# Référentiel des compétences de chimie thérapeutique pertinentes pour l'exercice contemporain de la pharmacie.

# A skills framework integrating professionally relevant medicinal chemistry proficiencies to strengthen the contemporary practice of pharmacy.

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*Dedicated to the memory of Professor Alain-Gueiffier*

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**ABSTRACT**

**Objective**: Our aim was to define a repository of competences in Medicinal Chemistry, to be developed during Pharmacy studies and expected in professional practices, while highlighting the fundamental character of the subject and its interdisciplinary links within the Pharmaceutical Sciences.

**Methods**: A first version, based on both our professional and educational experience, consolidated by a review of educational articles and good practice guidelines, was obtained by following a competency-based approach. It was then completed by Medicinal Chemistry teachers in various French Pharmacy Faculties to obtain a comprehensive data set. The final version was reviewed in the light of relevant comments from 15 experts from related disciplines.

**Results**: A comprehensive competency framework with extensive practical applications was developed.

**Conclusions**: This pilot study provides a teaching repository for medicinal chemistry for use by teachers of medicinal sciences. It highlights the fundamental role of the discipline within Pharmacy studies and provides links with professional practices. This repository will be useful to various teaching teams in a context of integrated disciplines and could be replicated in related disciplines.

**RESUME**

**Objectif :** Notre but était de définir un référentiel des compétences en chimie thérapeutique à développer au cours des études de pharmacie et attendues lors de la pratique professionnelle, tout en mettant en évidence le caractère fondamental de la matière et ses liens interdisciplinaires au sein des sciences pharmaceutiques.

**Méthodes :** Une première version, basée sur notre expérience à la fois professionnelle et pédagogique, consolidée par une revue d'articles de pédagogie et de directives de bonnes pratiques, a été obtenue en suivant une approche par compétences. Elle a ensuite été complétée par les enseignants de chimie thérapeutique des Facultés de Pharmacie de France jusqu'à saturation des données. La version finale a été revue à la lumière de commentaires pertinents proposés par 15 experts de disciplines connexes.

**Résultats :** Un référentiel de compétences exhaustif amplement illustré par des applications pratiques a été obtenu.

**Conclusions :** Cette étude pilote offre un référentiel de chimie thérapeutique à l'usage des enseignants des sciences du médicament. Elle met en lumière le rôle fondamental de la discipline au sein des études de pharmacie et fait le lien avec la pratique professionnelle. Ce référentiel sera utile aux équipes pédagogiques dans un contexte d'intégration des disciplines et pourrait être reproduit dans des disciplines connexes.

**Key words:** pedagogy, medicinal chemistry, competency-based approach, framework, content integration.

**Mots clés :** pédagogie, chimie thérapeutique, approche par compétences, référentiel, intégration du contenu.

**Highlights:**

- An exhaustive framework of Medicinal Chemistry skills.
- 40 skills explained and illustrated in terms of pharmaceutical practice.
- Complementarity of Medicinal Chemistry and other pharmaceutical disciplines.
- Replicability of this pilot study in other disciplinary fields.

## INTRODUCTION

As clinical or industrial professionals, Pharmacists are the universally recognized specialists for drugs and medicines. Among health-care professionals, they can rationalize strategies on the basis of molecular structures and have an in-depth knowledge of the chemical properties of drug compounds. Pharmacy studies lead to a large variety of professions and therefore encompass many scientific, economic, and human fields. During the Pharmacy curriculum, a specific discipline entitled Medicinal Chemistry is taught to students to bridge chemical considerations and therapeutic applications in a global molecular pharmaceutical overview. In 1998, the International Union of Pure and Applied Chemistry (IUPAC [1]) defined Medicinal Chemistry as "*a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their modes of action at the molecular level and the construction of structure-activity relationships*". Medicinal Chemistry, which covers the invention, design, chemical synthesis and chemical characterization of biologically active compounds according to pharmaceutical regulations and public health requirements, is related to drug discovery and development. It also embraces the physicochemical attributes of active pharmaceutical ingredients (APIs), the molecular mechanisms of their action and metabolism and structure-activity relationships. All these issues are extremely important to understand the teachings of related disciplines such as Pharmacodynamics, Pharmacokinetics, Toxicology, Biopharmacy, Clinical Pharmacy and beyond, and are fundamental to the overall practice of Pharmacy. Such considerations place Medicinal Chemistry among the key Pharmaceutical disciplines.

