CARB-X
Global Accelerator Network

C-CAMP
Centre for Cellular and Molecular Platforms

MAY 2022

AMR Innovations

From Discovery to Commercialization

CENTRE FOR CELLULAR AND MOLECULAR PLATFORMS

Bengaluru, India

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Disclaimer:

The white paper provides preliminary elements on the life cycle of AMR innovations through the different stages of development from discovery stage to availability in the market. This document reflects the opinions and perspectives of invited experts and stakeholders from the Indian AMR ecosystem. It does not claim to be an exhaustive representation of the topics mentioned in the whitepaper. The views will likely evolve further as the discussion and participation continues to expand on this very important public health challenge.

The facts, opinions and conclusions provided in the document are drawn from presentations by domain experts, however it does not explicitly imply opinion of all partners and stakeholders mentioned in the document.

The whitepaper is intended to encourage discussion on an important topic that would be of interest to the larger community and stakeholders in associated domains. It is not intended to be prescriptive, however, it is hoped that it will serve as a good reference for innovators, and stakeholders working in the domain of AMR innovations.

Context

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) as one of the top ten global public health threats facing humanity. Antimicrobial Resistance [AMR] is an emerging global threat. It is not only impacting the health system but also disrupting the efforts towards achieving the Sustainable Development Goals [SDG] of eradicating poverty, promoting good health and well-being, reduced inequality, decent work and economic growth, etc.

India needs to urgently step up its response to this emerging health emergency by convening expertise and resources for collective action. Concerted action has been initiated by many agencies in India in response to this healthcare crisis. Amongst them, the Centre for Cellular and Molecular Platforms (C-CAMP), has recognized the significance of AMR and has been working towards fostering and amplifying R&D efforts in this space. C-CAMP has launched many innovation-focused AMR initiatives in partnerships with major stakeholders and partners, internationally as well as within India. One notable partnership is with CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), the world's largest public-private partnership dedicated to accelerating antibacterial research to tackle the rising global threat of drug-resistant bacteria. As member of CARB-X's Global Accelerator Network (GAN), C-CAMP has been convening experts, in the field of AMR, while leveraging its own vast knowledge-base and networks in the country's innovation ecosystem, to identify and address key gaps in this area.

A virtual workshop 'AMR Innovations: From Discovery to Commercialization' was conceptualized and convened by C-CAMP earlier in 2022 with domain experts with the mandate of discussing and charting the roadmap for AMR innovators and how they can accelerate their solutions for the end-users by leveraging existing frameworks. A vast gamut of topics, was discussed, ranging from discovery to scale-up. This expert workshop forms the basis of the content shared in this document. C-CAMP has further endeavoured to collate and present this in a cohesive manner such that it benefits a larger audience working, or who have an interest, in the domain. The document also flags some suggestions, from an innovation viewpoint, that would be crucial in the successful implementation of these innovations for the end-user.

[1] **About C-CAMP (www.ccamp.res.in)**

The Centre for Cellular and Molecular Platforms - C-CAMP, is an initiative of the Department of Biotechnology, Ministry of Science and Technology, Government of India, and was established in 2010 as an enabler of cutting-edge innovation and deep-science-led entrepreneurship. C-CAMP today is considered one of India's most exciting Life Science ecosystems and has supported over 2500 research programs through its high-end technology platforms as well as funded, incubated and mentored over 700 start-ups across all domains of the Life Sciences.

Introduction & Scope

Anti-microbial resistance (AMR) is a leading cause of death around the world, with the highest burdens in low-resource settings. The World Health Organization (WHO) has declared AMR as one of the top ten global public health threats facing humanity. Experts estimate that about 10 million people will die every year by 2050 due to AMR. According to a January 2022 publication in the *Lancet* with data from 204 countries, drug-resistant infections were found to have killed 1.27 million people in 2019, this is more than many widely recognized causes of death, such as malaria and HIV/AIDs In about 5 million people, a multi drug resistance (MDR) infection contributed to their death[2]. 413,000 children under 5 years of age died due to bacterial infections, of which 417 of 100,000 were due to AMR. Majority of these deaths were reported from sub-Saharan Africa and south Asia. A large burden of these deaths was from India. A study by ICMR showed that resistance patterns to *Klebsiella*, *E.coli*, *Acinetobacter*, and *Pseudomonas* are on a rise in India and we are losing front line antibiotics[3]. Colistin is becoming commonly used in hospitals. The pandemic has further escalated the problem of AMR with increased and often unnecessary antibiotic consumption.

AMR is a multi-faceted global problem that requires a multi-pronged systemic approach. Aside from other efforts, advancements in therapeutics, diagnostics, prevention, and surveillance need to be integrated and leveraged in our efforts to effectively combat and control AMR. Experts agree that the fast incorporation of these solutions in public health efforts is going to be a crucial factor in effectively containing the spread of AMR[4]. In this context, the life cycle of these solutions from discovery to market becomes an important consideration for optimizing outcomes.

In this document, we will provide perspectives across the different stages of development of AMR focused innovations. Starting from the Discovery & Development of therapeutics and diagnostics, to Regulatory aspects, Clinical Development, supportive Funding, and finally, Scale-up and Manufacturing to reach the market and the end-user. The document aims to highlight aspects that would be crucial to consider and understand from an innovator's viewpoint to effectively navigate the different stages while working on AMR focused innovations. The document includes perspectives that on one end are very specific to the AMR domain, and on the other, are general and broadly applicable. It is our effort to include both since these are vital to building a concise, comprehensive and cohesive narrative on the topic.

We will conclude by providing key insights on how the pipeline for antibacterial and diagnostics be further strengthened in line with the demands of an evolving AMR ecosystem.

[2] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext
[3] AMRSN_annual_report_2020.pdf (icmr.nic.in)
[4] https://royalsociety.org/-/media/events/2021/07/tof-amr/transforming-our-future-amr-report-2021.pdf?la=en-GB&hash=54994A0BF40745815462DD35B16F1C59

SECTION - I

Discovery and Development: Therapeutics

Discovery is the first step in the life cycle of the AMR innovation, it is for this reason that it needs to be well-thought through keeping all subsequent steps that will have to be undertaken going forward. We need to assess this as a whole rather than in silos. At a micro-level, when studying infections, we study host-microbe interaction, host response etc. in an isolated manner, this needs to be addressed with an integrative approach as well.

Prior to the 1960s, the antibiotics produced were mostly driven by natural products, synthetic chemistry, and the serendipitous discovery of new molecules involving chemistry. After a long gap, during the 2000s the last molecule to be discovered was Daptomycin, and we struggled to bring new molecules to the market. The 1970s and late 1990s was a period of chemical evolution where the pharmaceutical industry was driven by the modification of existing early molecules which had been discovered earlier, for example, the development of broad-spectrum cefdinir, a fourth-generation cephalosporin.

Traditionally, the discovery and development of antibacterials started with synthetic antibacterial, natural antibacterials and then antibacterial through chemical evolution, however, this progression stopped thereafter. Among the many factors that contributed to this was the shift from chemistry-driven evolution to biology-driven evolution. This may be attributed to the progress made in human genome sequencing and subsequently, the availability of multiple drug targets. This genome-only-driven discovery had limited success. However, today there is a better rationalization for the use of multiple approaches together, including genome research, synthetic methods, repurposing molecules, etc.

It is important to assess the market opportunity when launching a drug discovery program since it is a long-drawn process, and multiple laboratories might be working on it at the same time. Thus, the speed of a drug discovery programme is of the essence, which may directly be associated with the resources being allocated, like funding milestones, patent application and its lifespan etc.

