point of view change in the next years? And will it be capable of answering all the questions and challenges we have today?

The field of Bioanalysis will surely be able to adapt to the various needs that will be created in the next future, modulating and changing its workflow according to the altered needs. From my point of view, there will surely be more and more work to be done in

the field of biotechnological compounds, of personalized medicine, in the forensic field (where new drugs of abuse or doping compounds are discovered every year). For this reason, Bioanalysis, and above all the Guidelines, which must be addressed to develop and validate reliable and reproducible methods, should also include the application of Chemometrics in the validation process. Another important element could concern the possibility of reshaping the Guidelines with a less long period, this to always be ready to respond to the changing needs.

Research activities and short biography

Prof. Locatelli's research activity is devoted to the development and validation of chromatographic methods for the qualitative and quantitative determination of biologically active molecules in complex matrices from human and animal (whole blood, saliva, serum, plasma, bile, tissues, feces, and urine), cosmetics, foods, and environmental.

It provides, to the study of all processes related to pre-analytical stages such as sampling, extraction and purification, separation, enrichment, even the application of conventional and hyphenated analytical methods for the accurate, sensitive and selective determination of biologically active molecules. Recently, particular attention is focused on innovative (micro)-extraction procedures like MEPS, FPSE, MIP, DLLME, and SULLE. These procedures have been applied to different compounds, from synthetic and natural origin (glucosamine, 5-amino-salicylic acid, natural or synthetic bile acids, anti-inflammatory, drugs association and fluoroquinolones, secondary metabolites from natural sources, heavy metals). In the development of the method are tested also predictive models and chemometric both for the optimization of extraction protocols and for final data processing. Particular attention is given to the new instrument configurations for the quantitative analysis in complex matrix.

He published more more than 158 manuscripts, presented 116 congress communications, has 1 patent subject to approval, 9 book chapters and 2 books, and is guest editor for more than 14 special issues attested scientific activity (based on Scopus (11th of June 2020), h-index 33, 148 papers, 2787 citations).

Besides, he is a reviewer of the following international journals: *Analytica Chimica Acta*, *Current Bioactive Compounds*, *Journal of Chromatography A*, *Talanta*, *Trends in Analytical Chemistry* (more than 100 International peer reviewed Journals). Member of the Italian Chemical Society (SCI, card number 13779), of the American Chemical Society (ACS, card number 30617260), and of the Italian Society of Phytochemistry (SIF).

It is included in the list of external experts for the evaluation of e-Cost research projects (European Cooperation in Science & Technology). He is a reviewer for the MIUR for National Projects (SIR) and is included in the REPRISE Register (Register of Expert Peer Reviewers for Italian Scientific Evaluation) in the "Basic Research" section. Referee for the VQR 2011-2014. He is referee for other universities for proposals, through competitive procedures, for the allocation of University funds for the activation of research grants (University of Insubria 2016, University of Florence 2017, and University of Insubria 2018).

Prof. Locatelli is a member of the Editorial Board of International peer-review Journals like "Molecules" section "Analytical Chemistry", "Current Analytical Chemistry", "Current Bioactive Compounds", "American Journal of Modern Chromatography", "Journal of Selcuk University Science Faculty", "Reviews in Separation Sciences", "Cumhuriyet Science Journal". He is Associate Editor of the magazine "Frontiers in Pharmacology" section "Ethnopharmacology", Review Editor of the journal "Frontiers in Oncology" section "Pharmacology for anti-cancer drugs", and Review Editor of the journal "Frontiers in Medical Technology" section "Nano-Based Drug Delivery".

He is a member of the Scientific Committee of the journal "Scienze e Ricerche", published by the Italian Book Association.