The Pharmacy curriculum is continually evolving to meet the new tasks of contemporary Pharmacists [2]. In this program, drug discovery and clinical aspects of Medicinal Chemistry have sometimes been split in independent courses resulting in the integration of Medicinal Chemistry to Pharmacology and Biopharmacy system-based, or pathology-based teaching units [3,4] with the laudable aim to include chemical reasoning in therapeutic or clinical decision making and professional arbitrations [5–12]. Meanwhile, molecular considerations and structural bridging between drugs families tend to be lost. Developing critical thinking and problem-solving capabilities are essential skills pharmacists should master to give relevant answers in an ever-progressing professional environment. In 2016, the accreditation council for pharmacy education [13] defined Medicinal Chemistry as the "*Chemical basis of drug action and behavior in vivo and in vitro, with an emphasis on pharmacophore recognition and the application of physicochemical properties, structure-activity relationships, intermolecular drug-receptor interactions and metabolism to therapeutic decision-making*". More tellingly, Medicinal Chemistry can be regarded as a transverse discipline aimed at providing students (and later professionals) with a unique molecular vision of drug action, which is the cornerstone of the pharmaceutical expertise [8,14–16].

In this context, it was deemed appropriate to list and illustrate skills related to Medicinal Chemistry for the use of teachers in the Pharmaceutical Sciences. In a competency-based approach, we arbitrarily compartmentalized the different positions taken by Pharmacists during their professional lives to distinguish 'Upstream Pharmacists' from 'Downstream Pharmacists', very much aware that this expertise border is and must remain truly permeable throughout the pharmacists' professional carreers. The starting points of our compilation work were 1) comprehensively gathered professional practices and 2) the survey of appropriate pedagogical articles on innovative methods to teach clinically relevant Medicinal Chemistry [7–12,14–20]. The framework under construction was then implemented by the members of the French National Association of Medicinal Chemistry Teachers (Association Française des Enseignants de Chimie Thérapeutique, AFECT). To appreciate the impact of AFECT representativeness, almost every French Medicinal Chemistry teacher is affiliated to AFECT, nearly every Faculty of Pharmacy is represented (22/24) and there are no other challenging associations in this field. Therefore, local teaching practices have been carefully taken into consideration, whilst considering a more global vision to propose a general framework integrating professionally-relevant Medicinal Chemistry proficiencies that were or could be useful in the contemporary practice of pharmacy. Once expanded, the framework was submitted to 15 experts in related disciplines. Thus, relevant remarks and constructive propositions have enriched its building. The present framework could now be regarded as a beneficial tool to position Medicinal Chemistry within the pharmaceutical curriculum, and more importantly, to consolidate the input of medicinal chemistry-based proficiencies to the numerous pharmaceutical professions.

## MATERIAL AND METHODS

The work group consisted of five AFECT members/authors in charge of 1) defining the aim and the process; 2) collecting data; 3) re-writing data as skills (if needed) and correcting/editing the proof according to experts reviewing; 4) illustrating every skill with relevant pharmaceutical examples and 5) coordinating and harmonizing the final framework.

