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THE ROLE OF GENOME EDITING TO BOOST BIOECONOMY SIGNIFICANTLY: OPPORTUNITIES AND CHALLENGES IN INDONESIA

Bambang Prasetya[1], Satya Nugroho[2]

[1] *Indonesia Committee for Biosafety of GMO/Research Center and HR Development-National Agency for Standardization-BSN*
[2] *Research Center for Biotechnology-Indonesian Institute of Sciences (LIPI)*

Abstract

Decreasing in quantity and quality of land including available land for crop cultivations leads to many efforts to develop appropriate technology for genetic improvement through biotechnology approach. A novel trending tools to perform genetic modification intensively discussed is genome editing, which is developing rapidly. By applying genome editing, many researches have been performed successfully to improve the genetic trait of organism by modification of DNA with no traces of foreign gene in the final products. There are research reports concerning the development of climate-compatible crops, high productivity, high quality and specific trait for animals and fish, effective and specifically targeted biocatalytic processes by using microorganism, health-promoting foodstuffs and environmentally friendly production using genome editing approach. The genome editing approach will be an important alternative for modern breeding, which is different to the existing GMO technologies, which has already been developed for almost 30 years. Many assessments concluded that genome editing will catalyze important innovations in the bioeconomy. This paper will discuss about the global trends of genome editing and the opportunity and challenge faced in Indonesia. Moreover, it will also discuss the roles of the existing regulations and how they adapt to respond to this new technology.

Keywords: *bioeconomy, decreasing quality of environmentally-available land for crop, genome editing, regulation*

1. Introduction

Nowadays, the world needs novel technology capable of solving a number challenges such as decreasing environmental quality, global warming, population (number and health quality) issues, deceasing number and quality of land for crops, emerging diseases and providing green energy (biofuel) [34]. One of the important driving tools is the development of efficient and environmentally friendly method by using modern biotechnological approach for supporting food and energy resiliency, environmentally friendly biomaterial products, pharmaceutical products, cleaner technology processes, fine chemicals, biocatalyst as well as vaccine for emerging disease. This meet with the bioeconomy concept which for many countries become top priority.

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[1] Corresponding author.
Tel. : +62-85216069001
E-mail : bambang.prasetya@gmail.com

Main contributor : Bambang Prasetya, Satya Nugroho
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Based on the International Advisory Committee on Bioeconomy Summit held in Berlin in November 2015, bioeconomy is defined as “knowledge-based production and utilization of biological resources, biological processes and principles to sustainably provide goods and services across all economic sectors”. Bioeconomy involves three elements, firstly the utilizations of renewable biomass and efficient bioprocesses to achieve sustainable productions. Secondly, enabling and converging technologies of nano technology, biotechnology and information technology. Beyond biotechnology, a key development is the combination of digitalization and ‘biologization’. Sustainable development is supported by applications, such as precision agriculture, satellite forestry monitoring, DNA barcoding of species, etc. In the IT industry, biological knowledge is applied to computer and chip designs, e.g. DNA data storages. Moreover, bioeconomy also concerns about the integration across applications, involving primary production regarding all living natural resources, industry (involving chemicals, plastics, enzymes, pulp and paper, bioenergy) and health care including pharmaceuticals and medical devices [21].

In this review 52 referred scientific papers, review papers, policy papers and online publication on biodiversity and their potential contribution to economy, and the application of genome editing to improve economically important crops, were used to perform the analyses of the importance of genome editing to support the acceleration of the acquirement of the full benefit of biodiversity by the implementation of bioeconomy in Indonesia. The method used in this review is based on descriptive analysis and on results of some expert group discussions concerning genome editing, The importance of the application of modern technology, such as genome editing, in harnessing the full potential of bioeconomy were analyzed by looking at the significant increase numbers of published papers on the application of genome editing for various crops improvements in the recent years, and the adoption of such technology by many public and private institutions.

2. Genome Editing and Its Implementation

a. Genome Editing

The developments of molecular biology is based on the discovery of DNA. (Deoxyribo-Nucleic-Acid) by Oswald Avery in 1944 and followed by the revelation of the X- ray diffraction images of DNA by Rosalind Franklin, which were the bases of the discovery of double helix DNA by Francis Crick, James Watson, and Maurice Wilkins. DNA is a molecule composed of two polynucleotide chains that coil around each other to for a double helix carrying genetic instructions for the development, functioning, growth and reproduction of all known organisms. The development of techniques for DNA modification have enabled many advances in biology and lead to rapid development of biotechnology. Initiated with the development of chemical methods for solid-phase DNA synthesis and culminating in the enabling detection and exploration of genome of organisms. Many techniques in molecular biology have provided tools to isolate genes and gene fragments, as well as to introduce mutations into genes in vitro, in cells, and in model organisms. This knowledge in combination with genomic sequencing technologies which can provide whole-genome sequencing data for diverse organisms, including humans, has accelerated the development of DNA modification technology including DNA recombinant technology for many different purposes. The continuing research and development to find out the effective method for modification of DNA indicate that genome editing technology, which was intensively developed in the last decade will bring breakthrough in molecular biology [19].