The Cycle of Drug Discovery and Challenges

In early discovery, the following aspects are important to address upfront;

- TPP, or Target Product Profile, needs to be defined even before initiating the actual process of drug development. This should be backed with an in-depth understanding of the unmet medical need that this would address, and thereby the market opportunities available down the line. This is crucial for raising initial investments to kick-start the efforts. For example, working on another compound for *Staph aureus* might have a lower investor interest as compared to compound for *Pseudomonas*, not because compounds are not required for *Staph aureus* but because a bigger technical clarity might be needed as to why the current portfolio of drugs or the standard of care are failing, and how the new drug would address those challenges. This thoroughness is a prerequisite when defining TPP.

Secondly, it is important to know the patients for whom the drug is intended, that is, will it be for hospitalized patients or community patients, for terminal patients or for early indications?

Ascertaining what mode of treatment, eg. oral, intravenous etc., the innovator wishes to undertake is also part of defining the TPP well. This itself would point to the ease of administering, the likely pathway of drug development, but would also define the patient to whom it is administered and for the indication for which it is administered. Eg.

Intravenous application would point to hospitalized patients, and to indications that require hospitalization as opposed to out-patient care.

Thirdly, being aware of the competitor landscape, or building one's competitive intelligence 'is another crucial aspect to address. This would include how one envisages their molecule to be superior to existing options, key differentiating factors, a timeline comparison to the market with competing molecules, and so forth.

TPP is dynamic and can change along the way as one finds new properties on the compound, and how the project has progressed.

- Target- the advantage of having a target in the drug discovery process is that good assays and molecular pathways can be identified.

From a regulatory perspective, knowing the target helps in ascertaining two perspectives:

i) Class-specific risk-for example, quinolones have an inhibitory effect on bone marrow, irrespective of modifications on the molecule, and

ii) Mechanistic risk- for example, if the target of interest is present in the bacteria but is also present in humans then the next aspect to address is whether the target's function in both is mechanistically similar, and if it is then what are the effects of inhibiting the target downstream. From a regulatory viewpoint, it will be assuring to know if the target's homolog is not present in humans.

Target assessment also helps in understanding whether the biological pathway it falls in is good enough to be addressed.

Many innovators might not know about their targets early on but will build more clarity as their work progresses.

- Inhibitory Effect- The molecule's potency and the mechanism of inhibition must be established early on.
  With the initial inhibition data, one needs to also establish their Freedom to Operate (FTO) by doing early patent research to understand the limitations, and areas where they can operate.

- From Compound to drug

i) Physiochemical properties are extremely important to assess at an early stage. For example, if solubility is an issue then this should be flagged in the beginning itself.

ii) Mechanism of Action (MOA) mapping by looking at preliminary efficacy in animal models

iii) Spectrum analysis to ascertain that the compound is working in most of the bacterial strains

iv) Frequency of resistance (FOR) is crucial to know as many pathways and targets might have an extremely high frequency of resistance and it would be best to avoid these.

v) Off-target interactions to be checked against a panel of human targets, e.g. kinases, to make sure that the compound does not have any target in the host

vi) Safety profiling, for example, risk of hemolysis or cytotoxicity etc.

Knowing these give an early advantage and an early lead to innovators working on drug discovery and development.

- Early Lead onwards

i) Balancing pharmacokinetics and pharmacodynamics of the compound forms the central point of anti-infective drug discovery. This helps in defining the dosage, dose regimen, the patient population etc.

ii) *In vivo* studies can help to assess efficacy dosage window etc.

iii) Disease condition and positioning by ascertaining what is the standard of care (SOC) and how the compound looks in comparison

- Robust Lead- Although the work might be still preliminary but by this stage, enough knowledge base on the properties of the compound, technical comparisons, market landscaping etc. would have been created to get investor interest or to start a grant application.
- Late Discovery- This requires a Detailed Tox package, positioning, IND submission etc. Positioning the compound as a standard of care, where it is going to the fit-resistant type or alternative type, and other aspects of candidate drugs like an opportunity for licensing etc., are other critical parameters to address.

SECTION - II

Discovery and Development: Diagnostics

Developing New Diagnostics

For innovators desirous to work in diagnostics there are two pathways to consider– i) Creating a new diagnostics product with no similar end-use. That is to say that nothing similar is available in the market and there is an opportunity to create a totally new path of discovery, or ii) Improving/ Replacing existing diagnostics platforms to make them more efficient, quicker, more cost-effective, enhance ease to use etc. In this case, the path is relatively clear. Both of these pathways have their share of novelty, innovativeness and challenges.

The end-user is always the patient; the model to reach them might vary and that is what defines the roll-out or the execution plan. Healthcare innovations have to have a patient-centred approach as the purpose is to save lives, prevent disabilities and save healthcare costs caused by life-threatening infections. The end goal is to have an actionable diagnostics tool in the hands of the healthcare provider. Diagnostics will be actionable when a doctor is able to make decisions based on the diagnostics results, and subsequently, decide on the patient's treatment plan. For example, in a clinical condition resembling sepsis, if a diagnostics test, such as Syndrome Analysis System (SES) that tests for all pathogens (bacteria, fungi, viruses) can test syndromes from a single sample at a time, shows a negative test, i.e does not show any pathogen, then will it lead the physician to not prescribe any antibiotics? Such diagnostics-led clinical decisions are important in the context of AMR.

Another scenario where diagnostics in AMR will be useful is for patients that are on antibiotics but have not been cured of their symptoms. In such patients, the pathogen will be identified, at best, in 15% for whom targeted treatment can be initiated; whereas a majority is left with no pathogen being identified, thereby leading to continued empirical treatment. To make matters worse, the presence or absence of pathogens is not known until 48-72 hours post sample collection with the present set of tests. Precious time is thus lost. In AMR, one of the main roles of diagnostics is thus to prevent this escalation in MICU where patients stay for multiple days and may be administered high doses of life-saving antibiotics. To illustrate this with an example, on day 1 PipTaz, Amikacin, or Ceftriaxone maybe administered; after 24 hours, Vancomycin and Linezolid might be given; after 48 hours, Meropenem and Imipenem are added to the panel; at 72 hours, high-end Colistin and Tigecycline join the arsenal; and finally at 96 hours, Fluconazole and Caspofungin are administered. If the patient still does not show respite from symptoms, then it is wondered if it's a refractory case.

This antimicrobial escalation in MICU is addressed in most hospitals by antimicrobial stewardship. To accentuate these antimicrobial stewardship efforts, diagnostics stewardship can run in conjunction to identify the pathogen and direct the physicians to targeted treatment.

Taking the analogy of burning the candle from both sides in the context of AMR, the OPDs prescribe antibiotics from the lower end to the upper end, whereas in ICUs the patients are given antibiotics from the upper end to the lower end. Both these approaches, in the absence of diagnostics-led targeted treatment, has the potential to aggravate the problem of AMR.

The Path for New Diagnostics

The path to the development of new diagnostics solutions requires consideration of a few key aspects;

- Identification of an unmet medical need
- Understanding Patient's need- Voice of Customer

- Understanding Clinician's need- Voice of Customer
- Understanding the Lab's need- Voice of Customer
- Understanding of where in the workflow is the diagnostics intervention actually required
- Adequate data to ascertain the features of a potential diagnostics solution
- Preliminary test with biomarkers on patients/ clinical samples to determine the feasibility of the proposed diagnostic solution

Product Profile

A thorough product profile sets the foundation for the future solution. Assessing the unmet medical need has to be ascertained in conjunction with concerned persons, like the clinicians and public health experts etc., by asking open-ended questions. Product profile should be made after interviewing 50-60 such experts. Checking for clues on how the doctors prescribe antibiotics, and what assessments are done prior to this prescription. And so on. Limitations of these assessments should also be considered, for example, is the test for gram-negative bacteria missing a potential co-infection by a resistant gram-positive bacterium?