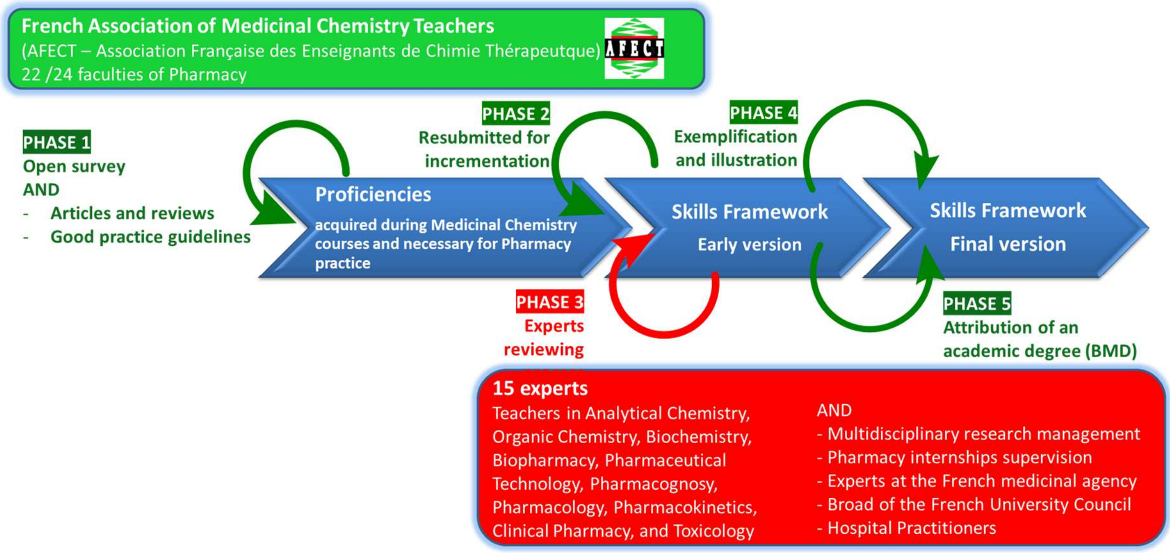


**Fig. 1**: approach used to build the skills framework.

During phase 1 (Fig. 1), an initial version was compiled starting from the authors professional experiences. Thus, as senior teachers in Medicinal Chemistry and Pharmacists, we listed proficiencies that are usually acquired during our Medicinal Chemistry courses which we consider essential for the practice of pharmacy. A competency-based approach was used. This draft was supplemented by pedagogical articles and reviews dealing with clinically relevant Medicinal Chemistry [7–12,14–16,19] and by good practice guidelines relative to dispensing, manufacturing, laboratory production and analyses.

A broad- questionnaire on teaching practice was sent to the AFECT-affiliated teaching teams to collect data relative to other professional experiences and expand our framework. Thus, Medicinal Chemistry teachers of each of the French Faculties of Pharmacy were solicited. Briefly, a survey comprising 17 questions (see Table S1 in supporting information for full survey) was drawn up and sent by e-mail to every AFECT teacher. Single, multiple-choice questions and open questions were proposed using the Google Form® (Microsoft) platform. We asked the surveyed teachers to work together within the same faculty and submit faculty-harmonized answers. Whereas single and multiple-choice items were more directive, open questions were asked to screen all local pedagogical practice and ~~to~~ document the sections tackled during a model medicinal chemistry course (either magistral, tutorial or practical). This survey was conducted between July and September 2019 and answers were translated into skills, if needed.

During phase 2, an early version of the framework was subdivided into two parts. To visually compartmentalize the different positions taken by Pharmacists during their professional life, we distinguished the 'Upstream Pharmacists' from the 'Downstream Pharmacists'. Upstream Pharmacists can mobilize and translate molecular considerations into research and innovation, pharmaceutical development and formulation solutions, production and batch analysis, registration, technical consulting, or management. Downstream Pharmacists can mobilize and translate molecular considerations into the analysis of a prescription, constructive propositions to a health team, conciliation, and fruitful physician-pharmacist interaction. This second version of competencies framework was submitted again to the above-mentioned representatives of our association for incrementation. Of the 24 surveyed French Pharmacy Faculties, 22 (92%) responded to the first framework and 21 (87%) to the second. Thus, each framework benefited from excellent representation. In addition, the full competencies framework was presented to the French Medicinal

Chemistry teaching community during the annual AFECT meeting. The high level of redundancy combined to the fact that no supplementary skills were added following the final editing stage suggest that data saturation had been achieved.

During phase 3, two experts from related disciplines (Analytical Chemistry, Organic Chemistry, Biochemistry, Biopharmacy, Pharmaceutical Technology, Pharmacognosy, Pharmacology, Pharmacokinetics, Clinical Pharmacy, and Toxicology) were chosen and solicited for their professional skills and pharmaceutical implications. 15 of those experts submitted reviews on the framework. All 15 were professionals with extensive views of the numerous pharmaceutical activities. Some of them manage multidisciplinary research teams, supervise pharmacy internships or are in charge of Masters programs, others are acting experts for the French Medicinal Agency (Agence Nationale de Sécurité du Médicament, ANSM), and are on the board of the French University Council (Conseil National des Universités, CNU), or work in hospitals. All of them accepted to review the in-progress framework. Thus, all disciplines typically engaged on theme-based pedagogical units, in direct or undirect relations with Medicinal Chemistry, were represented. Their insightful responses relative to their own teaching experiences and professional practices allowed us to refine skills and validate the scope of the framework. Corrections and amendments were made in accordance with their constructive propositions.