Out of four existing nuclease-based gene editing strategies (meganuclease, zinc finger protein (ZFN), transcription activator-like effector protein (TALEN) and CRISPR-Cas9), the

CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats- CRISPR- associated), has become more popular due to its ease of application and economic considerations as a low-cost technology [6]. CRISPR is a repetitive DNA sequence found in bacteria and archaea that will be transcribed into crRNA (CRISPR RNA). This technology works when the crRNA structure acts as a mechanism to defend themselves from foreign virus or plasmid by detecting the presence of viruses that have previously infected them. Bacteria and archaea have the ability to record the viral sequence by incorporating them in their genome in the form of repetitive sequence, which will be used to recognize the presence of virus in the future. Upon recognition by crRNA directions, to target the virus, the bacteria send the Cas9 protein to cut the viral DNA in the form of double strand breaks.

This repair mechanisms of the double strand breaks leads to two possibilities, the first is non- homologous end joining (NHEJ) that will result in a mutation in the DNA that may cause gene silencing, which is known as site directed nuclease I (SDN I). Or by homology directed re-combination (HDR) by using surrounding DNA as template to create insertion to the invaded strand, which was known as SDN II and SDN III, depending in the extent of the newly inserted DNA fragments. Using the second possibility, scientists can create their own final arrangement to customize the target DNA to suite their purpose [17]. Figure 1 and 2 showed the mechanism of gene editing using the CRISPR-Cas9 [30]. Table 1 shows the various techniques in gene modification, including genome editing [23].