To make early decisions, consider the problem of sepsis where data on culture is only 12% and thus extrapolations for the remaining 88% of cases is important. Treatment algorithms maybe different from hospital to hospital and should be well understood.

An understanding of the resistance patterns observed in hospitals should be checked from hospital data or by surveillance studies. The genetic markers of this resistance should be identified through basic research work involving genomic profiling and biomarker identification. These studies are crucial in diagnostics discovery.

It is important to assess who the target customer is. Is it the patient, the clinician or the testing laboratory? This focus defines the workflow as these are very different considerations and will also change the future strategy of reaching the end-user or customer.

Developing diagnostics is an iterative process as it needs to be tested in real-time on patients continuously and adapted accordingly.

SECTION – III

Regulatory Perspectives / Clinical Trial/Development Design

The design of clinical studies, phase I, II and III, are planned based on the regulatory requirements as the ultimate goal is to bring the product to the market. A start-up that has reached a certain clinical stage in a particular country has the ultimate goal of going global. Regulatory requirements across countries and authorities are different. This should not translate into multiple validations for different regulators, but should be a convergence that accounts for all that has been done and achieved before. The regulatory agencies have also tried to come together to match the inter-agency requirements so that any innovator that is coming with a product is not developing different programmes for different regulatory agencies. The intention should be to standardize processes and prevent unnecessary expenses in designing and developing different programs.

In the last few years, there have been a lot of challenges in India related to devising regulations and device laws as it has been lacking clarity in terms of what needs to be done at different points in time. Regulatory requirements across regulatory authorities are different although steps by regulators have been initiated in the past to converge on the requirements to reduce the impact on development programs. Idea is to have completely harmonized requirements across all regulatory authorities. It would be ideal if the same clinical development program satisfies the requirements of different regulatory authorities.

Transatlantic Task Force on Antimicrobial Resistance (TATFAR) has been seeking convergence on trial designs and endpoints for;

- Acute bacterial skin and skin structure infections (ABSSSI)
- Community acquired bacterial pneumonia (CABP)
- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI) and
- Hospital acquired/ventilator associated bacterial pneumonia (HABP/VABP)

An important area for discussion has been the clinical requirements for products addressing unmet needs related to AMR. Clinical trials for HABP/VABP are particularly relevant for new agents targeting serious infections, including those caused by multidrug-resistant organisms. FDA recommends a mortality endpoint, the EMA and PMDA recommend a clinical cure endpoint. Some level of innovation around data requirements and trial designs and agreements on the need to streamline clinical trial programs is required for such products. A well-executed trial in a specific type of infection due to organisms that are susceptible to an appropriate comparator with the support of PK/PD analyses should be an adequate data package. Additional support can be provided by data from small trials in patients with infections caused by MDR organisms.

Antibacterial Drug Development: Past to Present

In the 1960s-80s, patients with a variety of infections at different body sites were enrolled in the same trial. The objective was to demonstrate “comparable point estimates” for active control for a clinical cure for each of the different infection types. No formal inference testing was done. As the resistance rates were drastically low, it was possible. Indications were based on subsets of body sites of infections from within the trials. Antibiotics were developed and approved for less specific indications, like skin infections and lower respiratory tract infections. As we moved towards the 2000s, the focus was on site-specific trials.

In the 1990s and 2000s, the differences due to the natural history of different diseases,

endpoints and treatment duration, drug efficacy at different infection sites, and dosing for different sites were acknowledged and incorporated for revised guidelines. This led to the 1992 IDSA guidelines, and 1992 FDA Points to consider documents-Clinical Development and Labelling of Anti-Infective Drug Products. Recognizing the aforesaid differences in these documents represented an advance in clinical trial design.

During 2006, there was significant turmoil in the field; scientific questions were raised about non-inferiority (NI) trials. While one regulatory agency would approve NI trial, another regulatory agency wouldn't approve it. This proved to be a difficult situation. Considerable effort and stakeholder participation was made in designing scientifically sound NI trials, evidence-based NI margin justification, and trials conducted for common indications' usually two trials were conducted per indication.

Around 2012, the focus shifted to unmet needs, particularly to treat gram-negative infections. Streamlined drug development programs were pursued, this gradually led to single trial per indication, and a smaller safety database (~300-500).

In upcoming years, continued focus will remain on unmet need programs including 'difficult to study' indications and the development of non-traditional therapeutics.

In recent approvals, the types of data packages have included standard indications (cIAI, cUTI, ABSSSI, and CABP) where two trials per indication, or at least one trial per indication was accepted. In limited use indications, a single trial with supportive evidence (phase 2 study, *in vitro* studies, animal model of infection) was accepted. For LPAD Pathway, small data packages (single trial), well-defined, and within a limited population of patients were undertaken. Given the unmet need, there was some flexibility in benefit-risk considerations.

While we have made progress it appears that we are at a critical juncture in antibacterial drug development and multiple consortiums have come up to address these issues. There has been criticism regarding the clinical utility of some recently approved products and the registrational trials conducted to support their approval. While there is an unmet need for some difficult to study indications like osteomyelitis, and prosthetic joint infections, we need to work and ensure to map out the needs and potential solutions. While labelling is an important component of the discussion, addressing the scientific feasibility issue is the key.

When designing a program, the end has to be kept in mind, like, what is the label going to be? what is the upcoming product going to address? Work backwards and try to understand and design programs in that fashion because that's how the regulators will view it, and based on that, regulatory requirements and design accordingly.

Criticisms Regarding Recent Registration Trials

The trials demonstrate the efficacy of the product at the body site that provides reasonable safety information in a population with fewer confounding factors and allows for a step up to a more difficult to study condition. So, there is a need to balance the realities of drug development with the desire to study difficult conditions in populations. When the program is designed from a scientific point of view, one may not be able to get all the answers in a single trial and that is where one keeps multiplying programs. When the program is designed, it is not necessary to look at answering all the questions that one might have to address within a single study, as a lot of investment would have already gone into it.

The approach should be to get regulatory approval based on a basic concern, or the basic

question for the basic target disease, and then look at subsequent trials and add on indications and look at other aspects. By that time, some financial returns could be ploughed back. All of these are extremely critical parameters in terms of study design and in terms of the questions and the hypothesis that one desires while building the program.

Sometimes lack of data on patients with infections due to resistant organisms, can be a challenge in conducting a randomized controlled trial. Recently conducted trials in CRE infections were difficult to interpret as they were descriptive trials without any pre-specified hypothesis testing. As new therapies become available, the resistant phenotype of interest can change, this has to be especially considered. Potential trial designs that we look at for most of these antibacterial programs or anti-microbial programs are for finding superiority over the best available therapy. We can also enrich the trial population in an NI trial if an appropriate comparator is chosen. This depends on the chosen infection and the available antibiotics for that particular infection at that point in time.

Demonstrating superiority to currently available therapies is difficult which is why people try to get into a non-inferiority type of a study assuming that their product is as good as other available options available for the indication. Most drugs we use today were in fact approved based on findings of non-inferiority through superiorities. US FDA considers the number of patients enrolled, and approvals are typically based on incidence rates within the local population. For multiple reasons, enrolling patients into the trials might be difficult. General guidance indicates that at least half of the patients, or more, should be from the US if the registration is for the US. This has, however, not been strictly followed in the past.