Each item was thereafter multiply exemplified (phase 4) to improve clarity and professional projection. We carefully chose helpful visual examples so that colleagues and pharmacy students could understand the competences to be acquired (see supporting information). Molecular illustrations were deliberately favored to underline the unique contribution of Medicinal Chemistry concepts and justifications to the understanding of drug actions and properties.

Finally, during phase 5, grades related to the 'BMD' (Bachelor-Master-PhD) academic degrees were attributed to each skill. Grades 1, 2 and 3 correspond to General Bachelor in Pharmacy level, Master level and PhD level, respectively. In more detail, grade 1 skills encompass basic concepts and proficiencies used by undergraduates, pharmaceutical technicians, and bachelor grade students. Graduated Pharmacists should master and mobilize both grade 1 and grade 2 skills in their professional life. Grade 1, 2 and 3 skills are expected for PhD graduates and researchers in Medicinal Chemistry, notably those involved in drug discovery programs.

## RESULTS

### Toward a fine-tuned Pharmaceutical Expertise

We have listed and categorized the diverse positions and responsibilities Pharmacists are likely to attain during their professional careers. With their polytechnic and comprehensive formation, they are ready to become either 1) Upstream Pharmacists, usually working in industrial structures, in Research and Development sectors (R&D), Formulation and Production, Analysis, Registration, Quality Management, in other words, situated on the bench side; and/or 2) Downstream Pharmacists in direct contact with patients: in community pharmacies, working in hospitals or other health institutions and commonly situated at the patient's bedside. This compartmentalization is arbitrary, and we very much know that pharmacists are likely to occupy several positions during their professional careers, either to evolve within the same structure or company, or to change their professional environment or the unfolding of their career. This abundance of professional opportunities was also considered for the present listing of proficiencies. The solidity and the richness of the pharmaceutical learning base are all the more important in an ever-evolving health context.

**PART 1 - Upstream Pharmacists**

Pharmacists are present from the beginning to end in the drug life cycle process. Some pharmacists gain immediate employment in the Pharmaceutical Industry shortly after their studies. The reason for that is the wide platform of competences rolled out during their studies and noteworthy, the pertinence of numerous internships they could accumulate during their studies. For other pharmacists, complementary specializations are added to their initial curriculum, and they are fully able to take key-positions in the R&D sector, Formulation and Production, Quality Assurance-Quality Control (QA-QC), Management, Consulting, Registration or Pharmaceutical Regulatory Affairs where their global expertise is well-appreciated. Once again, additional orthogonal specializations are possible because of the variety of scientific and transversal fields (such as communication, or digital skills) tackled during the pharmacy curriculum. With all these projections available, we have listed the professional skills and knowledge pharmacists acquire along their medicinal chemistry courses that could be applied to such pharmaceutical positions.

To provide a practical synthetic overview, results have been presented in tables. For instance, skills in physico-chemistry, exploitation of recommendations and monographs and R&D have been listed in a didactic order following a logical unfolding. For example, a medicinal chemistry issue is situated within the drug discovery stages before linking an API to its conception process and discussing scientific approaches. An entry according to skill objectives is described using action verbs such as “applying”, “linking”, “practicing”, “deeply exploiting”. Intensive work was carried out to find matching examples for each item. Cases illustrating schematic examples have been separated to give a clear and concise overview of the expected skills*. They can be fully consulted in the supporting information section.*

**Table 1: Physicochemical aspects for the analysis of Active Pharmaceutical Ingredients (APIs).**

| | | |
|---|---|---|
| Finding information and linking to structure | grade 1 | Finding out and interpreting bibliographic information on physicochemical properties related or specific to medicinal chemistry from literature, pharmacopeia, and drug master files. |
| | grade 1 | Linking the chemical structure of an API to its physicochemical properties. |
| Developing an analysis | grade 2 | Identifying and justifying the choice of a physicochemical assay. |
| | grade 2 | Suggesting, selecting, and executing methods of identification, analysis, and dosage from an API chemical structure; adapting to a quality assurance system; interpreting results from quality control. *This skill also belongs to analytical chemistry skills.* |