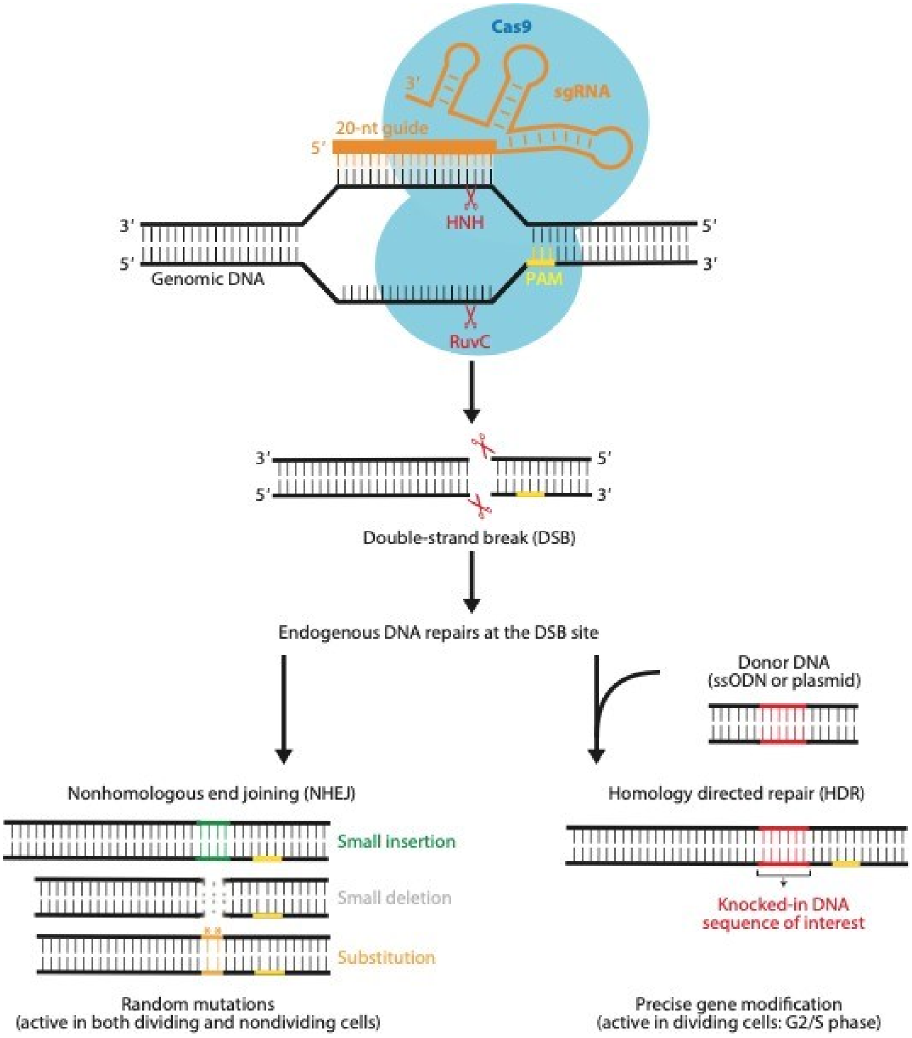

Figure 1. Mechanism of gen editing using CRISPR-Cas9

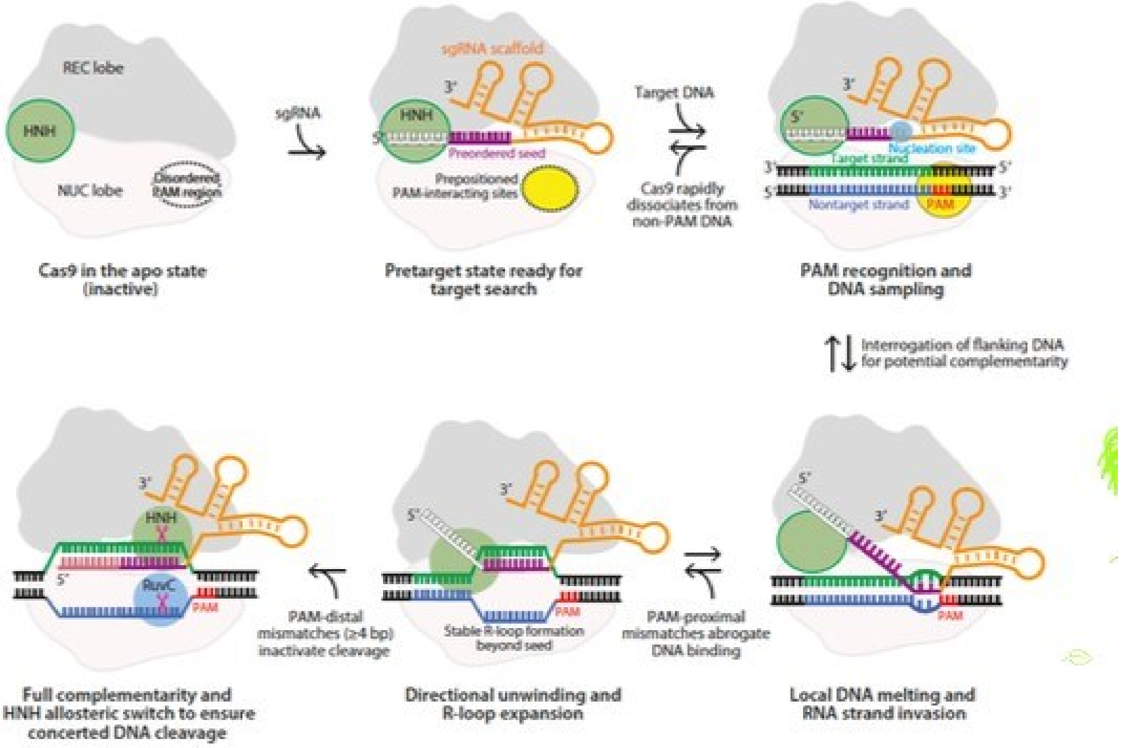

Figure 2. Schematic representation of the mechanism by which CRISPR-Cas9 recognizes and targets DNA for cleavage. Binding of sgRNA leads to a large conformational change in Cas9. In this activated conformation, the PAM-interacting cleft (dotted circle), becomes pre- structured for PAM sampling, and the seed sequence of sgRNA is positioned to interrogate adjacent DNA for complementarity to sgRNA. The process starts with PAM recognition, which in the next step leads to local DNA melting and RNA strand invasion. There is a step- wise elongation of the R-loop formation and a conformational change in the HNH domain to ensure concerted DNA cleavage. Abbreviations: bp, base pair; NUC, nuclease lobe; PAM, protospacer adjacent motif; REC, recognition lobe; sgRNA, single-guide RNA.

Table 1. Techniques in gene modification [23]

	Type of New Genetic Modification Techniques	New Genetic Modification Techniques
A	Genome editing with site- directed nucleases (SDN)	CRISPR-based systems for genome editing (CRISPR)
		TALE-directed Nuclease systems for genome editing (TALEN)
		Zinc-Finger-directed Nuclease systems for genome editing (ZFN)
B	Genome editing directed by oligonucleotides	Oligonucleotide-directed Mutagenesis (ODM)
		Multiplex Automated Genomic Engineering (MAGE)
C	Modification of gene expression	RNA-directed DNA Methylation (RdDM)
D	Variants of GM technology	Cisgenesis (CG) / Intragenesis (IG)
		Transgrafting (TG)
E	Breeding support techniques	Agro-infiltration (AI)
		Haploid Induction (HI)
		Reverse Breeding (RB)

b. Trend of research on genome editing and its implementation.