When we talk about well-designed comparative clinical trials, it teaches important and unexpected lessons and those lessons help to develop further programs. While designing studies, while it may not be possible to solve every single problem it's important to be aware of these points. These are the areas that one needs to look at especially how the regulators have reviewed the data in the past, what have been the questions and the concerns that the regulators have raised in terms of trial designs, outcomes and so on.

Labelling

The label is an extremely critical aspect because that's what ultimately categorizes the product, determines the regulatory design and determines the use of the product.

Two key considerations for labelling regulations are ensuring consistency, including information and labelling based on sound scientific evidence, which is helpful to all stakeholders, providers, payers, and patients. When the product reaches the market, it is the label that drives insurance agencies and the usage, the prescription patterns etc. It is very crucial that the trial design addresses that primary question- what the antibiotic will be used for? on which particular type of the patient will it be used? and if appropriate, which subset of the patients would most likely benefit? This will be based on the results of the trials.

A plan for a label has to be initiated upfront with specific requirements on content and format of labelling for human prescription drug and biological products and clinical study section. These are some of the general things which a label should have for drug products, other than biological products.

For drug products other than biological products, any clinical study that is discussed in prescription drug labelling that relates to an indication for or use of the drug must be adequate and well-controlled and must not imply or suggest indications or uses or dosing

regimens not stated in the 'Indications and Usage' or 'Dosage and Administration' section.

Label Claims

Same development program can result in different product labelling across the different agencies, particularly for indications in unmet need areas. It is also important that labelling recommendations be based on sound scientific evidence so that it is helpful and clear to all stakeholders including patients, clinicians, regulators, and payers. It is encouraging that, with most applications, the risk-benefit assessments of antibacterial products are fairly similar across the agencies. Differences in the judgement on risks and benefits leading to different regulatory decisions are not unique to anti-infective products, and it is not realistic to expect that scientific assessment by different experts will lead to the same risk-benefit assessment across all applications. Regulatory flexibility is important but it should be ensured that the scientific underpinning of clinical trials is not compromised.

Device Regulations

In India, all medical devices are to be regarded as drugs, as per the Medical Devices [Amendment] Rules, 2020.

The Indian law that regulates the quality and safety of medical devices has been amended and it will now apply to all medical devices, effective April 1, 2020. Prior to the amendment, only 37 categories of medical devices were regulated or were notified to be regulated in India.

- Before October 1, 2021, all presently unregulated medical devices would have to be registered by respective importers or manufacturers with the Drugs Controller General of India (DCGI). However, those medical devices which are already regulated or have been notified to be regulated are exempted from the requirement of registration[5].
- Before August 11, 2022, importers, manufacturers, distributors, whole sellers and retailers of presently unregulated Class A (low-risk) and Class B (low-medium risk) medical devices sold in India will have to compulsorily obtain a license.
- Before August 11, 2023, importers and manufacturers, distributors, whole sellers and retailers of presently unregulated Class C (medium-high risk) and Class D (high risk) medical devices sold in India will have to compulsorily obtain a license.

Class of medical device	Licensing Authority	Stipulated timeline for processing application
Class A and B (import)	DCGI	Up to 9 months from the date of application
Class C and D (import)	DCGI	Up to 9 months from the date of application
Class A (manufacture)	State-level Licensing Authority	Up to 45 days from the date of application
Class B (manufacture)	State-level Licensing Authority	Up to 140 days from the date of application
Class C and D (manufacture)	DCGI	120 – 180 days (estimated)

[5] All medical devices in India to be regulated as "drugs" – Medical Devices (Amendment) Rules, 2020 – Arogya Legal – The Health Laws Specialists

New Definition of Medical Devices

Until February 11, 2020, the Government of India had regulated or notified 37 categories of medical devices as drugs[6]. On February 11, 2020, the government exercised its powers to notify one or more categories of medical devices as "drug" to actually notify a new definition of medical devices.

All devices including an instrument, apparatus, appliance, implant, material or other article, whether used alone or in combination, including a software or an accessory, are intended by their manufacturer to be used specially for human beings or animals which does not achieve the primary intended action in or on human body or animals by any pharmacological or immunological or metabolic means, but which may assist in its intended function by such means for one or more of the specific purposes of;

- diagnosis, prevention, monitoring, treatment or alleviation of any disease or disorder
- diagnosis, monitoring, treatment, alleviation or assistance for, any injury or disability
- investigation, replacement or modification or support of the anatomy or of a physiological process
- supporting or sustaining life
- disinfection of medical devices
- control of conception

One must understand what falls under a device. If they are using the computer systems to analyse human, that will fall under a category of device. Anything with a computer system or an algorithm used is also a device.

Requirement of Registration

The manufacturers or importers of Newly Notified Medical Devices will be required to compulsorily register their medical devices with the Drugs Controller General of India. The DCGI also intends to start accepting applications for registration through a dedicated online portal called "Online System for Medical Devices". There is no time-frame prescribed as of now for processing of the application for registration by DCGI. The registrations will be done instantly after submission of all information and documents on the online portal i.e., without any examination of the information and documents submitted by the applicant at the hands of DCGI.

Device Regulations- Approval Process

- In order to obtain registration for medical devices, the importers and manufacturers of the medical devices have to be certified as compliant with ISO-13485 (Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes)
- The way DCA and MDR ensure quality and safety of notified medical devices at all levels of the supply chain is by enforcing a mandatory license requirement.
- All importers/manufacturers/sellers of notified medical devices must obtain a license from the appropriate licensing authority before undertaking any commerce in notified medical devices.
- A license is issued only after quality checks.
- The license holder's business premise is subject to periodic inspection.
- A license holder is also required to maintain detailed records of the sale-purchase undertaken in relation to notified medical devices and ensure traceability in the event of a quality or safety-related failure or complaint.
- Class B, C, and D IVDs require in-country performance testing through the National

[6] All medical devices in India to be regulated as "drugs" – Medical Devices (Amendment) Rules, 2020 – Arogya Legal – The Health Laws Specialists

Institute of Biologicals (NIB) or an accredited lab
- Class D IVDs require performance testing through the National Institute of Biologicals (NIB)
- Class B and C IVDs require performance testing through an accredited Indian lab
- Compilation of device application (Form MD-14)
  i) manufacturing facility information
  ii) device technical information
  iii) ISO 13485 certificate
  iv) Instructions for Use (IFU)
  v) testing results and clinical data (if applicable)
  vi) proof of approval in the US, EU, Australia, Canada, or Japan

Novel devices will also undergo a Subject Expert Committee (SEC) review. Devices novel to the Indian market (new technology, material, intended use) may face additional regulatory reviews.

A certificate of compliance with ISO-13485 (Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes) is mandatory for registration of Newly Notified Medical Devices. Therefore, an importer or manufacturer of a registered medical device will have to ensure that the requirements of ISO 13485 are met at all times. Broadly speaking, ISO 13485 requires creation, documentation and implementation of a quality management system which is to be supplemented by an independent audit from time to time.

Once an importer or manufacturer registers its medical devices, it will have to strictly conform to its documented quality management system.

Validation

In terms of validation testing, the design of the process for devices and trials is almost similar. There are no toxicology studies and other related aspects, but based on the outcome of the validation study, one can go for the registration of the device.