**Table 2: Recommendations and monographs.**

| | | |
|---|---|---|
| Applying | grade 2 | Finding, interpreting, and applying current recommendations, guidelines, and monographs. |
| | grade 2 | Establishing the compliance of an API to monograph specifications, including the European Pharmacopoeia. |

| | | |
|---|---|---|
| Developing and writing | grade 3 | Developing a strategy of analysis of a New Chemical Entity (NCE).<br>*This skill also belongs to analytical chemistry skills*. |
| | grade 3 | Anticipating residual compounds or degradation impurities from a synthesis pathway, with the specific aim of composing monographs. |

**Table 3: Research and development (R&D).**

| | | |
|---|---|---|
| Introduction to R&D by cases studies | grade 1 | Placing a medicinal chemistry issue in the R&D stages (hit to lead, lead optimisation…). E.g. screening and prodrug conception in hit identification and lead optimisation, respectively. |
| | grade 1 | Linking a lead API to its conception (serendipity, screening, rational design, optimisation, analogy…). |
| | grade 1 | Suggesting, analysing, and justifying pharmacomodulation based on structure activity relationships (SAR) and structure property relationships (SPR) to finely tune physicochemical properties, predict ADMET features, and/or try to improve drug/target affinity…. |
| | grade 1 | Suggesting a prodrug, or a soft drug, by addressing a pharmacokinetics problem. |
| Project-based learning and practicing | grade 3 | Suggesting and discussing an approach to a medicinal chemistry problem. |
| | grade 3 | Suggesting and discussing a synthesis pathway, overcoming constraints specific to the pharmaceutical sector (such as reproducibility, large scale, green chemistry). This skill also belongs to Organic Chemistry skills. |
| | grade 3 | Elucidating a New Chemical Entity from NMR, MS, IR and UV analyses. *This skill also belongs to Analytical Chemistry skills.* |

**PART 2 - Downstream Pharmacists**

The dispensing of medicines by the Pharmacist contributes to the security and optimization of therapeutics. The pharmaceutical analysis of the medical prescription, or of the patient request (over the counter, OTC medication) is based both on the knowledge of drugs and on a context analysis. During prescription analysis, the pharmacist checks contraindications, putative side effects, drug-drug interactions, and drug redundancy. He/she can also suggest a right dosage, an optimal route of administration and a drug intake planning, particularly for drugs with a narrow therapeutic range. Context analysis requires the consideration of the recommendations emitted by international and national instances and consensuses together with local/national economic constraints. The Pharmaceutical Act also mobilizes the concomitant pondering of the patient's physio-pathological state and his/her own compliance. From this analysis, the Pharmacist evaluates clinicals consequences and, if appropriate, proposes an alternative, either to add drugs for synergy, or to prevent or manage side effects, a dose adjustment, or a therapeutic follow-up. A Special attention is always paid to redundant medication leading to additive side effects. Thus, Pharmacists can make constructive propositions to a health team and should act at a fruitful and perpetual Physician-Pharmacist interaction toward the patient's health and wellbeing. With all these items in hands, we have listed hereafter the professional skills a Pharmacist gains along his/her Medicinal Chemistry courses that can be useful at the bedside.

**Table 4: Chemical basis of Biopharmacy and Pharmacokinetics:**

| | | |
|---|---|---|
| Linking structure to Pharmacokinetic properties | Grade 1 | Identifying organic functions and (hetero)cycles of an API, interpreting physicochemical properties and linking them to ADMET properties |
| | grade 1 | Linking a chemical structure to administration route (IV, IM, per os…). |
| | grade 1 | Commenting benefit and activation mechanism of a prodrug; ~~linking formulation based on physicochemical properties of an API~~. |
| Calculation and prediction of properties and consequence of change | Grade 1 | Calculating [based on Henderson Hasselbach equations], estimating and interpreting ionization rate and solubility in biological media, Log P of an API, deducing the primary site of absorption, predicting the consequences of changes in pH of the medium. |
| | grade 1 | Predicting and commenting solubility [Lemke rules, [21]], absorption [particularly Lipinski rule of five, [22]], distribution, metabolism and elimination of an API by addressing a molecular argument. |
| Deeply exploitation of chemical structures | grade 1 | Drawing main metabolites from the indications in the Summary of Product Characteristics; predicting putative toxic metabolites based on chemical structures; identifying APIs that need dose adjustments because of kidney or hepatic failure ~~and change in pH.~~ |
| | grade 1 | Anticipating physicochemical interactions and identifying organic functions that interact with drugs (API and excipients), food supplements, natural products, and food. |