Since gene editing using the CRISPR-Cas9 system is known as promising tools in genetic engineering due to its simplicity and high efficiency, there have been many genomes editing supported research and development in various organisms targeting different traits. CRISPR-Cas9 has now been utilized widely to edit the genome of various organisms, including bacteria, yeast, plants and animals [47]. In the medical field, genome editing, has the potential to both improve the understanding of human genetics and cure genetic diseases [20].

Table 2. Landscape of publications on genome editing [23]

	Genome Editing					**RdDM**	**CG**	**IG**	**TG**	**Support breeding**	
	CRISPR*	TALEN	ZFN	MN	ODM					AI	HI
Total Number (Jan 2011-Dec 2015	n.a	10	17	5	1	6	7	4	n.a	14	9
Total Number (Jan 2016-June 2017	114	8	7	1	1	1	2	4	23	4	7
SDN−1	99	5	4	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SDN−2	5		-	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
SDN−3	4	3	3	1	n.a	n.a	n.a	n.a	n.a	n.a	n.a
Base editing	4	-	-	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other types of genome editing	2	-	-	-	n.a	n.a	n.a	n.a	n.a	n.a	n.a
Method development	72	1	2	1	-	-	1	1	6		3
Basic research	22	1	2	-	-	-	-	-	7	4	1
Applied development	20	6	3	-	1	1	1	3	10		2

SDN, site-directed nuclease; CRISPR, CRISPR (Clustered regularly interspaced short palindromic repeat)-directed nuclease; TALEN, Transcription activator-like effector nuclease; ZFN, Zinc-Finger-directed nuclease; MN, Meganucleases; ODM, Oligonucleotide-directed mutagenesis; RdDM, RNA dependent DNA methylation; CG, Cisgenesis; IG, Intragenesis; TG, Transgrafting; AI, Agro-infiltration; HI, Haploid induction; Other types of genome editing: different variants of CRISPR-based genome editing, including use of nickases; n.a.: not applicable.

* For the use of CRISPR-based systems for genome editing and transgrafting literature was only screened for the time period Jan. 2016-June 2017. Bold values indicate total numbers of publications for individual nGMs for the indicated time periods.

In plants, it has also been reported to successfully and specifically edit the genome in plants [11]. Application of genome editing in *Arabidopsis thaliana, Nicotiana benthamiana,*, rice, wheat, sorghum , maize and tomato indicated that the system was effective [25]. In Indonesia, Santoso et al. [39] reported a successful gene editing in the Kitaake cultivar model using CRISPR-Cas9 technology. As shown in the Table 2 the application of CRISPR-Cas9 in crop breeding was reported in at least 37 publications which were released between 2017 to 2019. Table 2 also shows that genome editing using CRISPR-Cas9 system is the most published research compared to the other system such as TALEN and other DNA modification systems. There was a change in preferences as shown in Table 2 that the-five years publication from January 2011 to December 2015 on genome editing were dominated by ZFN and TALEN system, while from January 2016 to June 2017, CRISPR-Cas9 dominated with 114 publications [23]. The CRISPR-Cas9 system is already implemented in various plants (Table 3). Application of CRISPR-Cas9 in rice alone have been reported to target various traits, such as enhanced salinity tolerance, defective synthesis of chlorophyll and tiller-spreading phenotypes, enhance a higher proportion of long chains in amylopectin, blast resistance, bacterial blight resistance, herbicide resistant, grain number, thermo-sensitive genic male sterility, dense erect panicles, and larger grain size, respectively (Table 4) [22].

Table 3. The Number of publications related to CRISPR-Cas9 in various plants [22]

No	Crop Species	Number Publication	Groups
1	Maize	1	Monocotyledon
2	Sorghum	1	Monocotyledon
3	Wheat	3	Monocotyledon
4	Rice	10	Monocotyledon
5	Banana	2	Monocotyledon
6	Camelina sativa	1	Dicotyledon
7	Arabidosis thaliana	2	Dicotyledon
8	Tomato	9	Dicotyledon
9	Potato	1	Dicotyledon
10	Cucumber	1	Dicotyledon
11	Soybean	1	Dicotyledon
12	Grape	1	Dicotyledon
13	Orange	1	Dicotyledon
14	Grapefruits	2	Dicotyledon
15	Mushroom	1	Fungus

Table 4. Application of CRISPR-Cas9 in rice for various trait target [22]