Core Elements of a Clinical Study

- Research Question
- Hypotheses
- Core Design
- Study Participants
- Recruitment
- Allocation
- Masking (Blinding)
- Treatment Groups
- Data
- Analytical Issues
- Interpretation of Results

Research question is extremely critical in the design of the trials. Is it assessing the efficacy of an intervention or the effectiveness of the intervention? The difference between efficacy and effectiveness is, in efficacy typically when Phase 2 or 3 trials are carried out it is done under controlled conditions for testing treatment 1 versus treatment 2. For effectiveness, the intervention is done in uncontrolled conditions.

Comparative Trial/Superiority Trial

The objective is to demonstrate that a new therapy is superior to standard therapy in terms of incident outcome. The sample sizes here would be different.

Equivalence/Non-inferiority Trial

The objective is to demonstrate that a new therapy is no worse than the standard therapy in terms of incident outcome.

The common designs are;

i) Parallel trials: Here there are two sets of groups of patients-in one group, the new

therapy is introduced and in another the comparator therapy i.e the standard of care. Patients are assigned based on randomization based on allocation through a statistical system and a computer-generated allocation is done. Further, it can be single blind or double blind. In single blind the doctor is aware of the therapy given where as in double blind trial both doctor as well as patients are unaware of the therapy given. Double blind randomized trials are ideal for gaining regulatory approval.

ii) Cross-over trials: Trials can also be cross-over therapies where both sets of treatment are tested on both groups of patients. In-between the cross-over, there can be a washout period to remove the effects of the product depending on the type of product.

A typical trial process involves execution inside hospitals or clinical centres where the patients come to visit the doctor, all the recordings are undertaken at site, and lab tests are done periodically. The drug is distributed at hospitals or at clinical site. In case of devices, the device is allocated to the consulting physicians. The nurse and staff on site are available to collect patient related data, once requisite consent are taken. These are the traditional trials that are hundred percent site dependent.

Activities conducted onsite include;

- Periodic patient visits
- Laboratory tests
- Drug distribution
- Device allocation
- Physician consultation
- Nurse and site staff assistance
- Patient-related data collection
- In-person informed consent

With new technologies coming in, the trials are becoming remote, for few, if not for all activities. The basic purpose of virtual trials is to get quicker answers and reduce the costs. Use of technology is utilized to hasten the whole process of development.

Trials where there is no site dependence, but meta-sites exist;

- Utilize telehealth and telemedicine
- Patients do not visit sites
- Mobile healthcare providers are allies
- Tests conducted virtually, at community laboratories or mobile nurse-aided facilities
- Drugs and devices are shipped to patients' houses
- Virtual physician consultation—text, audio, video
- Virtual/in-home nurse assistance
- 24/7 patient support
- Patient-related data is collected virtually or mobile healthcare providers-aided
- Telehealth or mobile informed consent

Hybrid trials are where there is a mix of both on-site and off-site activities. Activities conducted onsite or offsite include;

- Patient check-ins
- Routine tests conducted
- Drug distribution
- Device allocation or shipment
- Physician consultation
- Combination of virtual and onsite consulting
- Nurse and site staff assistance
- Combination of mobile nursing, telemedicine, and onsite nursing
- Patient-related data collection
- In-person or using eSource

With the pandemic, the adoption of virtual consultations with doctors are now commonplace and is allowed for trials as well.

However, the feasibility of virtual trials is product dependent. For new chemical entities, where follow-up is needed and there is a need to watch for safety patterns it can be on-site at the start and eventually transitioned to virtual trials over time.

Over the last decade, there has been significant progress with the development of antibacterial drugs; new safe and effective therapies are available to patients. It is important to learn from our experiences and continue to refine our approaches to address patient needs.

Some considerations to encourage as we move forward:

- Need to identify the types of infections/patients in whom there is an unmet need
- Novel study designs/endpoints that are scientifically sound
- Improve clinical trial infrastructure
- Establish clinical trial networks
- Need to identify barriers and stimulate investigator interest in participating and enrolling in clinical trials for anti-infective products

SECTION - IV

AMR Innovation Funding and Compliance[#]

[#]This section only covers AMR Innovation funding available through C-CAMP and its partners.

Funding & Investment opportunities at C-CAMP for supporting AMR innovations[7]

AMR & C-CAMP: The Centre for Cellular and Molecular Platforms (C-CAMP) has been deeply involved in the efforts of identifying and supporting the Innovations which may play game-changing roles in the battle against AMR. These efforts include 'Funding Programs' for innovators, 'Incubation Services' for start-ups, and several dedicated 'Mentorship & Acceleration Programs' for bio-entrepreneurs. For specifically addressing important key areas of AMR, these programs are targeted at identifying and supporting new 'Drugs/Therapeutics & Vaccines', 'Diagnostics', 'Devices', and 'Preventative Solutions'. C-CAMP has also joined hands with several global organizations for creating an immediate impact against AMR, which includes the CARB-X global accelerator network.

Funding Programs at C-CAMP: C-CAMP offers a whole plethora of funding opportunities in collaboration with several different governments and private funding bodies as partners and are aimed at supporting life science innovators and start-ups at different stages of their innovation development. Some of these schemes are listed below that are open to supporting innovations in all thematic areas of life sciences and do emphasize 'AMR' as a key target area for support:

1) Early-stage Funding Support:

a) Biotechnology Ignition Grant (BIG) Scheme:

Funding Offered: Up to ₹ 50 Lakhs for taking innovations from the 'Idea'-stage to the 'Proof of Concept' (PoC)-stage

Open for: Young start-ups (< 5 years old), individual innovators (including academic researchers and students)

Application Call: Opens twice a year (on 1st January & 1st July)

b) MeitY Seed Fund / Technology Incubation & Development of Entrepreneurs (TIDE 2.0):

Funding Offered: For 'Digital-Tech' (IoT, AI, Block-Chain, Robotics, etc.) based solutions

- ₹ 4 Lakhs for 'Idea'-stage start-ups
- ₹ 7 Lakhs for start-ups at the prototype or MVP development stage
- Investment options also offered to mature start-ups

c) Start-up India Seed Fund Scheme (SISFS):

Funding & Investment Offered:

- Up to ₹ 20 Lakhs as grant-in-aid for start-ups (for validation of 'Proof of Concept', prototype development, product trials, etc.)
- ₹ 50 Lakhs as an investment for market entry, commercialization, or scaling up through convertible debentures or debt or debt-linked instruments

Open for: less than 2 years old start-ups (Early-stage) recognized by the DPIIT

Application Call: Open round the year

2) Bridge-Funding Support:

a) BIRAC Sustainable Entrepreneurship and Enterprise Development (SEED) Fund:

Investment Offered: Equity-based investment of up to ₹ 30 Lakhs for post-PoC stage companies

Application Call: Open round the year

b) National Initiative for Developing and Harnessing Innovations - Seed Support Scheme (NIDHI SSS):

Investment Offered:

- Investment support of ₹ 25 Lakhs based on Equity or Equity-linked instruments

[1] CCAMP

- Investment support may be raised to ₹ 100 Lakhs (upper limit) for exceptionally deserving start-ups

Application Call: Open round the year

3) **Late-Stage Funding Support for Acceleration & Scale-up:**

a) BIRAC Launching Entrepreneurs for Affordable Products (LEAP) Fund:

Investment Offered: Equity-based investment of up to ₹ 1 Cr

Application Call: Open round the year

b) C-CAMP – BNV Innovation Hub (CBIH) Program:

Investment Offered: Equity-based investment of up to $ 100K for start-ups in the selected theme

Application Call: Opens twice a year

For all these schemes, the application selection process involves careful & detailed scrutiny of the scientific basis of the proposed innovation along with its novelty and the competitive landscape, the business plan formulated for the deployment of the innovation, and the expertise of the applicant team.