**Table 5: Pharmacophore** (*in this table, pharmacophores are related both to the common structural features conveying the pharmacological activity and features that ensure drug/ target affinity)

| | | |
|---|---|---|
| Linking pharmacophore, INN, and clinical information | grade 1 | Identifying ~~and understanding the involvement of~~ a pharmacophore; linking the pharmacophore with the specific mode of action and possibly to a segment core of the International Nonproprietary Name (INN). |
| | grade 1 | Linking the core segment of an INN to a pharmaceutical class. |
| | grade 1 | Deducing clinically relevant information from pharmacophore and INN. |
| Deep exploitation of the chemical structures | Grade 1 | Identifying key chemical functions that interact with the drug target. |
| | grade 1 | Identifying asymmetric centres involved in a pharmacophore, distinguish eutomer (active enantiomer) from distomer (inactive enantiomer), calculating eudismic ratio (activity of eutomer / activity of distomer). |
| Practice | grade 3 | Superimposing a series of API and suggesting a pharmacophore. |

**Table 6: integration of Medicinal Chemistry and Pharmacodynamic**

| | | |
|---|---|---|
| Linking chemical structure to molecular mechanism | grade 1 | Linking a mechanism of action at the molecular level with a therapeutic target and linking configuration (and possibly conformation) with activity. |
| | grade 1 | Establishing the mechanism of an enzyme inhibitor (reversible, irreversible, transition state analogs …) and relating to the duration of action. |
| Deep exploitation | grade 1 | Gleaning parameters (solubility, log P…) and chemical information (stability, compatibility…) for clinical use (choice of an API in a specific |

| | | |
|---|---|---|
| of chemical structure | | clinical situation – such as a hepatic failure – adaptation of the administration route). |
| | grade 1 | Comparing APIs of the same pharmaceutical class and identifying relevant functions and parameters for choosing the best API in a specific clinical situation (and for hospital market). |
| | grade 1 | Predicting a pharmacodynamic property from a chemical structure. |
| Practice of Med Chem | grade 3 | Predicting the mode of inhibition (competitive, non-competitive, mixed), site of action (allosteric *versus* isosteric) and strength (complete or partial) and propose an assay aiming at demonstrating and studying affinity, activity, and molecular mechanism of action. |

**Table 7: Integration of Medicinal Chemistry and Pharmacologic properties**

| | | |
|---|---|---|
| Linking structure to incompatibility | grade 1 | anticipating putative physicochemical incompatibility within a solute or by combining API for example during perfusion |
| Argue based on chemical structure | grade 1 | Discussing physicochemical features involved in drug interactions based on Pharmacokinetics and/or Pharmacodynamics. |
| Practice of med chem | grade 3 | Predicting a change or a variation in the pharmacological effect resulting from a change in structure. |

**Table 8: Linking Medicinal Chemistry and medicine related iatrogenesis.**

| | | |
|---|---|---|
| Linking chemical structure to side effects | grade 1 | -Linking side effects with the similarity of a pharmacophore, an organic function, a class effect, or a toxic metabolite |
| | grade 1 | Identifying organic function and heterocycles that may generate toxicity: ROS, photo-sensibility, alkylation, inhibition of CYP450 or carbonic anhydrase. |

**Table 9: Appling SAR and SPR to a specific clinical situation**

| | | |
|---|---|---|
| Argue based on chemical structure | grade 1 | Linking clinical decisions to chemical structures, galenic form and/or physicochemical parameters. |
| | grade 1 | Using RSA or RSP to suggest and discuss clinical applications (indication, doses, administration routes). |

**DISCUSSION**

To be as exhaustive as possible, the present work was built following a continuous quality improvement approach. A preliminary framework was structured by translating some professional case studies, based on our own pharmaceutical experience, into skills. The framework was enriched with pedagogical literature and, more importantly, from the answers to a broad-ranging questionnaire about teaching practices collected from our association members. Second and third versions of the framework were submitted for incremental improvement, with the high level of participation (89% of French Pharmacy Faculties) ensuring high representability. The fact that no supplementary skills were added following the final editing stage suggested that data saturation was reached. 15 experts, selected for their expanded professional vision of the numerous pharmaceutical activities, participated in the fine tuning and validation of the draft. All disciplines included in theme-based units, either directly or indirectly related to Medicinal Chemistry were represented: Analytical Chemistry, Organic Chemistry, Biochemistry, Biopharmacy, Pharmaceutical Technology, Pharmacognosy, Pharmacology, Pharmacokinetics, Clinical Pharmacy, and Toxicology. Many pharmaceutical jobs and responsibilities were represented too. The constructive responses allowed us to refine the skills and validate the scope of the framework, especially considering responses obtained from specialists in Organic Chemistry, Analytical Chemistry, Pharmacodynamics or Pharmacokinetics.