No	**Target Trait**	**Target Gen**	**Role**	**Modification**	**Reference**
1	Enhanced salinity tolerance	*OsRR22*	Transcription factor	Inactivating mutations	[53]
2	Defective synthesis of Chlorophyll b and tiller- spreading phenotypes	*CAO1 and LAZY1*	Synthesis of Chl b from Chl a and regulating shoot gravitropism, respectively	Genes disruption	[54]
3	Higher proportion of long chains in amylopectin	*SBEI and SBEIIb*	Determining the amylose content, fine structure of amylopectin, and physiochemical properties of starch	Genes disruption	[55]
4	Enhanced grain number, dense erect panicles, and larger grain size, respectively	*Gn1a*, *DEP1*, *GS3* and *IPA1*	Regulators of grain number, panicle architecture, grain size and plant architecture, respectively	Gene disruption	[56]

5	Enhanced rice blast resistance	*OsERF922*	Negative regulator of Rice blast resistance	Gene knockout	[44]
6	Bacterial blight resistance	*OsSWEET13*	Sucrose transporter. Negative regulator of bacterial blight resistance	Gene knockout	[57]
7	Haploid seed formation	*OsMATL*	Encodes a pollen- specific phospholipase	Gene disruption	[58]
8	Herbicide resistance	*ALS*	Acetolactate synthase encoding gene	Gene replacement	[59]
9	Herbicide resistance	*ALS*	Acetolactate synthase encoding gene	Gene knockout	[60]
10	Thermo- sensitive genic male sterility	*TMS5*	Thermo-sensitive genic male sterility gene	Gene knockout	[61]

In term of research fields there are around 72 publications dealing with method developments, 22 publications on basic researches and 20 publications on applications and developments. The types of the targeted mutation by using the CRISPR-Cas9 system were classified into SDN 1 (99 publications), SDN 2 (5 publications) and SDN 3 (4 publications), which indicates the current preference and aim of the studies [23]. This report and trend of utilization method would be important information, especially for the benchmarking and assessment for a formulation of regulations.

c. Trends of regulation in Genome Editing.

Global consensus of biosafety for genetic engineering product is mainly based on the Cartagena Protocol on Biosafety which was adopted on 29 January 2000 and entered into force on 11 September 2003. It is an international treaty that governs the transfer, handling, and use of genetically modified organisms (GMO) [37]. On international food standard, the Codex Alimentarius Commission of the FAO/WHO in 2003 adopted a set of "Principles and Guidelines on foods derived from biotechnology" to help countries coordinate and standardize regulation on GM food to help ensure public safety and facilitate international trade. The guideline on import and export of food were updated in 2004 [15]. Because genome editing was established approximately one and half decades after the recombinant DNA technology was developed and implemented, there are still open debates about the regulations. Until now, many countries are revising and drafting regulations for GMO and genome-editing products with due observance of regulations in force in other countries, especially the United States, Canada, Australia, the European Union, Argentina and Brazil. However, only EU countries categorize all genome editing products as PRGgenetically modified [36], [24], [41].

El-Mounadi et al. [22] summarized the regulation of genetically modified and genome edited plants across countries as shown in Table 5. According to this report countries, such as USA, Australia and Japan which conduct regulation on GMO, decided not to regulate genome edited product. Argentina, Brazil and Chile implement partial regulation but mostly do not regulate genome editing products. Canada, European Union, India, Malaysia, Mexico, New Zealand, South Africa and Thailand belong to countries which regulate both GMO and genome editing products, although debates and reassessment of this regulations are still being done to gain the best solution. The issues on concerns related to the current regulatory approach, policy development regarding new genetic modification (nGM) (mostly based on genome editing), and focus of policy amendments are shown in the Table 6 [24]. As an additional information it is also reported about current experiences with nGM applications.

Table 5. Regulatory Approaches of GMO and Genome Editing Products in various countries [22]

No	Country	Genetically modified plants*)	Genome-edited plants**)
1	Argentina	Regulated	Case-by-case, mostly non-regulated
2	Australia	Regulated	Non-regulated
3	Brazil	Regulated	Case-by-case, mostly non-regulated
4	Canada	Regulated	Regulated
5	Chile	Regulated	Case-by-case, mostly non-regulated
6	European Union	Regulated/opposed	Regulated/opposed
7	India	Regulated	Regulated
8	Japan	Regulated	Non-regulated
9	Malaysia	Regulated	Regulated
10	Mexico	Regulated	Regulated
11	New Zealand	Regulated	Regulated
12	South Africa	Regulated	Regulated
13	Thailand	Regulated	Regulated
14	United States of America	Regulated	Non-regulated

*) Refers to the final product containing transgenes, such as selection markers or other form of foreign DNA used during the process.