Funding & Investment Opportunities at CARB-X for Supporting AMR Innovations[8]

Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a global non-profit partnership accelerating antibacterial products to address drug-resistant bacteria, a leading cause of death around the world. The CARB-X portfolio is the world's most scientifically diverse, early development pipeline of new antibiotics, vaccines, rapid diagnostics, and other products. CARB-X is the only global partnership that integrates solutions for the prevention, diagnosis, and treatment of life-threatening bacterial infections, translating innovation from basic research to first-in-human clinical trials. CARB-X is funded by a global consortium of governments and foundations. CARB-X headquarters are located at Boston University.

CARB-X accelerates a diverse portfolio of innovative antibacterial products towards clinical development and regulatory approval with funding, expert support and cross-project initiatives. They focus on the dangerous bacteria identified by the WHO and CDC priority lists[9,10].

Previous Funding Rounds by CARB-X

The previous funding rounds have focused on;

- Non-traditional approaches
- Vaccines and Biotherapeutics
- Diagnostics
- Direct-acting small molecule

CARB-X does not fund basic research/drug discovery including screening for novel targets. It funds early development projects that address serious bacterial threats;

- Antibiotics and therapeutics
- Prevention such as vaccines, Microbiome, Antibodies
- Rapid diagnostics (pathogen ID/AST)

The projects must target specific bacteria from the priority pathogen list. Projects are selected through a globally competitive process. Science Advisory Board reviews applications and makes recommendations. The Joint Oversight Committee makes funding decisions.

[8] Home - Carb-X
[9] WHO publishes list of bacteria for which new antibiotics are urgently needed
[10] 2019 Antibiotic Resistance Threats Report | CDC

Evaluation is done in multiple stages. Initially, an Expression of Interest (EoI) is submitted. If shortlisted, the applicant is invited to fill out a Short Form. Further, the shortlisted candidates are invited to submit a Long Form. Throughout the application process, CARB-X's Global Accelerator Network (GAN) members, such as C-CAMP, handhold and facilitate the applicant to enable them to navigate through the process.

Application to CARB-X

There are certain requirements that the applicant needs to be aware of before making the application;

- The applications for a specific CARB-X funding round are invited from applicants that have a legal entity.
- Applicants must be able to contribute at least 20% of the cost of the project/program ('cost-share') – base and option stages. At the time of execution of the sub-award (contract), applicants must have secured cost-share funds for the base stage of the project and have a viable strategy to achieve/maintain financial sustainability. To qualify for CARB-X funding, product developers are obligated to contribute a 30% cost share. Some non-profits may qualify for a lower cost share percentage.
- At the time of execution of a sub-award (contract), applicants must own or have rights to the intellectual property and reasonable expectation of freedom to operate required to carry out the project.
- Applicants must have operations or capabilities in place to support product development, particularly through the development stages in scope for CARB-X.
- Applicants must be able to comply with UK NC3R requirements and US regulatory requirements for animal and human subjects' research.
- Applicants from non-commercial centers or academic institutions must meet additional requirements to demonstrate R&D/business capabilities.

CARB-X welcomes applications from around the world. Expressions of Interest applications must be submitted online, only during the periods indicated.

[11] 190430 CARB-X 2019 Funding Rounds_FINAL_

SECTION - V

Scale-up and Manufacturing

When a solution is developed by a research institute it starts as an idea that is researched upon and then undergoes a proof-of-concept study. The next step of prototype development followed by product development and finally, commercialization requires a partnership with an industry entity or a small and medium enterprise (SME). It is in this phase of prototype to scaling up & manufacturing for commercialization when aspects of technology transfer, licensing, material transfer agreements (MTAs), Collaborative and Sponsored Research Agreements, etc. come in to play. The innovators need to be aware of these modalities to successfully scale their solutions for the market.

The Need to License a Technology Or an Intellectual Property (IP)

License is consent by the owner of the IP (licensor) to the use of the IP by a third party (licensee). A license is a legally binding agreement. This enables the scale-up of a solution from the laboratory bench in an academic institution to a commercial scale by an industry partner.

The benefit of licensing to the Licensor (Institute) includes;

- Recovery of the money spent on R&D of the solution
- Receives royalty in the form of sales of the product
- The faculties can get a share of these benefits

On the other hand, the Licensee (Company) draws the following benefits;

- The rights to make use of the technology or the IP
- Receive sub-licensing rights whereby the licensee can give sub-licensee to fulfil different stages of product development to other developers with requisite expertise in a given domain.

Use of a technology or an IP by a third party without the license qualifies as infringement and can be subject to legal action by the owner of the technology or IP.

Types of IPs

- **Patents:** A. patent that has been filed, under examination, or one that has been granted can be licensed. This applies to product and process patents or both.
- **Know-how:** It is the technical knowledge necessary to carry out a particular process relating to experimental procedures and should not have been published, or mentioned in a patent or another public domain.
- **Design:** For example, 3D designs of a product

It is possible to merge more than one patent, design, or know-how into a single licensing agreement. This enhances the cumulative value of the license agreement.

Types of Licenses

- **In-license:** This includes technology licensed from a third party
- **Out-license:** This includes a license issued to a person or entity as i) Trial license-This is a time-limited license for conducting trials with the technology or IP, ii) Prototype Development license- This is also a time-bound license, one that enables the use of the technology or IP up till the stage of developing a prototype, and iii) Product development/or use license- This license enables the person or entity to use the technology or IP for development of the product of commercialization, or if the product is available then this license can

enable the use of this product for specified purposes. This may also include a distributor license whereby the person or entity can distribute the licensed product.

- **Cross-license:** This enables the exchange of IP between two different parties. For example, an academic entity may exchange its IP with a start-up using a cross-license.

IP Licensing process, in brief

This is a multi-step process for both the patent filed as well as for patent granted;

- Technology Brief (marketing): This includes details on the actual problem that the technology is addressing, the advantages of the technology, and the potential applications of the technology.
- Technology Evaluation (market potential): This includes a techno-commercial evaluation of what market potential of the technology, the duration that this technology is likely to stay in the market, etc. This also includes an evaluation of the market size and in which all countries this technology can be commercialized.
- IP Valuation (pricing the technology): This depends on the stage of the technology and its readiness for the market.
- Potential Licensee search: This assesses the key market players who would be interested in the technology
- Licensing Strategy: This assesses the strategy with which the technology can be licensed to the licensee, for example, should this be given to a single licensee or if it should be divided into more than one license.
- Term Sheet (document for negotiation): The term sheet mentions all the legal and financial conditions of the license based on how the technology is foreseen to be commercialized through one or more licensees. Once the term sheet is mutually agreed upon, the agreement is drafted.
- License Agreement: This is an agreement between the Licensor and Licensee detailing the term of use of the IP.
- Revenue & Compliance Monitoring

This encompasses the IP licensing process in general followed by most IP firms working with innovators.

Techno-Commercial Evaluation

In this, the technology is evaluated technically and the developmental stage or the technology readiness level (TRL) is assessed. The status of the patent (filed, under examination, or granted) is assessed and the field of use or application is evaluated. For example, a technology for one indication may be checked for application in other indications to increase commercial value. An in-depth market analysis helps in identifying licensees and countries.