Pharmacy is the art of both preparing and dispensing drugs. Skills that refer to the preparation of drug compounds were included in the upstream part of the framework. In the second part the framework, downstream skills illustrate the adjustment of modern Medicinal Chemistry to modern concepts of pharmaceutical care (20). The rising number and complexity of active substances, the introduction of cost-effective medication and polypharmacy management emphasizes the requirement for a well-founded choice of the right product to the right patient at the right time. In this context, a relevant structural comparison between molecules, a molecular-based analysis, and an ADMET-connected (Absorption Distribution Metabolism Elimination Toxicology-connected) expertise are of the utmost importance. Thus, Medicinal Chemistry links structures, physicochemical properties and biological effects. Consequently, it provides a strong molecular basis for comparing drug compounds of the same class (3.1, entry 3), identifying structure related to toxicity, or side effects (3.3, entry 2) and anticipating physicochemical incompatibilities (3.2, entry 2) and bioavailability. Of course, the achievement of the present framework has caused unavoidable slight overlaps with related disciplines such as Biopharmacy, Pharmacokinetics and Pharmacodynamics. To deliver a clearer message, each skill has been widely exemplified, illustrating the tight connection between Medicinal Chemistry and other medicinal/pharmaceutical sciences whilst defining the borders between the various disciplines whenever possible.

In 2011 in France, the specific first year composing pharmacy studies disappeared in favor of a first year providing a common platform toward Medicine, Pharmacy, Midwifery, Odontology and Physiotherapy studies. That led to a noticeable reduction of the hourly volume of general chemistry, including organic chemistry, courses. Further reforms are in progress throughout France in which have also led to decreases in the hourly volumes of Chemistry. Within this general trend of reduction, the current framework proposes a basis that could help pedagogical teams to focus the teaching of Pharmaceutical Chemistry immediately on practical and essential professional skills.

Before 2012, the French curriculum for Pharmacy studies was strictly based on disciplines, with most theme-based teaching units appearing shortly afterwards. A difference persists between the individual French Faculties of Pharmacy in that each one is totally independent in its choice of teaching. Nevertheless, theme-based teaching units usually synchronize Physiopathology, Biochemistry, Pharmacology, Toxicology, Clinical Pharmacy and Medicinal Chemistry around systems like cardiovascular, respiratory, central nervous systems or therapeutic areas such as infectiology or endocrinology. Consequently, Medicinal Chemistry has frequently been fragmented and its objectives have often been confused, notably by students, with those of molecular pharmacology. Clarification was thus absolutely necessary. Integration of Medicinal Chemistry within Pharmacotherapy courses during the early stages of pharmaceutical studies is an opportunity to enrich the content of Medicinal Chemistry courses with practice and applications. Furthermore, Keserũ [23] and Lajiness [24] have demonstrated that rules and cut-offs used in medicinal chemistry practices still depend more on work experiences than learning [25]. Therefore, even in postgraduate stages (Master and Doctorate), it is interesting to have a sound knowledge of many drugs and to be able to refer to a wide range of examples.

Interestingly, this framework could also help switch from classical passive courses to active learning [26,27] especially by clearly defining prerequisites and objectives. Moreover, it should allow Medicinal Chemistry teachers to integrate evidence-based solving-problem such as structurally based therapeutic evaluations (SBTE) [9,10]. Thus, the present skills framework could help Medicinal Chemistry teachers to shift from a traditional unintegrated lecture-based teaching to an integrated problem-based approach. Here, most of the listed skills provide a way to link Chemistry with Medicinal Sciences. As Chemistry belongs to the so-called “hard sciences”, Medicinal Chemistry provides a specific way to discuss and deal with a question by evidence-based solving-problem. Tutored by their professors, students could develop critical thinking by linking the ‘why’ and the ‘how’.