**) Refers to the final product lacking transgenes that might have been used during the process.

Table 6. Regulatory approaches of Genome Editing Products from various countries [24]

Country	Current Regulatory Approach	Policy Development Regarding nGMs	Focus of Policy Amendments	Current Experiences with nGM applications
European Union	Determination if specific types of nGMs are subject to GMO legislation	No amendment of Directive 2001/18/EC proposed by Europ. Commission, but Europ. Court of Justice ruled that directed mutagenesis is subject to GMO legislation (ECJ 2018)		No experience on European level with applications for unconfined release and placing on the market; however field trials with some nGM applications are conducted (SAM, 2017)
Argentina	Determination if nGM product is subject to GMO legislation	Supplementary resolution adopted 2015 providing criteria for case-by-case decisions (Resolution No. 173/2015)		Until June 2018 12 requests were evaluated according to Resolution No. 173/2015, incl. 10 applications of genome editing, mostly in plants, mostly not regulated (OECD, 2018)
Australia	Determination if nGM process is subject to GMO legislation	OGTR proposed technical amendments to legislation, consultation in progress	Genome editing (SDN-1)	No applications for unconfined release; field trials with some nGM applications are conducted
Brazil	Determination if nGM product is subject to GMO legislation	Supplementary resolution adopted in January 2018 (Normative Resolution No 16) comparable to supplementary regulation in Argentina)		Use of nGMs in contained use facilities; two yeast lines modified by genome editing were evaluated according to Resolution No 16 (not regulated)
Canada	Determination if individual nGM product is novel	Review of risk assessment requirements initiated		Several applications authorized (e.g., cisgenic potato, genome edited oilseed rape)
New Zealand	GMO legislation is currently applied for all nGMs	Government adopted policy to direct technical ruling by NZ-EPA, no immediate policy changes foreseen	GMO legislation only exempts chemical or radiation induced mutagenesis	Use of nGMs for research and development activities; some genome editing determined to be regulated
Norway	Determination if specific types of nGMs are subject to GMO legislation	Technical discussions to inform further steps (following EU approach)		No applications for unconfined release submitted
South Africa	GMO legislation is currently applied for all nGMs	Discussion on policy amendment ongoing		No applications for unconfined release submitted; use of nGMs in contained use facilities
Switzerland	Determination if specific types of nGMs are subject to GMO legislation	Stakeholder discussions to inform future policy		No applications for unconfined release; field trials with some nGM applications are conducted
USA	Determination if individual nGM product is regulated	Consultations on policy to deregulate certain techniques (e.g., cisgenesis)		Several decisions to exempt nGM applications from regulation; a number of nGM applications in regulatory review

3. Significance Technology Genome Editing for boosting Bioeconomy

To support the bioeconomy, biotechnology plays a key role and used as the basis for numerous processes for the production of food and feed, pharmaceuticals, chemical products and bioenergy. The scopes of processes are developed from time to time due to innovation in methodologies. Recombinant technology, which already existed for around three decades show the significant achievement in many fields of processes. Some conventional processes have been improved in genetic breeding in plants, animals, as well as microorganisms. Through protein recombinant technology (genetically modified organism, GMO), bioeconomy in many sectors have been developed and colorization in the global market. The global genetically modified organism's food market will grow at a compound annual growth rate (CAGR) of 3.2% by the end of 2021. The production of genetically modified crops will increase from 112 million tons in 2015 to 130 million tons in the year of 2021 [51].

The World Economic Forum (WEF) estimates that the potential revenue for new business opportunities in the biomass value chains could globally amount to about USD 295 billion by 2020, that is three times the amount of 2010. In health, the value of the drug trade will also increase. Value of biochemicals products (other than drugs) will jump from 1.8% in 2005 to between 12% and 20% by 2015. Biofuel production is shifting away from G1 ethanol based on starch (starch) or cane sugar to ethanol G2 from such lignocellulosic biomass grass and wood. By 2030, it is estimated that biotechnology products will be more developed both in terms of quantity and quality, and also variant. Moreover, it estimated biotechnology could contribute up to at least 2.7 percent of GDP by 2030 [26].