Exclusive and Non-exclusive license: The technology can be licensed to a single licensee under an exclusive license, or it can be divided between more than one licensee for the different development processes, or applications. The non-exclusive license also depends on the TRL or stage of the technology.

IP Valuation: This defines the pricing of the technology. The factors that determine the valuation are; i) IP (patent/know-how/design) ii) TRL (proof of concept or prototype) iii) Market potential (mapping competitive products) iv) Comparable market transactions v) Market need (end user assessment and availability to consume) vi) Exclusive or Non-exclusive vii) Territory for licenses or specific application viii) Licensee's expected revenue (business model). Projection may be set for the first ten years to begin with.

Anatomy of a license agreement: This legally binding document between the Licensor and the Licensee details all the terms of usage of the IP. It incorporates i) Details of the contracting parties, ii) Background & definitions relevant to the technology iii) IP details and the scope of the given license iv) Territory of usage, that is in which countries or geographies can the license be in effect v) Field of use, i.e. the applications for which the license can be commercially exploited vi) Nature of the license, i.e. whether it is an academic license, commercial license, exclusive or non-exclusive license, etc. vi) Financials, like signing fee, milestones-based disbursements, royalties' amount and terms of payment, etc. vii) Terms mentions all the applicable conditions and clauses viii) Termination and claw-back details the circumstances in which the licensor holds the right to terminate the licensing agreement due to unsatisfactory performance or commercial returns by the licensee ix) Confidentiality clauses x) Warranties and finally xi) Dispute resolution.

Collaborative and sponsored Research: A void of Applied Research exists amidst the Academic Institutes' focus on basic research, and Industry's focus on product development and commercialization. The void can be filled by drawing the expertise of the industry and academia to complement each other in a collaborative research project so that the respective mandate is fulfilled. Within this agreement, the scope of work, schedules and deliverables against each, publication rights, ownership of IP rights, confidential information, material transfer among collaborating parties, and the rights to terminate are included and agreed upon prior to commencing the project.

Material Transfer Agreements (MTA): This refers to the transfer of tangible materials between two parties. MTA is legally binding and it controls the distribution of biological material for commercial or non-commercial (research) purposes. With MTA, materials like transgenic animals. Cell lines, culture, antibodies, vectors, nucleotides, chemicals (drugs), etc. can be transferred. The MTA, along with the patented technology can both be covered under a single licensing deal.

The MTA controls the distribution of the propriety material by defining the permitted use of the materials, prohibited use of the material, and the IP clause. Within the permitted use of the material the specific field of use (pre-clinical and internal research), and the sharing, handling, usage, storage, and disposal clauses can be detailed. Under the prohibited use, the disallowance of distribution to a third party, commercial usage or use in humans for different applications can be mentioned

Steps Involved from Technology Transfer to Commercialization: The innovator develops the technology at a laboratory scale, however, its scale-up requires the use of quality controlled regulatory framework, know-how, documentation and, standardized processes in well-equipped labs with the requisite expertise and infrastructure.

Process Sequence: Through technology transfer, the R& D lab licenses its technology to an industrial partner with the requisite expertise and infrastructure to scale up the production of the laboratory product. Once the product is scaled up in a limited batch-size, it is subject to stringent quality control processes. The batch which passes QC is then used for necessary regulatory approvals after demonstrating its ability to efficiently do the necessary action. Post the regulatory approvals, the product is commercialized and distributed through various channels to the identified markets and customer segments.

Pilot Study: Firstly, a pilot study is undertaken to assess the scale-up potential of the laboratory product. In other words, the pilot study enables researchers to prepare for larger production and subsequent trials. The pilot identifies challenges in scaling up and subsequently rectifies the same before commencing with commercial batch production. The first three batches are considered validation batches. From the pilot stage, there is a gradual progression to scale-up. At the same time, downstream processes can be defined and streamlined as well.

Salient Objectives: The expected outcomes or the objectives of undertaking the different steps from laboratory scale to commercial scale are highlighted below. These align the product, processes, and infrastructure for standardized production to distribution.

- **Pilot**:

i) Identify critical features of the process
ii) Assess feasibility to produce stable products
iii) Develop guidelines for production and process control
iv) Provide master manufacturing formula

- **Commercial**:

i) Transfer of process/ methods for commercial production
ii) Ensure availability of approved Batch Manufacturing Records (BMR's), tests and methods are in place
iii) Use of approved raw materials and packaging materials
iv) Area qualification/ equipment qualification and calibration
v) Validation of initial 3 batches
vi) A trained and competent workforce

- **Distribution**:

i) Understand customer requirements
ii) Fair understanding of regulatory requirements in the country of sale
iii) Identify the effective supply chain model
iv) Follow good distribution practices

Quality Systems[12,13]: Quality cannot be an afterthought, rather it needs to be thought through before commencing work. The cost for quality assurance should also be factored in upfront as this assessment of the new product is crucial for scale-up and commercialization.

To achieve the requisite scale-up, the guidelines for Quality Systems need to be followed strictly. Once the commercial batch is ready, the supply chain models are engaged for distribution.

5 production systems that come within Quality Systems that assess if the necessary systems are within control. These are;

- Production System
- Facilities and Equipment System
- Laboratory Controls System
- Materials System
- Packaging and Labeling System

The 5 production systems come within 6 quality systems which need to be adhered to for successful audits and to market in different countries. These are;

- cGMP- Current Good Manufacturing Practices
- GDP- Good Documentation Practices
- GLP- Good Laboratory Practices
- ALCOA- Attributable, Legible, Contemporary, Original, and Accurate as per DI Requirements
- CSV- Computer System Validation as per GAMP-5

WHO, FDA, and ISO provide guidelines for following these quality systems.

[12] ICH Official web site : ICH
[13] WHO handbook for guideline development, 2nd Edition

The manufacturing unit has to ensure that all equipment, associated data, etc. used in validation needs to be documented and recorded. Once the commercial batch is ready, necessary QC needs to be followed. Any deviation needs to be documented and any discrepancies found can be questioned by the Quality Analyst (QA). In cases of severe deviations, they can even request a repetition of the entire process.

Quality Management System (QMS) documents have to be brought to the notice of the QA. In the comparison reports if there are any discrepancies observed then QA can mark the specific batches as validated or not validated. If not validated then the reason for the same and the requirements for revalidation will be explicitly given, the same need to be documented and rectified.

QA Responsibility: Prior to commencing scale-up, a formal change control proposal should be initiated and coordinated by the QA. The purpose, Gap analysis, risk analysis, impact, control, mitigation, etc. for the process should be incorporated. The parameters that define in range'' and out of specifications should be defined. Lastly, a guide to production should be maintained.

As part of the QC process the following needs to be assured;

- All raw materials should be approved from validation batches
- All documents should be as per the guide
- Specific analysis methods should be approved
- Reserve samples should be kept for testing
- Stability assessment as per approved protocol
- Analysis at periodic intervals as per the guide
- Product stability summary should be documented
- Submit all documents for approval by QA

Dispatch of a product should be undertaken once the QA and company have validated and approved the same for use.

SECTION - VI

Strengthening the Antibacterial and Diagnostics Pipeline

Here we switch gears from the life cycle of AMR innovations through different stages from discovery to commercialization to the very need of building a robust pipeline of antibacterial and diagnostics innovations to increase our collective success rate of introducing interventions and solutions against a fast-evolving global AMR crisis.