Nowadays, healthcare teams are pluri-professional. The Pharmacist is seen as the Chemist of the care team and in this context, Medicinal Chemistry skills definitely underpin his/her chemical expertise. Nonetheless, the basic principles of Medicinal Chemistry could be integrated in the curriculum of other health professionals who manipulate drugs, such as nurses, dentists, midwifes and physicians. In addition, graduate schools for nurses and pharmacy technicians are experiencing an “Universitization” process [28,29], requiring strong fundamental scientific training. Local managers of those pedagogical projects could find here an overview of the useful skills to be conveyed in Medicinal Chemistry.

Until now, there has been no national framework available for the teaching of Medicinal Chemistry in France. The framework presented here has been developed by French teachers and is suitable to French practices and the objectives of Medicinal Chemistry courses, especially in theme-based teaching units. The recommendations are in accordance with the developments in Medicinal Chemistry courses in Spain [6] and the direction that the Gulf Cooperation Council countries wish to aim towards for the PharmD degree [30]. They also meet the pioneering development initiative to introduce clinical relevance in Medicinal Chemistry objectives in the U.S.A. through case studies [12,14,16] treatment algorithm [31] and the concept of structural based therapeutic evaluation (STBE)

[9,10]. Thus, this framework meets the requirement of the instructional model proposed by Alsharif *et al*. [8] and the study objectives of Medicinal Chemistry in the Pharmacy curriculum discussed by Faruk Khan et al. [32] and improvements requested by French Students and professionals [33].

## CONCLUSION

Hourly reductions in fundamental chemistry courses, increasing numbers and molecular complexities of drug compounds, sophistication of health care strategies and new missions devoted to ~~the~~ pharmacists within the health team have urged to change modes of teaching. Integrated approaches in teaching have made it necessary to clarify the unique input of Medicinal Chemistry proficiencies to the Pharmaceutical practices. Here and for the first time, an exhaustive framework of Medicinal Chemistry skills has been established and deeply exemplified. This serviceable tool promotes the visibility of Medicinal Chemistry and contributes to its positioning within the Pharmaceutical curriculum. The proposed framework fully consolidates the impact of structure-based competences within the multifaceted pharmaceutical professions. There is no doubt that the framework needs to be adapted to local teaching practices, but it could serve as the basis for the tight integration of medicinal and pharmaceutical sciences. Further work could be engaged in every connected discipline following this pilot study.

## DECLARATION OF INTERESTS

The authors declare that they have no conflict of interest with this article.

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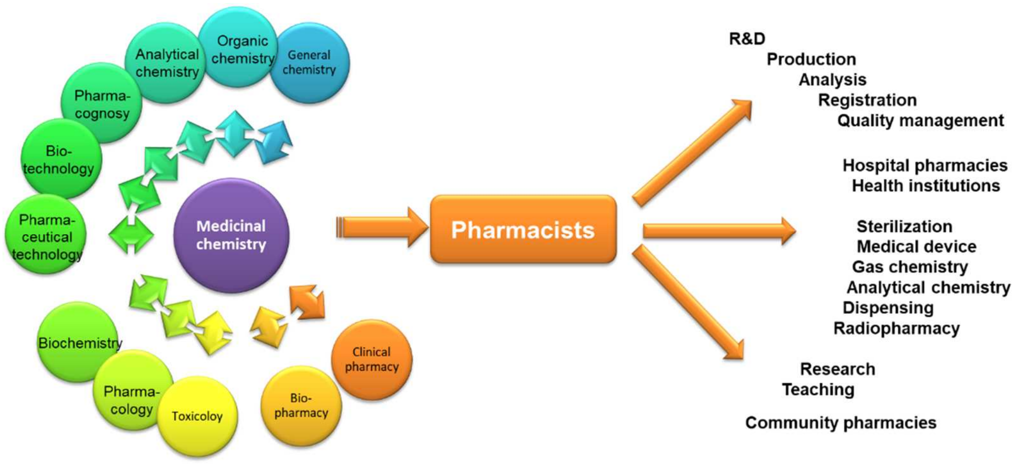
Organic chemistry
General chemistry
Analytical chemistry
Pharma-cognosy
Bio-technology
Pharma-ceutical technology
Medicinal chemistry
Biochemistry
Pharma-cology
Toxicoloy
Bio-pharmacy
Clinical pharmacy
Pharmacists
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Production
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