Recently, genome editing has made an impact in plant engineering, including easier and more efficient in editing of a wider range of plants. Therefore, these applications have clear economic implications, with opportunities for crop improvements (e.g. drought tolerance, pest resistance, higher yields) as a major driver. CRISPR-Cas9 has the potential to greatly expand basic knowledge about the links between genotypes and phenotypes in plants. Previously, studies largely depended on mutagenized plants or transposon libraries, which have to be bred for many generations to reliably isolate a gene or mutation of interest. Expression studies can be done by overexpression and gene knock down facilitated by the RNAi technology, which are not as accurate or reliable as genome editing by CRISPR-Cas9. Multigenic traits (those that depend on multiple genes) have been particularly challenging to study. Improved knowledge of this basic biology is likely to expand the types of traits that can be engineered. In animal breeding, a wide range of new insect applications is likely to become available, including for pest control and agricultural purposes. CRISPR-Cas9 based tools will also allow for easier editing of mammalian genomes, with most applications focusing on germline (heritable) edits. Several genome editing applications have already been demonstrated, including the development of cattle that were hornless [10], [13].

A published survey on patent on the CRISPR-Cas9 landscape until 2019, show a high number in patent registrations. The total number of patents in technical improvement was 1052, in agriculture was 374, in medical was 614 and in industry was 192 [33]. This could boost various biotech products generated by genome editing employing CRISPR-Cas9 to make the genetic engineering of plants, animals, microorganisms and human therapy much more efficient [18], [22]. A number of research firms have published market projections for gene editing products using CRISPR-Cas9 and other technologies. Application areas include human therapeutics, research tools, crops, livestock, yogurts, cheeses, and more. In August 2018, Ireland-based Research and Markets estimated that the global market for gene editing will grow at a compound annual growth rate (CAGR) of 33.26% from US $551.2 million in 2017 to US $3.087 billion in 2023. Zion Market Research estimated that the CRISPR-Cas9 gene editing market in 2017 was US $477 million and projected that it will reach US$4.271 billion by 2024, a CAGR of 36.8%. A February 2017 projection by the U.S.- based market research firm Grand View Research anticipates the global market for gene editing products will reach US $8.1 billion by 2025 [16].

In the near future, it is predicted that the market based on genome editing will be stronger, since the industry relies on the availability of tools and platforms of genome editing technology that are constantly progressing. There are many companies and other entities that provide genome editing (especially CRISPR-Cas9) constructs, reagents, and tools. However, there are other areas where genome editing may also have significant economic impacts including bioeconomic which is very important and can be used as strategic tools for facing challenges such as population growth, climate change, increasing greenhouse gas emissions, and need for food and water. Bioeconomic is expected to increase resilience food, produce healthier food, and reduce negative environmental impacts from the agricultural, marine and manufacturing industries. Bioeconomic can also assist in the world's switching from fossil sources for energy needs and industrial raw materials to more sustainable sources [34].

4. Opportunities and Challenge in Indonesia

a. Research and Capacity

Genome editing is one of the strategic technologies to support the national strategic plans in which involve food resilience, energy resilience, environment protection and health. It becomes more significant since the technologies already proven in many countries fo more than 5 years. Therefor development of genome editing must be a mainstream. National capacity right now become better both the human resources and research facilities. Experiences during handling Covid-19 many institutions facilitated with better equipment with various equipment which working on molecular biology. Some research activities about genome editing have already been carried out in many research centers such as Biotechnology Research Center-LIPI, BBBiogen-Ministry of Agriculture, Gadjah Mada University, the Indonesian Center for Biotechnology and Bioindustry Research, etc. Research activities mainly dealing with plants such rice, chili, artemisia, citrus, palm oil, cassava for various superior properties.

Bahagiawati et al. [3] reported about the research progress on genome editing and the necessary regulation for genome editing. Research related to genome editing applications, especially those using the CRISPR-Cas9 technique, has also been initiated in Indonesia. For example, the application of CRISPR technology has been tested to overcome the biotic stress of ganoderma disease in palms [8] and accelerate flowering in orchids [28]. Several research institutions that have conducted pilot research using genome editing techniques include the Agricultural Research and Development Agency (ICABIOGRAD) [39], the Indonesian Biotechnology and Bioindustry Research Center (PPBBI) [8], The Indonesian Institute of Sciences (LIPI) and Gadjah Mada University (UGM) [28]. Genome editing research activities with CRISPR-Cas9 that are being carried out at ICABIOGRAD include improving rice plants for semi dwarf properties, resistance to bacterial leaf blight, and increasing the number of grains [39] [40]. A basic research on rice about molecular and phenotypic analyses of Rice Inpari HDB/K15 F2 lines containing much efficient mutant gene resulted from genome editing method is recently also reported [27]. In addition, ICABIOGRAD also carries out genome editing on citrus, chili and artemisia plants respectively for huang long bing (HLB) resistance, Gemini virus resistance, and high artemisin levels [5]. At the Research Center for Biotechnology-LIPI, in collaboration with Kyoto University, currently, the roles of transcription factors in lignin biosynthesis in rice are being investigated. In the meantime, the Indonesian Biotechnology and Bioindustry Research Center are focusing on combating diseases reducing the productivity of oil palm.

b. Consideration for Regulation

Government Regulation on genetically modified organisms was established on the basis of the precautionary approach in accordance with the Cartagena Protocol on Biosafety. This Protocol has been ratified by Indonesia by Act No. 21/2004. In this regulation, it has been determined that every person who conducts research and development on biotechnology products must prevent and / or overcome the negative impact of its activities on human health and the environment. The regulation for the release of biotechnology products (microbes, plant, fish, animal) is available in Indonesia as stipulated in the Government Regulation (PP No. 21/2005).