Tackling the AMR challenge requires a well-rounded systems view. A pipeline in diagnostics & drug development is required to build a large number of candidates/ technologies through different development stages and to nurture them so they become a deployable product. A number of high-quality products are in the pipeline that needs to be supported while interfacing with policy, government, non-government entities, regulators, investors, and the market. Highlighting here some key insights on how this challenging terrain be successfully navigated to maximize our outcomes. Through these insights, certain unmet needs in the AMR domain are repeatedly highlighted, bringing to the foray an urgent need to address them through innovations.

Key insights and perspectives

- Awareness of the judicious use of antibiotics by physicians should be promoted. Understanding the choices that impact their decisions, and behavioural aspects of the high demand for antibiotics by the patients, and clinicians need to be considered.
- Since AMR disproportionately affects LMICS, a databank of requirements and challenges curated from patients, clinicians, end-users of interventions and health systems can be made publicly available for innovators to consider at the R&D stage.
- A patient-centric approach to treating infections can be facilitated with companion diagnostics.
- Companion diagnostics with antibiotics prescription in a single setup, for example antibiotic susceptibility testing (AST) with specific & broad-spectrum antibiotics for prescription of the right anti-infectives for the right pathogen. It is imperative that diagnostic platforms direct this important clinical decision.
- Diagnostic solutions that can identify the pathogen and its type within a few hours to a few minutes can be game-changing in the clinics.
- Information across hospitals in particular geography on pathogens responsible for the high number of infections will be useful in making informed clinical decisions.
- Surveillance data from different sources, including from different pharma companies, need to be collated and used to assess gaps and opportunities.
- Rapid antibiogram can drastically change in-patient and out-patient outcomes.
- Vaccines, like those for pneumococcal, HIB, and flu infections, can reduce overall infections, and the need for antibiotics to treat them. It is crucial to prevent patients from reaching this stage by supporting vaccine development for infections, especially those with a high incidence rate.
- Collaborative action with engagement and support of the government, academia, hospitals, and industry, among others, can lead to furthering the antibiotics stewardship programs.
- Stewardship efforts are limited in scope unless nosocomial infections are reduced drastically, highlighting the need for infection prevention and control measures in healthcare facilities.
- A clear pre-regulatory pathway for R&D in antibiotics is required for innovator interest.
- Models to expedite the process involving innovations are urgently needed. Proof of concept to market-ready deployments should follow standard protocols.

- Since there is low funding available in AMR globally, push mechanisms, like CARB-X and BIRAC; and pull mechanisms, like those being used in the US, UK, and other western countries must be explored. Financial models to fill the funding gap in the Indian market needs immediate consideration.
- Financial incentivization is required for innovators to develop products for AMR in LMICs.
- The Indian innovation ecosystem is among the best in the world and it needs to be leveraged to support these innovations. Contextual innovations emerging from India, and for use in India, will be of the essence in the fight against AMR.
- Identify aspects in India to its advantage, for example promoting clinical trials. More patients are MDR with *Klebsiella* and *Acinetobacter* in India than anywhere else in the world. Taking cues from COVID regulations, the approvals for antibiotics in India can be accelerated using our patient population. India can take a leadership position through regulatory changes to make datasets coming from India valuable to the rest of the world. When the solution is developed together then, through appropriate policy action, it can be ensured that the population is also among the first beneficiaries of the new interventions or product.

Summary

AMR continues to spread globally at a fast rate, with LMICS being the ones disproportionately affected[14]. It is imperative that LMICS, like India, gain self-reliance in promoting and fast-tracking innovations for deployment in the domestic market, as well as in other LMICs, for maximal impact to combat AMR.

In the early discovery of drugs, establishing the Target Product profile and inhibitory effects of your compound is essential. In the progression of the compound to a drug, it is vital to establish Physiochemical properties, MoA, Spectrum analysis, FoR, Off-target interactions, and safety profile. From the stage of early lead onwards, pharmacokinetics and pharmacodynamics studies should establish the dosage, efficacy, SoC etc. The Late lead stage should comprise the detailed Tox package, positioning, and IND submission, among others.

For diagnostics for AMR, antimicrobial escalation in MICU, and other healthcare settings is addressed in most hospitals by antimicrobial stewardship. To accentuate these antimicrobial stewardship efforts, diagnostics stewardship can run in conjunction with identifying the pathogen and directing the physicians to targeted treatment. In this context, the product profile, and where you see the product in the standard of care sets the foundation for the future solution

Regulatory requirements across regulatory authorities are different although steps by regulators have been initiated in the past to converge on the requirements to reduce the impact on development programs. Innovators need to be aware of these developments to leverage them to their advantage in reaching more geographies in a cost-efficient manner. Few other aspects to keep in mind are the development in technology, product labelling & registrations, study designs, and different mode of clinical trials in recent years.

Funding for AMR innovations is available through AMR focused initiatives on one hand, and applicable in broader healthcare funding initiatives, on the other. Innovators with solutions at different stages of development are applicable for different initiatives available through C-CAMP, and its partner networks, including CARB-X.

When the innovators reach the stage where they are ready to scale their product manufacturing from small-scale to large-scale for deployments, they need to take cognizance of the various modes available to them directly, or through licensing or sub-contracting. To choose the best mode of manufacturing to maintain the required quality parameters for regulatory compliances, while securing their IP. Innovators need to chart this pathway in discussion with concerned authorities and experts.

To conclude, antimicrobials are inherently challenging to work with as they have a small shelf life due to eventually resistance build-up and are a high value-low volume product. The fragmented business market, uncertainties in regulation and unclear policy environment has led to many major pharmaceuticals leaving this domain, barring a few. On the other front, positioning diagnostics for crucial clinical decision-making and treatment planning is imperative; and it requires seamless integration of newer innovations in the health systems. In the past few years, innovations and newer solutions, primarily from the start-up ecosystem and Small and Medium Enterprises (SMEs) have been the major drivers. For innovators, it is important to bear this in mind while strategizing their technical and business roadmaps. From the viewpoint of ecosystem enablement, supporting AMR innovations across their life cycle is an absolute necessity, and synchronizing efforts would require a multi-sectoral effort.

A thorough understanding of the ecosystem, and ways to navigate it, becomes a prerequisite for any innovator in the domain, regardless of the stage of their innovation development.

[14] https://www.orfonline.org/research/public-awareness-on-antimicrobial-resistance/

Note: Insights and perspectives included in the whitepaper were shared by domain experts, stakeholders, and partners from the Indian AMR ecosystem. The discussions took place in a virtual workshop/forum conceptualized, curated, and convened by C-CAMP in March 2022.

The names of the speakers who presented and shared their views and inputs are listed below. The order of the names is as per the appearance of respective sections in the document for which the speakers shared their inputs;

Dr. T. S. Balganesh, President and Member of the Board, Gangagen Biotechnologies
Dr. B. V. Ravikumar, Chairman and Managing Director, XCyton
Dr. Surinder Kher, Executive Head – Clinical Research, Aster Hospitals & Advisor, BioQuest Solutions
Dr. Vishal Bharadwaj. Scientific Consultant, C-CAMP
Dr. Swati Subodh, Lead, Science & Policy – AMR, C-CAMP
Dr. Jaishree Jeyaraman, OTT, C-CAMP
Dr. Vani Nagarajan, Head QA, Laurus Bio
Dr. Taslimarif Saiyed, CEO & Director, C-CAMP
Dr. Anand Anandkumar, CEO and Managing Director, Bugworks Research,
Dr. Sai Sethuraman, Head, R&D, Product Development, Pfizer,
Dr. Ashwini Pawar, Head, Medical Affairs, GSK,
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