Due to its superiority and relative simplicity in its application, in the future research and application of genome editing techniques in Indonesia are predicted to play important roles and can encourage new breakthroughs in the development of new seeds, products and processes that can boost the bioeconomy and the national competitiveness. Genome editing requires a genetic engineering process for editing the genome, however the products obtained can have similarities with the results of natural mutations. So that after validation using the molecular biology approach it can be categorized as non-GMO.

The types of genome editing results are commonly known as SDN1, SDN2 and SDN3 depending on the mechanism of repair process of the target DNA cut by the DNA nuclease enzyme; either independently repaired by non-homologous end joining/NHE (SDN1), or with a template for introducing repair of the base sequence (SDN2) or with a template for integrating sufficiently long DNA fragments (knock-in) (SDN 3) via homologous recombination. SDN 1 can be categorized as non-GMO, while SDN2 and SDN3 can be categorized as non-GMO depending on the final results. The Focus Group Discussion (FGD) held in LIPI Cibinong 28 February 2020 which was attended by representative from Research Institutions, regulators and international expert concluded that the genome editing of SDN 1, SDN 2 and SDN 3 which are classified as non- GMO should be determined separately from GMO by the National Committee on Biosafety (KKH). Furthermore, the FGD recommend that KKH conduct a review of PP21 / 2005 concerning Biosafety of GMO on its suitability with the latest technological developments such as genome editing.

c. The role of genome editing for bioeconomy of Indonesia

According to Conservation International (CI), Indonesia belongs to *Megadiversity* Countries which has 20% of the 1,605 bird species (323 species) and 53% of the world's 720 mammal species (382 species) that are found to live naturally in the territory of Indonesia. In relation to ecosystem, Indonesia also has 19 types of natural ecosystems which are scattered in various regions from Sumatra to Papua. Moreover, as an archipelagic country, Indonesia has a coastline of not less than 95,181 km2 which is surrounded by tropical seas, thereby increasing the high level of biodiversity.

The potential of biodiversity will strengthen the bioeconomy of Indonesia. Biodiversity has very significant roles for human life and the environment, among others, as a source of food and medicine, a place for water reserves (reservoir), maintaining the carbon cycle and the source of useful traits. It is estimated that contribution of the biodiversity to bioeconomy in the form of food sources from terrestrial, semi terrestrial and marine ecosystems, in the form of food biomass, which consists of food crops, vegetable crops, fruit crops, plantation crops and biomass from livestock and livestock right is Rp. 1,334.7 trillion (in 2012) in total value. Bio-pharma-plants (approximately 449,300 tons) for the provision of medicinal, health and cosmetic ingredients in 2012 contributed a total value of Rp. 4 trillion. Those were underestimated values because the overall contribution of biopharmaceuticals, especially those from household businesses, may not be recorded since there is no official data. Furthermore, energy supply services, in the form of biomass for energy (18.4%) and for hydrothermal energy sources (2.1%) have an economic contribution value of Rp. 336.88 trillion (equivalent to USD oil price. 112.7/barrel. Meanwhile, for plants that provide varieties of wood for building, plant sap for rubber and other adhesive industrial materials, contributed to a value of Rp. 1,081.26 trillion to the economy [4].

Genome editing technology which is already proven in many countries will be key driving factors to make various process and products. The value of biodiversity will be increase both for our own needs and for exports. In addition, genome editing can also be utilized to develop processes to rehabilitation of damaged environment, develop green material, green energy and green manufacturing processes, as well as pharmaceutical products and health care.

5. Conclusion

To support bioeconomy, genome editing could play a key role in various goals to develop effective and efficient processes for manufacturing product and services. Genome editing as the basis for numerous processes can be combined with bioinformatics, nano technology and other state of the art technologies. Implementation of genome editing will be able to strengthen food resiliency, energy resiliency, feed products, fiber products, pharmaceutical products and chemical products which are environmentally friendly, and human therapy. The conversion of potential biodiversity to more valuable products and services will create new jobs and new businesses. The bioeconomy of Indonesia will be nurtured by the development of genome editing technology. To accelerate the implementation of genome editing, however, appropriate regulations are needed.

6. References

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